Universidade Estadual Paulista "Júlio de Mesquita Filho"
Faculdade de Odontologia de Araçatuba (FOA-UNESP)
Programa de Pós-Graduação em Odontologia
Área de Concentração: Estomatologia

GABRIELA LOPES DOS SANTOS

Beta-adrenergic pathway activation in head and neck cancer: A comprehensive analysis of the clinical and genomic features using integrated bioinformatics

Araçatuba - SP
2020

GABRIELA LOPES DOS SANTOS

Beta-adrenergic pathway activation in head and neck cancer: A comprehensive analysis of the clinical and genomic features using integrated bioinformatics

Dissertação apresentada à Faculdade de Odontologia de Araçatuba, Universidade Estadual Paulista "Júlio de Mesquita Filho'' - UNESP, para obtenção do título de 'Mestre em Odontologia. Área de Concentração: Estomatologia.

Orientadora: Profa. Dra. Kellen Cristine Tjioe
Coorientador: Prof. Ass. Dr. Daniel Galera Bernabé

Araçatuba - SP
2020

Catalogação na Publicação (CIP)

Diretoria Técnica de Biblioteca e Documentação – FOA / UNESP

Santos, Gabriela Lopes dos.

S237b Beta-adrenergic pathway activation in head and neck cancer: a comprehensive analysis of the clinical nd genomic features using integrated bioinformatics / Gabriela Lopes dos Santos. – Araçatuba, 2020 139 f. : il. ; tab.

Dissertação (Mestrado) – Universidade Estadual Paulista, Faculdade de Odontologia de Araçatuba
Orientadora: Profa. Kellen Cristine Tjioe
Coorientador: Prof. Daniel Galera Bernabé

1. Receptores adrenérgicos beta 2 2. Carcinoma de células escamosas de cabeça e pescoço 3. Proteínas da membrana plasmática de transporte de norepinefrina 4. Estresse psicológico I. Título

Black D6
CDD 617.63

Claudio Hideo Matsumoto CRB-8/5550

Dedicatória

À **Deus** e **Nossa Senhora de Aparecida**, pela oportunidade de estar realizando mais esse sonho;

À **minha amada família**, pela sustentação, amor incondicional, confiança e oportunidade.

Agradecimentos

À **Deus** e **Nossa Senhora de Aparecida**, por todo zelo e sustentação a mim e minha família. Muito obrigada por todas as oportunidades oferecidas e planejadas em nossos caminhos.

À você meu **pai Gerson** (*in memoriam*), agradeço sua alegria e leveza em levar a vida. Espero estar conseguindo levar seus melhores traços em cada momento em minha vida. Obrigada por nunca me abandonar, em cada momento de dificuldade e por sempre ter se esforçado para me fazer sorrir. Hoje, o senhor não está aqui presente fisicamente, mas estará em nossos corações e em cada pedacinho de nossas vitórias. Espero continuar o orgulhando, e trazendo o sorriso que sempre me trouxe.

À você minha **mãe Lucimara,** me faltam palavras para descrever os meus sinceros agradecimentos. Obrigada não apenas por ser minha SUPER mãe, mas também por ser minha amiga, companheira e confidente. Muito obrigada por permitir e proporcionar a realização desse e todos os outros objetivos. Obrigada por acreditar, confiar em mim e nos meus sonhos, e além de tudo sonhar eles comigo!

À você **meu irmão Rodrigo**, obrigada por sempre estar presente em minha vida. Obrigada pelo homem integro, trabalhador, estudioso e maravilhoso em que se tornou. Obrigada por estar cuidando de nossa mãe, quando eu não estava presente! Obrigada por cuidar de mim, mesmo distante fisicamente.

À minha **porquinha da índia** e **filha Kim**, obrigada por ser esse bebê maravilhoso, e por alegrar meus dias com suas sapequices!

À **minha linda** e **amada família**, dedico essa dissertação e todos os outros trabalhos, essa vitória é nossa! Obrigada por lutarem e sonharem comigo. Amo muito vocês!

À minha **avó Nair, meus tios e primos,** todos sempre dispostos a me apoiar na concretização de cada um dos meus sonhos e objetivos. Muito obrigada pelo amor e carinho incondicional.

À meu namorado **Guilherme Paixão,** por sempre acreditar em mim e em nós. Obrigada ser meu grande amigo antes mesmo de sermos namorados. Obrigada por todos esses anos de amor e cumplicidade. Obrigada por sonhar comigo e planejar cada pedaço dessa grande vitória. Muito obrigada por me ouvir, apoiar em todos os objetivos traçados e sempre estar disposto em me ajudar para conquista-los. Te amo muito!

À família **Paixão,** em especial à: Luciana, Clodoaldo, Giulia e vó Judith por cada momento extremamente especial vividos juntos. Obrigada por me amarem e tratarem como filha. Vocês são parte da minha família! Amo vocês.

À minha orientadora e grande inspiração**, Profa Dra. Kellen Cristine Tjioe.** Obrigada não “apenas” por me orientar, mas também por acreditar na garota que chegou perdida na FOA/Unesp. Obrigada por depositar sua confiança no desenvolvimento desse e, tantos outros projetos. Agradeço especialmente cada ensinamento, oportunidades, conselhos e paciência. A senhora me mostrou que a pós-graduação pode ser vivida de maneira leve, sempre com um sorriso no rosto e acreditando que poderíamos sempre fazer mais e melhor. Muito obrigada por ser a melhor e mais presente orientadora que poderia ter. A senhora é um grande exemplo de honestidade, paixão pelo ensino e pesquisa que pude conhecer. Muito obrigada por me fazer crescer como ser humano, futura professora e pesquisadora. Espero poder leva-la por toda minha trajetória acadêmica.

Aos professores da disciplina de Estomatologia: Meu coorientador, **Prof. Dr. Daniel Galera Bernabé**, por contribuir para meu crescimento profissional e pessoal. Muito obrigada por disponibilizar do seu tempo sempre que possível; Ao **Prof. Dr. Glauco Issamu Miyahara**, atual diretor da FOA/Unesp, por me permitir conhecer o programa quando almejei a pós-graduação. Obrigada por sempre mostrar de maneira cristalina e honesta o meio acadêmico. Saiba que o senhor serve de exemplo para muitos de nós; Ao **Prof. Dr. Éder Ricardo Biasoli**, por contribuir para meu crescimento profissional e pessoal. Obrigada por permitirem minha participação como aluna no Programa de Aperfeiçoamento e Apoio à Docência no Ensino Superior (PAADES).

As professoras da disciplina da Radiologia Odontológica e Imaginologia, **Profa. Dra. Leda Maria Salzedas Pescini** e **Profa. Dra. Carla Renata Sanomiya Ikuta**, por gentilmente consentirem o uso do banco de dados da Universidade para o desenvolvimento do meu projeto de Qualificação. Obrigada por permitirem minha participação como aluna no Programa de Aperfeiçoamento e Apoio à Docência no Ensino Superior (PAADES).

Aos professores das disciplinas de Patologia Geral e Bucal, e Microbiologia da FOA /Unesp, **Profa. Dra. Cristiane Furuse, Prof. Dr. Marcelo Macedo Crivelini, e Profa. Dra. Renata Callestini, Profa. Dra. Ana Cláudia Okamoto e Prof. Dr. Elerson Gaetti Jardim Filho**, muito obrigada por todo auxílio e parceria ao longo desta jornada.

À meus professores da **Faculdade de Odontologia de Lins**, por me proporcionarem conhecimento teórico e prático para conseguir concluir mais uma etapa. Em especial a minha querida e amada **Profa. Dra. Nancy Alfieri Nunes**, obrigada por confiar plenamente em minha capacidade e proporcionar a oportunidade

de continuarmos trabalhando juntas. Se hoje segui o caminho do Diagnóstico foi porque a senhora me inspirou. Muito obrigada por tudo!

Ao Centro de Oncologia Bucal (COB) da FOA /Unesp, supervisionado pelo **Prof. Dr. Daniel Galera Bernabé** e vice-supervisionado pela **Profa. Dra. Daniela Micheline dos Santos** pela oportunidade de conviver com os pacientes oncológicos e pelo aprendizado adquirido. Aos funcionários do COB, **Adriana de Paula (Dri!), Anne Cocato, Daniene Ribeiro, Francisco Collado, Gabrielle Duarte, Regiane Nogueira e Sebastião Neto** por contribuírem com todo meu aprendizado e crescimento dentro desses quase dois anos. Em especial a funcionária e ex-funcionária: **Dri e Jane**, pela amizade e carinho. Obrigada por sempre me ajudarem e me escutarem em nossas manhãs e tardes. Vocês são muito queridas e amadas por cada um de nós.

Ao **Prof. Dr. André Luiz Fraga Briso**, coordenador do Programa de Pós-Graduação em Odontologia, por todo apoio e suporte necessário para que eu pudesse cumprir as exigências do Programa e concluir meu curso. Aos professores da Área de Concentração em Estomatologia, **Prof. Dr. Daniel Galera Bernabé** (coordenador da Área), **Prof. Dr. Glauco Issamu Miyahara** e **Profa. Dra. Kellen Cristine Tjioe** pela confiança e pela oportunidade de realizar meu curso de pós-graduação.

À Faculdade de Odontologia do Campus de Araçatuba, da Universidade Estadual Paulista “Júlio de Mesquita Filho” (FOA /Unesp), representada pelo **diretor Prof. Dr. Glauco Issamu Miyahara e vice-diretor Prof. Dr. Alberto Carlos Botazzo Delbem**, pela oportunidade de aprender e de me desenvolver como pesquisadora na área de Estomatologia.

Às funcionárias da Seção de Pós-Graduação da FOA - UNESP, **Valéria Cristiane e Lilian** pelas orientações precisas e toda dedicação. Vocês são indispensáveis para que os alunos alcancem seus títulos e nosso Programa de Pós-Graduação em Odontologia funcione da melhor forma.

Aos funcionários da Biblioteca da FOA/Unesp, em especial, **Ana Cláudia e Cláudio**, pelas orientações precisas, atenção, disponibilidade e contribuição com a formatação desta dissertação.

Aos meus amigos e colegas da pós-graduação, **Maria Clara, Ana Daniela, Daniela Cantieri, Tamara, Jessica, Saygo, Giseli, Bruna, Daniela Bastos, Vitor, Winicius e Felipe**. Muito obrigada pela convivência dentro e fora do COB ao longo dessa trajetória. Obrigada a **Maria Clara, Tamara, Jessica e Saygo** por cada jantar, filmes e festas juntos, vocês tornaram meus dias em Araçatuba muito mais leves. À minha amiga e companheira de apartamento **Maria Clara**, muito obrigada por cada risada, conversa e gordices vividas juntas. Acredite sempre em você e em seu potencial, e nunca permita dizerem que você não é capaz!

Aos meus amigos de **Borborema e Lins**: **Aléxia, Rodrigo, Juliana, Gabriel, Carol, Ana Paula, Maísa, Fernanda, Iuly, Thamara, Júlio e Felipe** por sempre estarem presentes em minha vida. Amo cada um de vocês!

A todas as pessoas que fizeram parte da minha trajetória até aqui e que contribuíram para que este momento acontecesse, deixo registrado a minha eterna gratidão.

Epígrafe

“Acredite! Acredite que sonhar
Também é compreender
Que nem sempre o que se sonha
É o melhor pra você
E que não realizar
Nem sempre será sofrer
Sonhe sempre
E seja grato pelo sonho que já tem
Repare em cada detalhe
Das coisas que lhe faz bem
Que o pouco, que hoje é seu,
Já é muito pra alguém
Ter um chão para pisar
Um sol pra lhe dar calor
Ter o ar pra respirar
Ter saúde, ter amor
Tudo isso já lhe faz
Também realizador
Seja sempre inquieto
E vez por outra paciente
Parece contraditório
Soa meio diferente
Mas às vezes pisar no freio
Também é andar pra frente
A vida meu povo
A vida não é tão simples
Viver não é só sorrir
A lagarta que rasteja
Rasteja pra evoluir
Se transforma em borboleta
Depois voa por aí.”

Bráulio Bessa

Resumo

Santos GL. Ativação da via beta-adrenérgica no câncer de cabeça e pescoço: Uma análise abrangente das características clínicas e gênomicas utilizando a bioinformática [dissertação]. Araçatuba: Faculdade de Odontologia da Universidade Estadual Paulista; 2020.

RESUMO

O estresse crônico leva à ativação da via de sinalização beta-adrenérgica. Sua ativação tem sido implicada na progressão de diferentes tipos de câncer, mas seu papel nos carcinomas espinocelulares de cabeça e pescoço (CECPs) permanece indefinido. O objetivo deste estudo foi investigar o papel da ativação da via beta-adrenérgica na progressão dos CECPs, avaliar seu impacto na sobrevida dos pacientes e buscar possíveis terapias para pacientes que encontravam-se com a via beta-adrenérgica ativa. Quinhentos e vinte pacientes do The Cancer Genome Atlas com CECPs primários foram divididos em dois grupos: $ADRB2^{baixa}$ / $SLC6A2^{baixa}$ e $ADRB2^{alta}$ / $SLC6A2^{alta}$. A associação de características clinicopatológicas e genômicas entre os grupos foram analisadas utilizando bioinformática. Os genes diferencialmente expressos (DEGs) foram identificados através da análise da expressão diferencial. A análise de sobrevida também foi realizada com base nas expressões ADRB2 e SLC6A2. Foram identificados medicamentos em potencial para tratamento de CECPs com base nos DEGs. Houve associação entre as expressões ADRB2 e SLC6A2 com idade, raça, localização do tumor, grau histológico, invasão perineural e status do HPV p16. Foram identificados 898 DEGs entre os grupos. Foi demonstrado que a expressão $ADRB2^{alta}$ / $SLC6A2^{alta}$ influenciou a proliferação, adesão e invasão de células CECPs além da angiogênese. Pacientes com carcinomas espinocelular de laringe e faringe apresentando expressão $ADRB2^{alta}$ / $SLC6A2^{alta}$ tiveram menor sobrevida. Por fim, 56 drogas antineoplásicas e imunoterápicas aprovadas pelo Food Drugs Administration foram identificadas como potenciais alvos para o tratamento personalizado.
Significância: Estes achados sugerem fortemente um papel proeminente da sinalização beta-adrenérgica no CECPs ao estimular um fenótipo tumoral mais agressivo. Estas alterações tiveram um impacto negativo no prognóstico dos pacientes com CECP em região de faringe e laringe.

Palavras-chaves: Receptores Adrenérgicos Beta 2. Carcinoma de células

escamosas de cabeça e pescoço. Proteínas da Membrana Plasmática de Transporte de Norepinefrina. Estresse Psicológico.

Abstract

Santos GL. Beta-adrenergic pathway activation in head and neck cancer: A comprehensive analysis of the clinical and genomic features using integrated bioinformatics [dissertation]. Araçatuba: UNESP - São Paulo State University; 2020

ABSTRACT

Chronic stress leads to the activation of the beta-adrenergic pathway. Its activation has been implicated in the progression of different types of cancer but its role on head and neck squamous cell carcinomas (HNSCCs) remains undefined. The aim of this study was to investigate the influence of the beta-adrenergic pathway activation in the progression of HNSCCs, assess its impact in the survival of the patients, and explore the potential targets. Five hundred and twenty The Cancer Genome Altas patients with primary HNSCCs were divided in two groups: $ADRB2^{low}$ / $SLC6A2^{low}$ and $ADRB2^{high}$ / $SLC6A2^{high}$. The association of clinicopathological and genomic features between the groups was analyzed using a bioinformatic approach. Differentially expressed genes (DEGs) were identified through differential expression analysis. Survival analysis was also performed based on ADRB2 and SLC6A2 expressions. Potential drugs for treatment of HNSCC were identified based on the DEGs. There was association between ADRB2 and SLC6A2 expressions with age, race, tumor site, histologic grade, perineural invasion, and HPV p16 status. It was identified 898 DEGs between the groups. It was demonstrated that $ADRB2^{high}$ / $SLC6A2^{high}$ expression influenced HNSCC cells proliferation, adhesion, invasion, and angiogenesis. Patients with larynx and pharynx squamous cell carcinomas presenting $ADRB2^{high}$ / $SLC6A2^{high}$ expression showed had lower survival rates. Finally, 56 Food Drugs Administration-approved antineoplastic and immunotherapeutic drugs were identified as potential targets for the personalized treatment.

Significance: These findings strongly suggest a prominent role of beta-adrenergic pathway in HNSCC by stimulating a more aggressive tumoral phenotype. These alterations were shown to negatively impact the prognosis of patients with larynx and pharynx squamous cell carcinomas .

Keywords: Receptors, Adrenergic, beta-2. Squamous Cell Carcinoma of Head and Neck. Norepinephrine Plasma Membrane Transport Proteins. Psychological stress.

Lísta de fíguras

LISTA DE FIGURAS

Figure 1 - **ADRB2 and SLC6A2 status in 520 head and neck squamous cell carcinomas (HNSCC).** A) Correlation of RNA expression of ADRB2 and SLC6A in HNSCC. Spearman's rank correlation coefficient. B) Lollipop plot showing mutations of ADRB2 and SLC6A2 in HNSCC (www.cbioportal.org). 38

Figure 2 - **Differentially expressed genes (DEGs) based on ADRB2 and SLC6A2 expression in head and neck squamous cell carcinomas (HNSCC)**. A) Representation of the 898 DEGs between $ADRB2^{low}$ / $SLC6A2^{low}$ group versus $ADRB2^{high}$ / $SLC6A2^{high}$ group. Genes in green had logFC>±3. B) Heatmap showing the top 100 DEGs (50 upregulated and 50 downregulated) between $ADRB2^{low}$ / $SLC6A2^{low}$ group versus $ADRB2^{high}$ / $SLC6A2^{high}$ group. Complete data in Supplementary file 1. 43

Figure 3 - **GO and pathway enrichment analysis of DEGs in HNSCCs.** A) Downregulated and B) Upregulated biological processes identified in $ADRB2^{high}$ / $SLC6A2^{high}$ group. The interaction network of the pathways DEGs. C-D) Enrichment maps showing the interactions among the processes from A and B. Complete data in Supplementary file 2. 45

Figure 4 - **Upregulated processes in $ADRB2^{high}$ / $SLC6A2^{high}$ HNSCC.** DEGs and their relationship with the biological processes within the A) angiogenesis, B) cell proliferation, and C) microenvironment classifications. The biological processes identified in the GO analysis were group according to their major role in HNSCC. 46

Figure 5 - **Protein-protein interaction (PPI) network of the DEGs in HNSCC.** A) Functional protein interactions network; B) Microenvironment-related interactions in $ADRB2^{high}$ / $SLC6A2^{high}$ group; C) Cancer stem cell-related interactions; D) Average stemness score of $ADRB2^{high}$ / $SLC6A2^{high}$ compared with $ADRB2^{low}$ / $SLC6A2^{low}$ group. Student's t test: *P<0.05. 48

Figure 6 - **Overall HNSCC and tumor site survival analyses between the groups ADRB2 and SLC6A2 expressions.** A) HNSCC survival; B) Oral Cavity cancer survival; C) Larynx and pharynx squamous cell carcinomas survival. Kaplan-Meier method and the comparison of the survival curves was performed using log-rank test: P<0.05. 50

Figure 7 - **Drug-gene interaction analysis and potential therapeutics for HNSCC.** Heatmap showing the top drugs and target-DEGs in HNSCC. Complete data in Supplementary file 3. 52

Lísta de tabelas

LISTA DE TABELAS

Table 1 - Clinicopathological characteristics of ADRB2^{low} / SLC6A2^{low} and ADRB2^{high} / SLC6A2^{high} head and neck squamous cell carcinomas. 40

Lista de abreviaturas

LISTA DE ABREVIATURAS

ADRB1 Beta-adrenergic receptor 1

ADRB2 Beta-adrenergic receptor 2

$ADRB2^{high}$ / $SLC6A2^{high}$ high expression of beta-adrenergic receptor 2 / high expression of solute carrier family 6 member 2

$ADRB2^{low}$ / $SLC6A2^{low}$ low expression of beta-adrenergic receptor 2 / low expression of solute carrier family 6 member 2

ADRB3 Beta-adrenergic receptor 3

ALDH1A1 Aldehyde Dehydrogenase 1 Family Member A1

BDNF Brain Derived Neurotrophic Factor

BP Biological process

CC Cell components

COX2 Cytochrome C oxidase II

CSF2 Colony stimulating factor 2

DEG Differentially expressed gene

DGIdb The Drugs Gene Interaction Database

E Epinephrine

ECM Extracellular Matrix

EMT Epithelial-Mesenchymal Transition

EYA1 Eyes Absent Transcriptional Coactivator And Phosphatase 1

FDA Food and Drugs Administration

FDR False Discovery Rate

GDC Genomic Data Commons

GO Gene Ontology

HIF3A Hypoxia Inducible Factor 3 Subunit Alpha

HNSCC Head and Neck Squamous Cell Carcinoma

HPV Human Papilloma Virus

IBM International Business Machines

ICAM4 Intercellular Adhesion Molecule 4

IL1A Interleukin 1 Alpha

LAMA3 Laminin Subunit Alpha 3

LAMC2 Laminin Subunit Gamma 2

LEF1 Lymphoid Enhancer Binding Factor 1

LogFC Log Fold Change

M Metastasis

MF Molecular function

MMP Matrix Metalloproteases

MMP1 Matrix Metallopeptidase 1

MMP10 Matrix Metallopeptidase 10

MMP13 Matrix Metallopeptidase 13

MMP3 Matrix Metallopeptidase 3

mRNA Ribonucleic Acid Messenger

N Node

NCI National Cancer Institute

NE Norepinephrine

NET Norepinephrine Transporter

NGF Nerve Growth Factor

PPI Protein-Protein integration

PTGS2 Prostaglandin-Endoperoxide Synthase 2

RNA Ribonucleic Acid

RNA-Seq Ribonucleic Acid Sequencing

SLC6A2 Solute Carrier Family 6 Member 2

SOX2 Sex Determining Region Y (SRY)- Box Transcription Factor 2

SPSS Statistical Package for the Social Sciences

STRING Search Tool for the Retrieval of Interacting Genes

T Tumor size

TCGA The Cancer Genome Atlas

TNM TNM staging system

TSS Tissue Source Sites

TTD Therapeutic target database

VCAM1 Vascular Cell Adhesion Molecule 1

VEGFC or VEGF-C Vascular Endothelial Growth Factor C

SUMÁRIO

1 GRAPHICAL ABSTRACT 27

2 INTRODUCTION 29

3 MATERIAL AND METHODS 32

3.1 Access to the data 32

3.2 Clinical data 32

3.3 RNA expression and mutation data 32

3.4 Beta-adrenergic pathway activation 33

3.5 Differentially expressed genes 33

3.6 Gene Ontology and pathway enrichment analysis 34

3.7 Protein-protein interaction network analysis 34

3.8 Survival analysis 34

3.9 Drug-gene interaction analysis 35

4 RESULTS 37

4.1 Beta-adrenergic pathway activation in HNSCC is mediated by ADRB2 and SLC6A2 37

4.2 ADRB2 and SLC6A2 expression is associated with histologic grade, perineural invasion, and HPV p16 status in HNSCC 39

4.3 Overview of DEGs in ADRB2^{low} / SLC6A2^{low} vs ADRB2^{high} / SLC6A2^{high} HNSCC 42

4.4 GO analysis links ADRB2high / SLC6A2high HNSCC to angiogenesis, cell proliferation, and ECM plasticity 44

4.5 PPI network and tumor growth ADRB2^{high} / SLC6A2^{high} expression 47

4.6 ADRB2high / SLC6A2high predicts worst prognosis of patients with pharyngeal and laryngeal squamous cell carcinoma 49

4.7 Drug-gene interaction analysis reveals potential therapeutic options for HNSCC 51

5 DISCUSSION 54

REFERENCES 59

Anexo A - Supplementary files 64

Anexo B - Comitê de Ética em Pesquisa: The Cancer Genome Atlas Program 125

Anexo C - Normas de publicação da Cancer Research 137

Beta-adrenergic pathway activation in head and neck cancer: A comprehensive analysis of the clinical and genomic features using integrated bioinformatics *

Gabriela Lopes dos Santos[1], MSc Student, Daniel Galera Bernabé[1,2], PhD, Glauco Issamu Miyahara[1,2], PhD, and Kellen Cristine Tjioe[1], PhD.

[1] Oral Oncology Center, São Paulo State University (Unesp), School of Dentistry, 1193 José Bonifácio St., SP 16015-050, Araçatuba, São Paulo, Brazil.

[2] Psychoneuroimmunology Laboratory, Psychosomatic Research Center, Oral Oncology Center, São Paulo State University (Unesp), School of Dentistry, 1193 José Bonifácio St, SP 15050-015, Araçatuba, São Paulo, Brazil

RUNNING TITLE: Beta-adrenergic pathway and HNSCC

KEYWORDS: Adrenergic beta-Receptors; Squamous Cell Carcinoma of the Head and Neck; Norepinephrine Transport Protein; Psychological stress.

FINANCIAL SUPPORT: None to declare.

CORRESPONDING AUTHOR:
Dr. Kellen Cristine Tjioe
Oral Oncology Center.
Address: Rua José Bonifácio, 1193. Postal code: 16015-050 - Araçatuba, São Paulo, Brazil
E-mail: kellentjioe@gmail.com

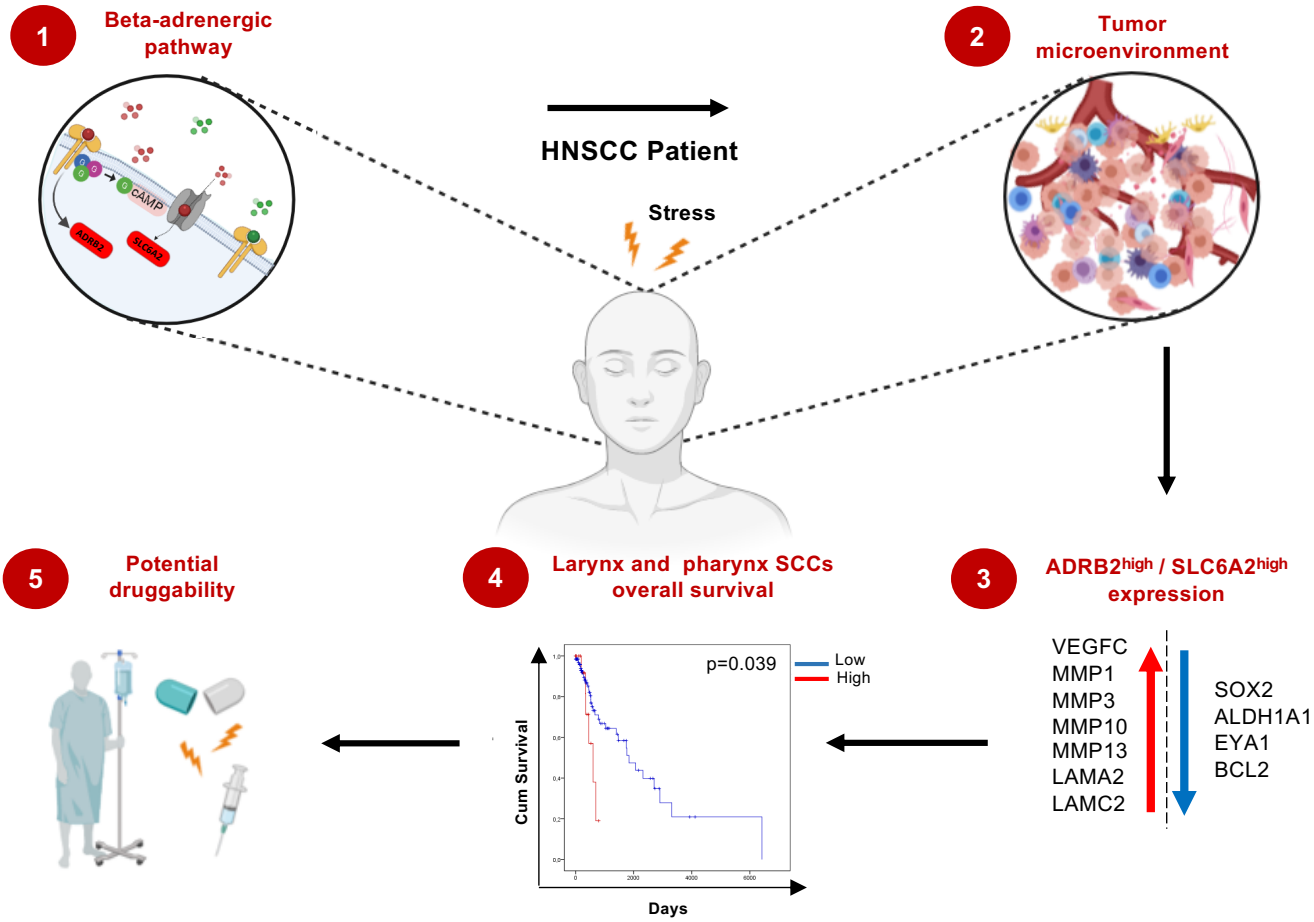
CONFLICT OF INTEREST: The authors declare they do not have conflict of interest.

WORD COUNT: 3.872
FIGURES: 7
TABLES: 1

* Formatado de acordo com as normas de publicação da Cancer Research (Anexo C)

Graphical abstract

1 GRAPHICAL ABSTRACT



Introduction

2 INTRODUCTION

Psychological chronic stress has been linked to the onset or to the worst outcome of several diseases such as depression, anxiety (1), cardiovascular (2) and gastrointestinal (3) illnesses, and cancer (4). In individuals under chronic stress, higher levels of the hormones norepinephrine (NE) and epinephrine (E) are released, respectively, by the terminal sympathetic nerve fibers locally and by the adrenal gland systemically (5). Then NE and E binds to the alpha- or beta-adrenergic (ADRB) receptors, that are thoroughly expressed across the body, and activate the adrenergic pathway. Interestingly, clinical studies have found association between the activation of the alpha- or beta-adrenergic signaling pathway and a worst prognosis (6), perineural invasion (7), and metastasis (8) in different types of cancer. Furthermore, *in vitro* studies have shown that the overactivation of the adrenergic pathway plays a role in the pathogenesis of several malignant tumor types including skin (9), pancreas (10), and brain (11) by increasing tumoral progression, dissemination, and proliferation. The local activation of the adrenergic receptors has also been shown to play an important role in the alteration of the tumoral microenvironment by inducing the epithelial-mesenchymal transition (EMT) (12), and angiogenesis (13).

Conflicting evidences about the role of chronic stress in the head and neck squamous cell carcinoma (HNSCC) progression have been discussed over the years. While some *in vitro* studies have shown that the activation of the beta-adrenergic pathway is implicated in increased proliferative activity (14), invasion, and EMT (15) of head and neck cancer cells, other studies have had opposing findings. The stimulation of HNSCC cells with agonists of the beta-adrenergic receptors has resulted in decrease in HNSCC cell migration, invasion (16,17), and EMT (18). Clinical studies have obtained dissonant findings as well. Beta-adrenergic receptor 2 (ADRB2) has been found as a positive predictive factor for oral cancer in one study (15) or to do not influence the prognosis of oral cancer in other investigation (19). These apparently opposing pieces of evidence raise doubts about the function of the beta-adrenergic pathway activation in the biology of HNSCC.

Thus, this study was designed to address the enigma about how the beta-adrenergic pathway activation affects the development of HNSCC and the impact it has on the patients' prognosis. For that purpose, it was performed a comprehensive clinical and genomic analysis of 520 patients with HNSCC using a bioinformatic approach. Markedly, 898 genes were found differentially expressed in tumors with high versus low activation of the ADRB pathway. By exploring these genes, we found that the beta-adrenergic pathway overactivation led to upregulation of several processes closely related to increased aggressiveness of HNSCC, such as cell proliferation, invasion, and angiogenesis. On the other hand, genes related to cell stemness were downregulated. All these molecular findings were confirmed by the clinical data: the adrenergic pathway activation was shown to be a negative prognostic factor for HNSCC. Finally, this study also identified potential targets for the personalized treatment of HNSCC based on the beta-adrenergic pathway status.

Material and Methods

3 MATERIAL AND METHODS

3.1 Access to the data

Clinical and molecular data of patients with head and neck cancer were retrieved through the National Cancer Institute's (NCI's) Genomic Data Commons (GDC - www.portal.gdc.cancer.gov) Legacy Archive from The Cancer Genome Atlas (TCGA). The database was accessed using TCGAbiolinks package (20) in the RStudio software (Integrated Development for RStudio Inc., Boston, MA, USA - http://www.r-project.org). The selection criteria were: 1) patients with primary head and neck squamous cell carcinoma; and 2) patients with clinical and genomic information available. A total of 520 patients fulfilled the inclusion criteria.

3.2 Clinical data

Clinical information was downloaded and imported into RStudio using the TCGAbiolinks package (20). Socio-demographic (gender, age, and race), clinical (tumor site, TNM clinical, and tumor stage), microscopical (lymphovascular invasion, perineural invasion, histologic grade, and HPV p16 status) information were analyzed. The histological grade and TNM clinical following system American Joint Committee on Cancer.

Fisher test was used to verify the association of the adrenergic pathway activation with gender, tobacco consumption, alcohol consumption, lymphovascular invasion, perineural invasion, and HPV p16 status. Chi-square test was used to assess the association of the adrenergic pathway activation with age, ethnic group, tumor site, T, N, M clinical, tumor stage, histologic grade. Data analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) Version 20 (Chicago, USA). $P<0.05$ was considered statistically significant.

3.3 RNA expression and mutation data

RNA-Seq data (Illumina HiSeq RNAseqv2) were downloaded from the GDC Data Portal and imported into RStudio. RNA expression data were obtained using the functions GDCquery, GDCdownload, and GDCprepare of TCGAbiolinks package (20).

The TCGAnalyze_Preprocessing function, which calculates the Array Array Intensity correlation for each sample, was used to detect possible outliers. The cut was set at 0.6 to define the samples with low correlation (outliers). As we did not find any outliers, we continued with the analysis of the 520 HNSCCs. Afterwards, we normalized the RNA expression among the samples (TCGAnalyze_Normalization) using the EDASeq package (21). Finally, we filtered (TCGAnalyze_Filtering) those RNAs with low signal across the samples (cut=0.25) and obtained a final number of 14,899 RNAs.

The gene mutation data of HNSCCs samples were retrieved from cBioPortal (22). Five-hundred and twelve patients had this information available. To calculate the stemness index (23) of the HNSCCs, the argument TCGAanalyze_Stemness of the TCGAbiolink package (20) was used.

3.4 Beta-adrenergic pathway activation

A hallmark of the beta-adrenergic pathway activation is the overexpression of the adrenergic receptors (5). They bind to the hormones epinephrine and norepinephrine, which are secreted in response to stress. Among the upstream beta-adrenergic RNAs, only ADRB2 were expressed in HNSCC. Both ADRB1 and ADRB3 presented low signal and did not pass the filter. Solute Carrier Family 6 Member 2 (SLC6A2) encodes the norepinephrine transport (NET) protein, which is responsible for the reuptake of NE into presynaptic nerve terminals and is a regulator of norepinephrine homeostasis (24). SLC6A2 is mostly expressed in neural tissue however we observed that most of our sample was positive for SLC6A2. Considering that this gene is upregulated when there is higher concentration of NE, we selected SLC6A2 to pair with ADRB2 and define their overexpression as a readout for the beta-adrenergic pathway activation.

The patients were divided into two groups according to the ADRB2 and SLC6A2 expression in $ADRB2^{low}/SLC6A2^{low}$ and $ADRB2^{high}/SLC6A2^{high}$.

3.5 Differentially expressed genes

Differentially expressed genes (DEGs) between the HNSCC with $ADRB2^{low}$/$SLC6A2^{low}$ and $ADRB2^{high}$/$SLC6A2^{high}$ expression were determined with the TCGAbiolinks package (20) using the function TCGAanalyze_DEA. RNA expression data were batch-corrected using the tissue source sites (TSS) method and also submitted to voom transformation. Genes with false discovery rate (FDR)<0.01 and log fold-change (logFC)≥1 or ≤-1 were considered DEGs. DEGs were upregulated when logFC≥1 and downregulated, when logFC≤-1. DEGs between the groups were represented using ComplexHeatmap package (25).

3.6 Gene Ontology and pathway enrichment analysis

Gene Ontology (GO) resource is one of the most comprehensive and widely used database with the functions of thousands of genes (26). GO group genes related to the same function in processes and classified them in: biological process (BP), cell components (CC), and molecular function (MF). In this study, we performed the GO enrichment analysis to verify the relationships among the DEGs using the packages Cluster Profiler (27) and GOplot (28). Only the process with a minimum of 5 genes and p<0.05 were considered enriched. Of note, in our analysis, the logFC and FDR values for each DEG were used to define if the gene was down- or upregulated.

3.7 Protein-protein interaction network analysis

The Search Tool for the Retrieval of Interacting Genes (STRING) is a database used to predict protein-protein interactions (PPI) (29). We queried the STRING database with the DEGs names, logFC, and FDR values to build a protein-protein interaction network, which was analyzed in the Cytoscape (30).

3.8 Survival analysis

Overall survival rates were calculated using Kaplan-Meier method and the comparison of the survival curves was performed using log-rank test. Data analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) Version 20 (Chicago, IL, USA). P-values below 0.05 were considered statistically significant.

3.9 Drug-gene interaction analysis

To determine which drugs might be potentially effective against the DEGs identified between the ADRB2^{low}/SLC6A2^{low} and ADRB2^{high}/SLC6A2^{high} groups, the Drugs Gene Interaction Database (DGIdb) (31) was consulted. The DGIdb compiles information of other four databases: 1) DrugBank; 2) Therapeutic target database (TTD); 3) PharmGKB; and, 4) ClinicalTrial.gov. Using DGIdb in September 2020, we evaluated pharmacological data of components potentially effective towards our collection of DEGs. Only anti-neoplastic and immunotherapeutic drugs that were Food and Drugs Administration (FDA)-approved were analyzed.

Results

4 RESULTS

4.1 Beta-adrenergic pathway activation in HNSCC is mediated by ADRB2 and SLC6A2

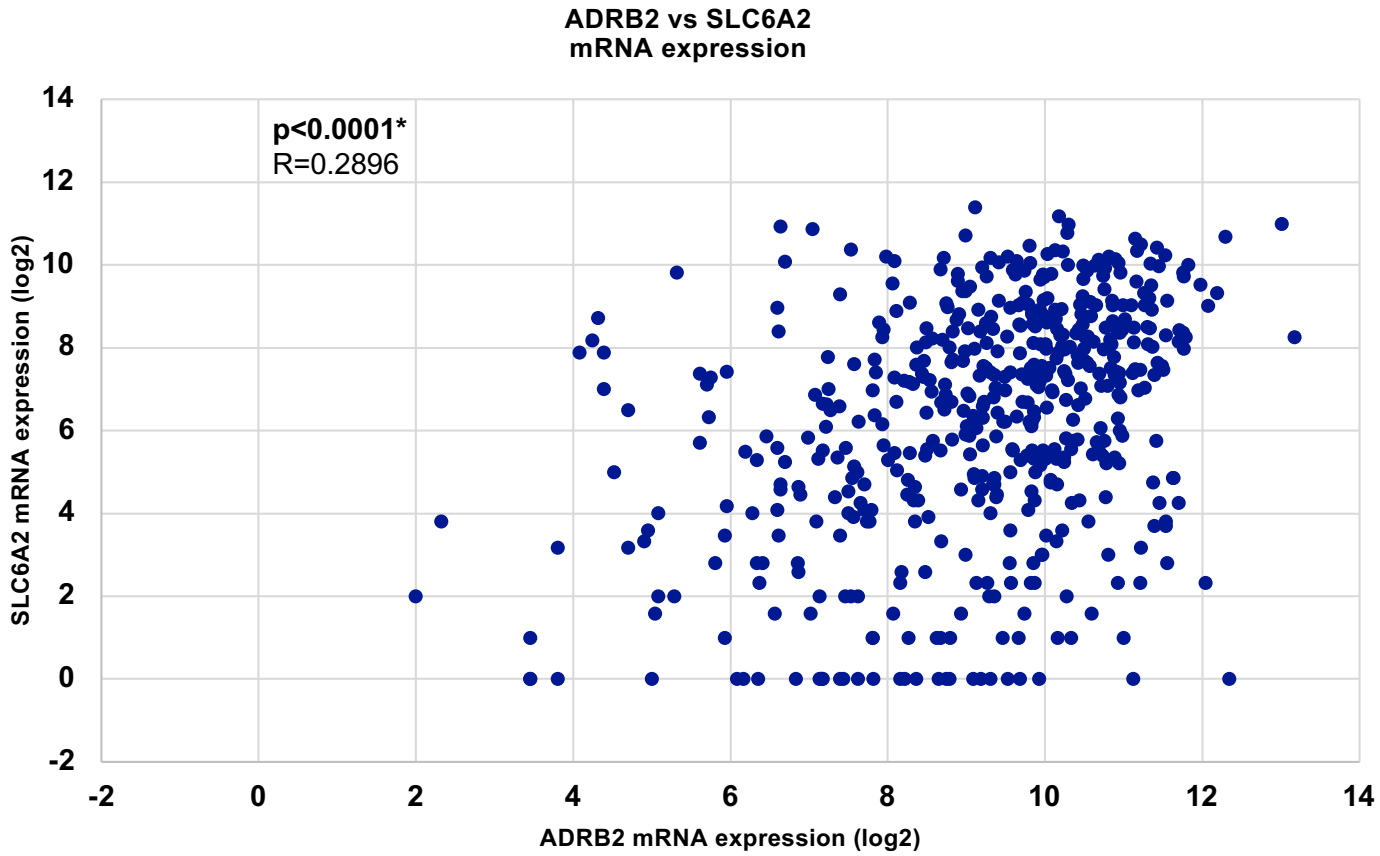
The first step to study the role of the beta-adrenergic pathway in HNSCC was to define the key genes that were representative of its activation. We have selected the genes that encode the beta-adrenergic receptors – namely ADRB1, ADRB2, and ADRB3 - which bind to NE and E. In addition, we included in the analysis the gene SLC6A2, that encodes the NET protein. NET is responsible for the reuptake of extracellular NE into the cell in neuronal tissues. Curiously, NET expression has also been observed in some types of cancer (32,33). After determining the global gene expression of all 520 HNSCCs and filtering those genes with low signal across the samples, it was obtained a final number of 14,899 RNAs that were expressed in HNSCC. ADRB1 and ADRB3 did not pass the filter and were excluded from the analysis. On the other hand, ADRB2 and SLC6A2 exhibited expression in HNSCC and were used as a readout for the activation of the beta-adrenergic pathway in this study.

To further confirm if ADRB2 and SLC6A2 were simultaneously expressed in HNSCC, Spearman's rank correlation coefficient was calculated. Notably, the expression of ADRB2 was positively correlated with the expression of SLC6A2 ($p<0.0001$, $R=0.2896$, Figure 1A).

As the overexpression of some genes in cancer can be driven by their mutation, we also searched for genomic alterations in ADBR2 and SLC6A2 in HNSCCs. Figure 1B shows that only 0.2% and 2.4% of the 520 HNSCC patients presented at least one type of mutation in ADRB2 and SLC6A2, respectively. These data confirm that the activation of the adrenergic pathway was mediated by the overexpression of the ADRB2 and SLC6A2 genes rather than by any type of mutation.

Next, we classified the HNSCCs into two categories based on the average value of ADRB2 (882.03) and SLC6A2 (235.99) expressions: ADRB2 / $SLC6A2^{low}$ and $ADRB2^{high}$ / $SLC6A2^{high}$. Tumors with high expression of ADRB2 and low expression of SLC6A2 or *vice-versa* were excluded. After the application of the exclusion criteria, the total sample included 343 patients: 256 (74.6%) with $ADRB2^{low}$ / $SLC6A2^{low}$ expression and 87 (25.4%) patients with $ADRB2^{high}$ / $SLC6A2^{high}$ expression.

A



B

Figure 1. ADRB2 and SLC6A2 status in 520 head and neck squamous cell carcinomas (HNSCC). A) Correlation of RNA expression of ADRB2 and SLC6A in HNSCC. Spearman's rank correlation coefficient. B) Lollipop plot showing mutations of ADRB2 and SLC6A2 in HNSCC (www.cbioportal.org).

4.2 ADRB2 and SLC6A2 expression is associated with histologic grade, perineural invasion, and HPV p16 status in HNSCC

The clinicopathological features of the HNSCCs included in this study are shown in Table 1. The great majority of HNSCC patients were male (p=0.257) and older than 55 years-old. The group $ADRB2^{high}$ / $SLC6A2^{high}$ presented higher number of young individuals than the group $ADRB2^{low}$ / $SLC6A2^{low}$ (14.94% vs 4.69%, p=0.006). Regarding the race, most patients were white in both groups. There were more Asian individuals in the $ADRB2^{high}$ / $SLC6A2^{high}$ group (p=0.024). The most frequent tumor site was the larynx (30.8%) in the $ADRB2^{low}$ / $SLC6A2^{low}$ group and the oral tongue (39.08%) in the $ADRB2^{high}$ / $SLC6A2^{high}$ group (p=0.001).

In both groups, moderately differentiated (G2) HNSCCs were more frequent. However, when it came to less differentiated states, $ADRB2^{low}$ / $SLC6A2^{low}$ group exhibited higher number of tumors graded as G3 and G4 (p=0.020). Tumors of the $ADRB2^{low}$ / $SLC6A2^{low}$ group also presented less perineural invasion (40%) than tumors of the $ADRB2^{high}$ / $SLC6A2^{high}$ group (57.14%, p=0.026). Almost all cases in the group $ADRB2^{high}$ / $SLC6A2^{high}$ were negative for HPV p16 expression (93.33%), contrasting with the 35.48% of positive cases in the $ADRB2^{low}$ / $SLC6A2^{low}$ group (p=0.031). There was no difference between the groups regarding gender, tobacco and alcohol consumption, T, N, and M clinical, tumor stage, and lymphovascular invasion (p>0.05).

Table 1. Clinicopathological characteristics of ADRB2^{low} / SLC6A2^{low} and ADRB2^{high} / SLC6A2^{high} head and neck squamous cell carcinomas.

Variables	Head and neck squamous cell carcinoma				p
	ADRB2^{low} / SLC6A2^{low}		ADRB2^{high} / SLC6A2^{high}		
	N	Percentage (%)	N	Percentage (%)	
Gender					
Male	194	75.78	60	68.97	0.257
Female	62	24.22	27	31.03	
Age					
<45	12	4.69	13	14.94	
46-55	58	22.66	20	22.99	**0.006**
>55	186	72.66	54	62.07	
Ethnic group*					
White	222	89.16	69	81.18	
Black	25	10.04	11	12.94	**0.024**
Asian	1	0.40	4	4.70	
Indian or Alaska native	1	0.40	1	1.18	
Tumor site					
Alveolar ridge	5	1.95	4	4.60	
Base of tongue	18	7.03	1	1.15	
Buccal Mucosa	11	4.30	4	4.60	
Floor of mouth	33	12.90	10	11.49	
Hard palate	3	1.17	1	1.15	
Hypopharynx	5	1.95	1	1.15	**0.0001**
Larynx	77	30.08	13	14.94	
Lip	3	1.17	0	0	
Oral cavity	30	11.72	15	17.24	
Oral tongue	42	16.40	34	39.08	
Oropharynx	6	2.34	2	2.30	
Tonsil	23	8.99	2	2.30	
Tobacco consumption*					
Smoker	144	56.25	48	55.17	0.901
Not reported	112	43.75	39	44.83	
Alcohol consumption*					
No	81	32.53	35	40.70	0.189
Yes	168	67.47	51	59.30	
T clinical*					
T1	17	6.64	6	6.98	0.679
T2	72	28.12	24	27.91	
T3	64	25.00	26	30.23	

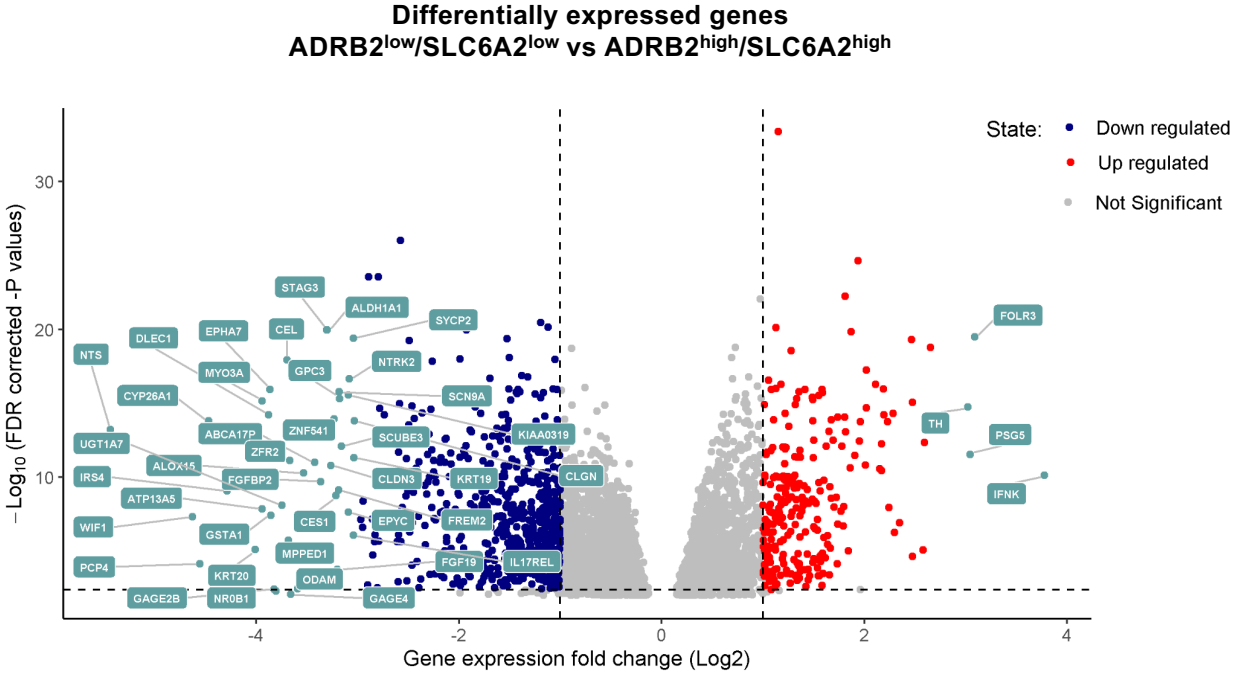
T4	93	36.33	29	33.72	
TX	10	3.91	1	1.16	
N clinical*					
N0	109	42.58	41	47.65	
N1	46	17.97	18	20.93	
N2	86	33.59	23	26.74	0.723
N3	6	2.34	1	1.16	
NX	9	3.52	3	3.49	
M clinical*					
M0	238	93.33	82	95.34	
M1	3	1.18	2	2.33	0.371
MX	14	5.49	2	2.33	
Tumor stage*					
I	8	3.23	3	3.53	
II	43	17.34	17	20.00	0.872
III	50	20.16	19	22.35	
IV	147	59.27	46	54.12	
Histologic grade*					
G1	26	10.24	13	14.94	
G2	136	53.54	59	67.82	
G3	75	29.53	13	14.94	**0.020**
G4	6	2.36	0	0	
GX	11	4.33	2	2.30	
Lymphovascular invasion*					
No	97	59.15	40	65.57	0.443
Yes	67	40.85	21	34.43	
Perineural invasion*					
No	102	60.00	27	42.86	**0.026**
Yes	68	40.00	36	57.14	
HPV p16 status*					
Negative	40	64.52	14	93.33	**0.031**
Positive	22	35.48	1	6.67	
TOTAL	**256**	**100**	**87**	**100**	

*Patients with unknown information excluded. Fisher test used for gender, Tobacco consumption, Alcohol consumption, Lymphovascular invasion, Perineural invasion, HPV p16 status. Chi-square test used for Age, Ethnic group, Tumor site, T, N, M clinical, Tumor stage, Histologic grade. $P<0.05$ was considered statistically significant.

4.3 Overview of DEGs in ADRB2^{low} / SLC6A2^{low} vs ADRB2^{high} / SLC6A2^{high} HNSCC

To understand better the molecular mechanisms regulated by the activation of the beta-adrenergic pathway in HNSCC, we performed the differentially expression analysis. A total of 898 DEGs were identified between ADRB2^{low} / SLC6A2^{low} and ADRB2^{high} / SLC6A2^{high} groups based on RNA-Seq data: 258 upregulated and 640 downregulated DEGs (Figure 2A and Supplementary File 1). The heatmap in Figure 2B shows the top 50 downregulated and top 50 upregulated DEGs between the groups ADRB2^{low} / SLC6A2^{low} and ADRB2^{high} / SLC6A2^{high}.

A



B

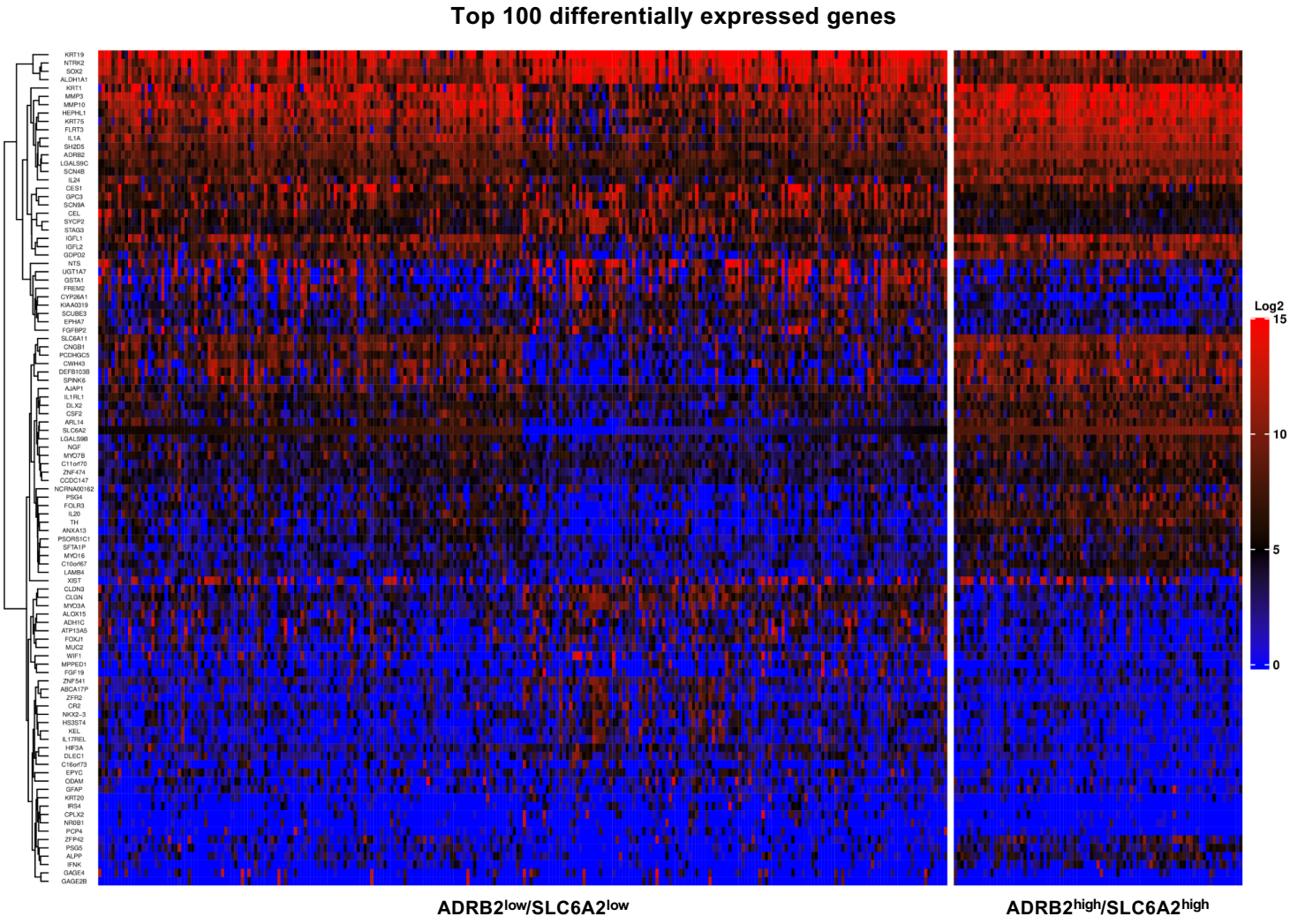


Figure 2. Differentially expressed genes (DEGs) based on ADRB2 and SLC6A2 expression in head and neck squamous cell carcinomas (HNSCC). A) Representation of the 898 DEGs between ADRB2low / SLC6A2low group versus ADRB2high / SLC6A2high group. Genes in green had logFC≥3. B) Heatmap showing the top 100 DEGs (50 upregulated and 50 downregulated) between ADRB2low / SLC6A2low group versus ADRB2high / SLC6A2high group. Complete data in Supplementary file 1.

4.4 GO analysis links ADRB2^{high} / SLC6A2^{high} HNSCC to angiogenesis, cell proliferation, and ECM plasticity

To assess how the DEGs were related and to identify potential mechanisms that might distinguish the ADRB2^{low} / SLC6A2^{low} HNSCC from ADRB2^{high} / SLC6A2^{high} HNSCC, we performed the over-representation enrichment analysis using the GO database. We divided the DEGs between the groups ADRB2^{low} / SLC6A2^{low} and ADRB2^{high} / SLC6A2^{high} in upregulated and downregulated genes according to their logFC values. The GO analysis revealed that there were 768 downregulated (Figure 3A) and 528 upregulated processes in the ADRB2^{high} / SLC6A2^{high} group (Figure 3B). The downregulated processes were divided in 671 biological processes, 18 cell components, and 78 molecular functions. Among the upregulated processes, 410 were biological processes, 37 cell components, and 80 molecular functions (Supplementary File 2).

The enrichment maps of the top 30 biological processes (Figure 3C-D) show that the ADRB2^{high} / SLC6A2^{high} presented multiple processes related to the tumoral progression that were upregulated: keratinocyte differentiation, extracellular matrix (ECM) metabolism, and cell adhesion. On the other hand, processes associated with the development of different types of tissue, and cellular metabolism were downregulated in the ADRB2^{high} / SLC6A2^{high} group.

Next, the processes closely related to the tumor progression were manually curated and grouped according to their main role. These grouped biological processes accompanied by their involved genes are represented in Figure 4. One can observe that processes associated with angiogenesis, proliferation, and microenvironment are upregulated in ADRB2^{high} / SLC6A2^{high} tumors.

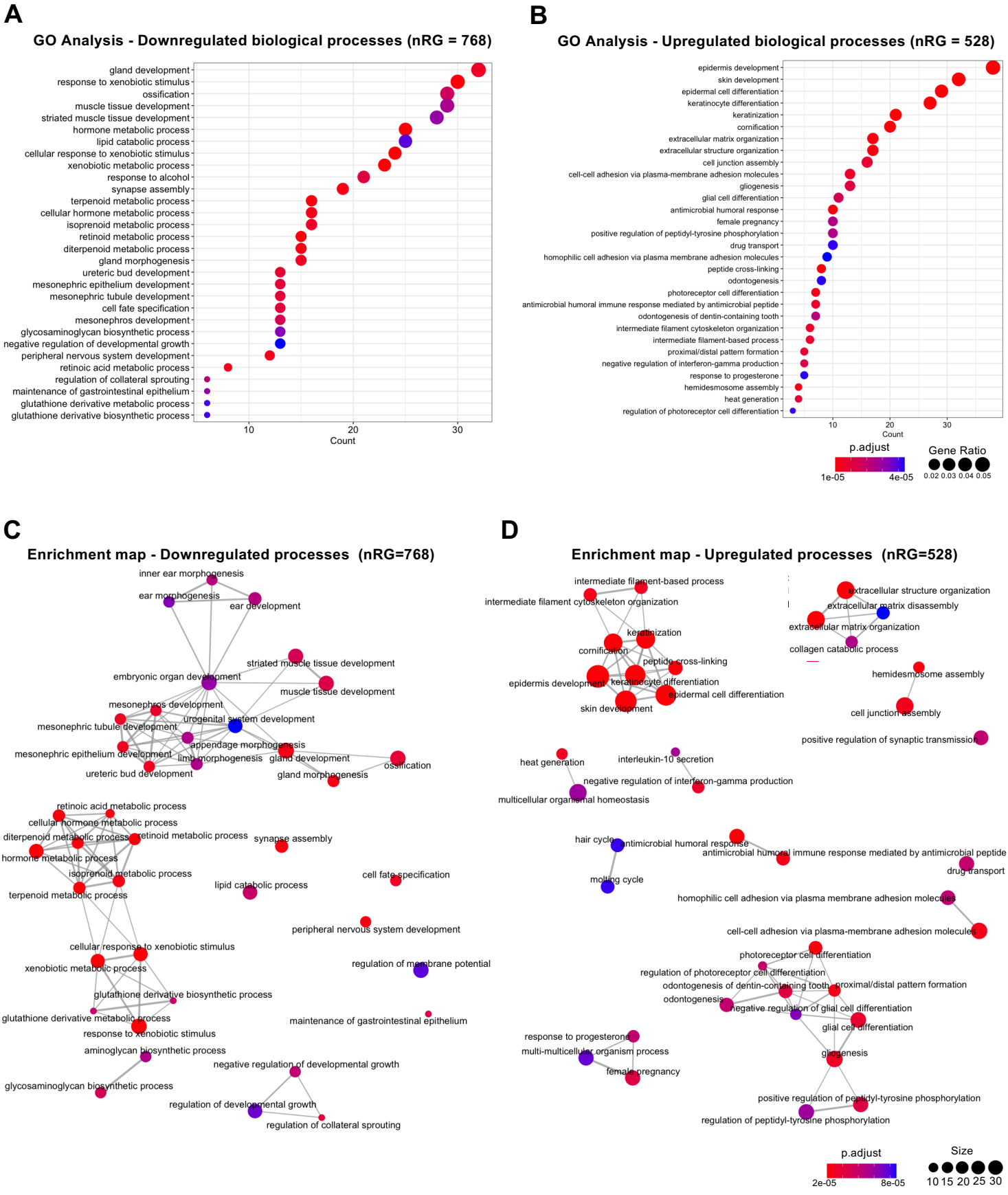
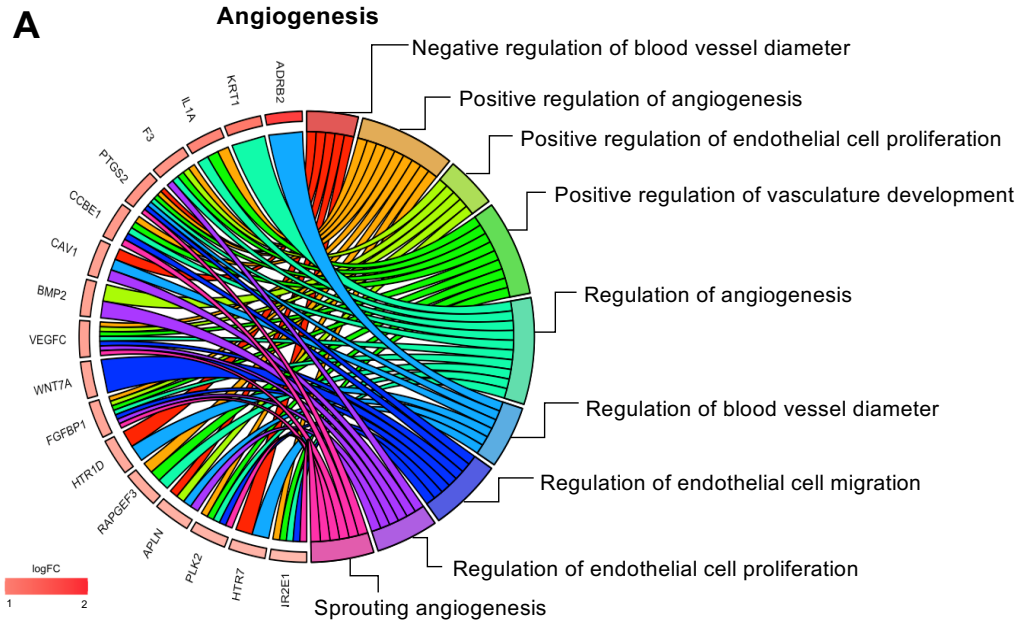
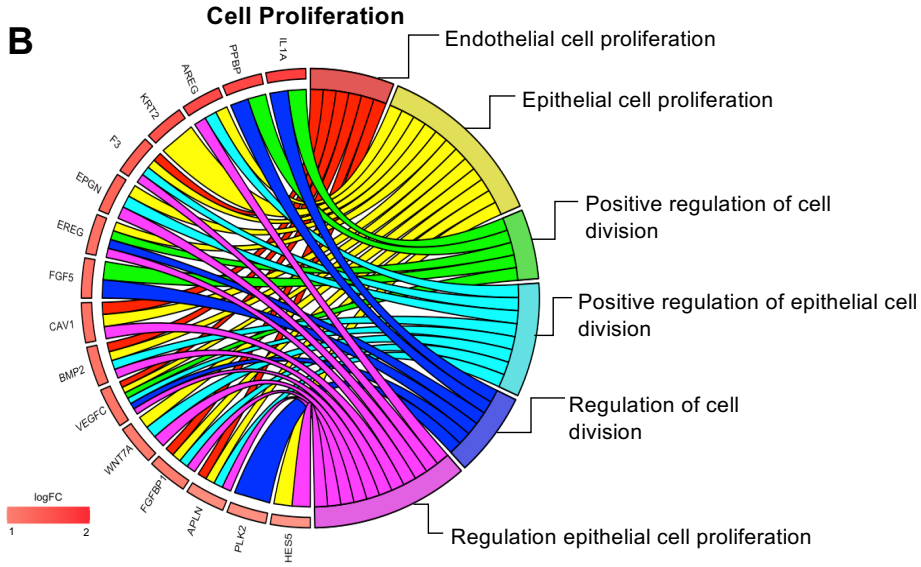


Figure 3. GO and pathway enrichment analysis of DEGs in HNSCCs. A) Downregulated and B) Upregulated biological processes identified in ADRB2high / SLC6A2high group. The interaction network of the pathways DEGs. C-D) Enrichment maps showing the interactions among the processes from A and B. Complete data in Supplementary file 2.





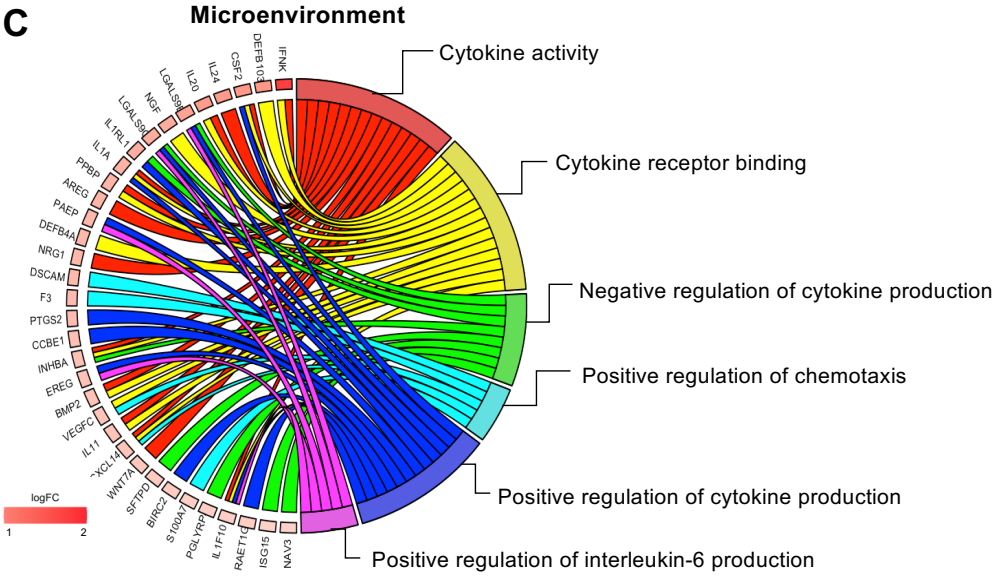


Figure 4. Upregulated processes in ADRB2high / SLC6A2high HNSCC. DEGs and their relationship with the biological processes within the A) angiogenesis, B) cell proliferation, and C) microenvironment classifications. The biological processes identified in the GO analysis were group according to their major role in HNSCC.

4.5 PPI network analysis in ADRB2^{high} / SLC6A2^{high} vs ADRB2^{low} / SLC6A2^{low} HNSCC

PPI network is a widely used tool to map predicted physical and functional interactions among proteins in a large scale. In this study, the STRING was chosen once this is the most comprehensive and up-to-date PPI database. To visualize the interactions among the DEGs, we firstly constructed the PPI network inputting all DEGs names, logFC values, and FDR. The resulting network included 868 nodes and 3,060 edges. Each node in the network represented one protein. The edges represented the relationships between the proteins. Because the network was too large to obtain additional important information, we manually curated the most altered DEGs and/or DEGs that are related to known tumoral processes. Starting from one node, the first neighbors were selected successively and clean networks were generated. The network of the Figure 5A includes the proteins that were most closely related to ADRB2 and SLC6A2 and contains 146 nodes and 701 edges. In the Figure 5B, the findings of this study are confirmed: proteins that regulate the tumor invasion and spread in HNSCC are shown to be overexpressed. Upregulation of MMP-1, 3, 10, and 13, and CSF2 and downregulation of VCAM1 and ICAM4 are implicated in the cancer cells migration and stromal invasion. Additionally, the overexpression of VEGF-C, and NGF and underexpression of LEF1 are indicatives of the local influence of the beta-adrenergic pathway activation on the vascular and nervous tissues.

Interestingly, proteins related to cancer cell stemness, namely SOX2, ALDH1A1, and EYA1 were underexpressed (Figure 5C) in ADRB2^{high} / SLC6A2^{high} group. To further assess if ADRB2^{high} / SLC6A2^{high} group was associated to a lower degree of stemness, we calculated the stemness score (23) of both groups. Indeed, we found higher stemness index in ADRB2^{low} / SLC6A2^{low} HNSCCs than in ADRB2^{high} / SLC6A2^{high} HNSCCs ($p=0.0417$, Figure 5D).

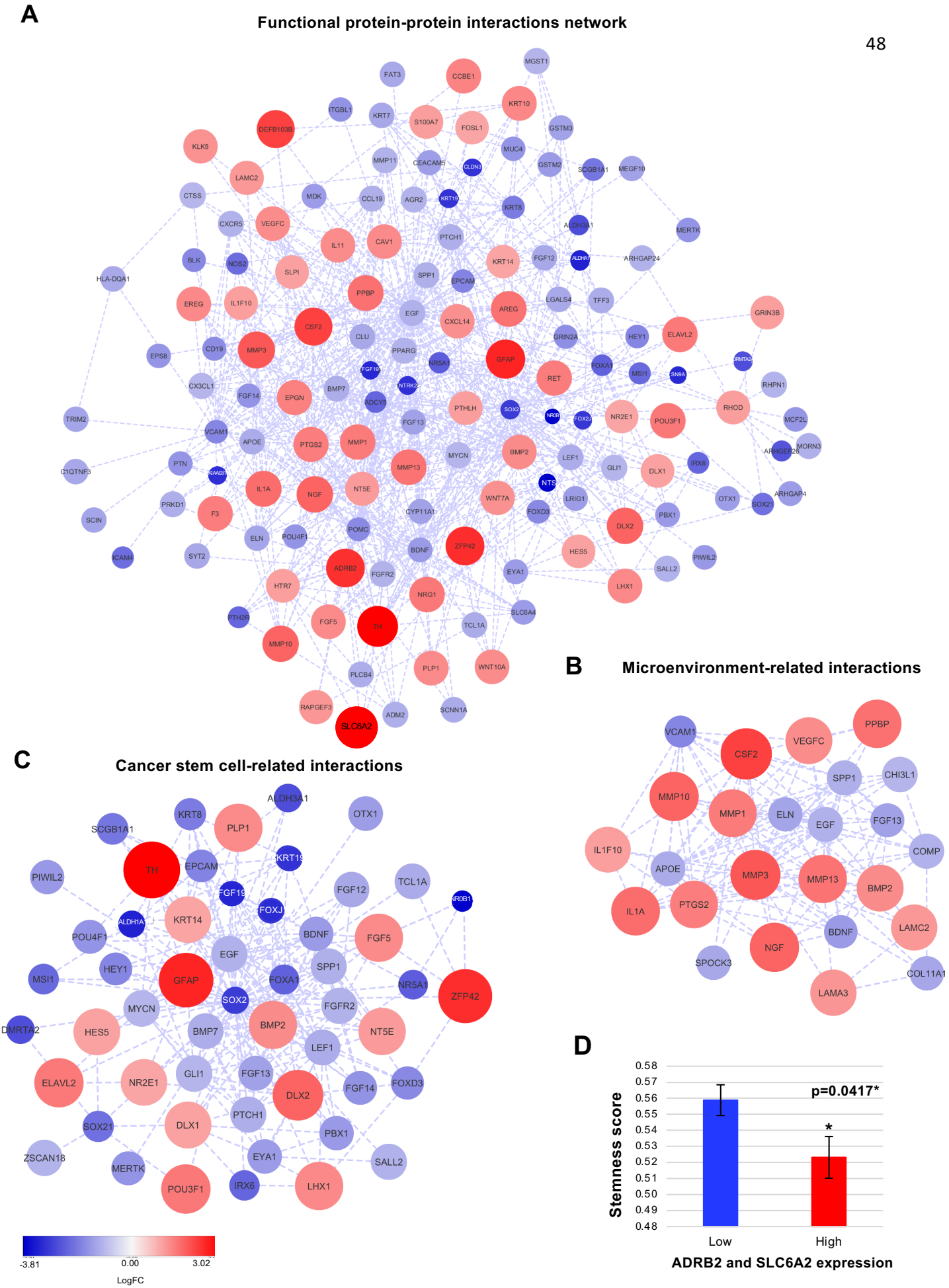


Figure 5. Protein-protein interaction (PPI) network of the DEGs in HNSCC. A) Functional protein interactions network; B) Microenvironment-related interactions in ADRB2high / SLC6A2high group; C) Cancer stem cell-related interactions; D) Average stemness score of ADRB2^{high} / SLC6A2^{high} compared with ADRB2^{low} / SLC6A2^{low} group. Student's t test: *P<0.05.

4.6 ADRB2^{high} / SLC6A2^{high} predicts worst prognosis of patients with pharyngeal and laryngeal squamous cell carcinoma

Clinical follow-up of the 343 patients with HNSCC ranged from 0 to 6417 days. Survival analysis indicated that the beta-adrenergic pathway activation did not influence the prognosis of the patients with HNSCCs (p=0.173, Figure 6A). When the tumors were analyzed according to their anatomic location, patients with larynx and pharynx squamous cell carcinomas presenting ADRB2^{high} / SLC6A2^{high} expression had lower survival rates than patients with HNSCC presenting ADRB2^{low} / SLC6A2^{low} expression (p=0.039, Figure 6C). Beta-adrenergic pathway was not a prognostic predictor factor for oral cavity HNSCCs (p=0.839, Figure 6B).

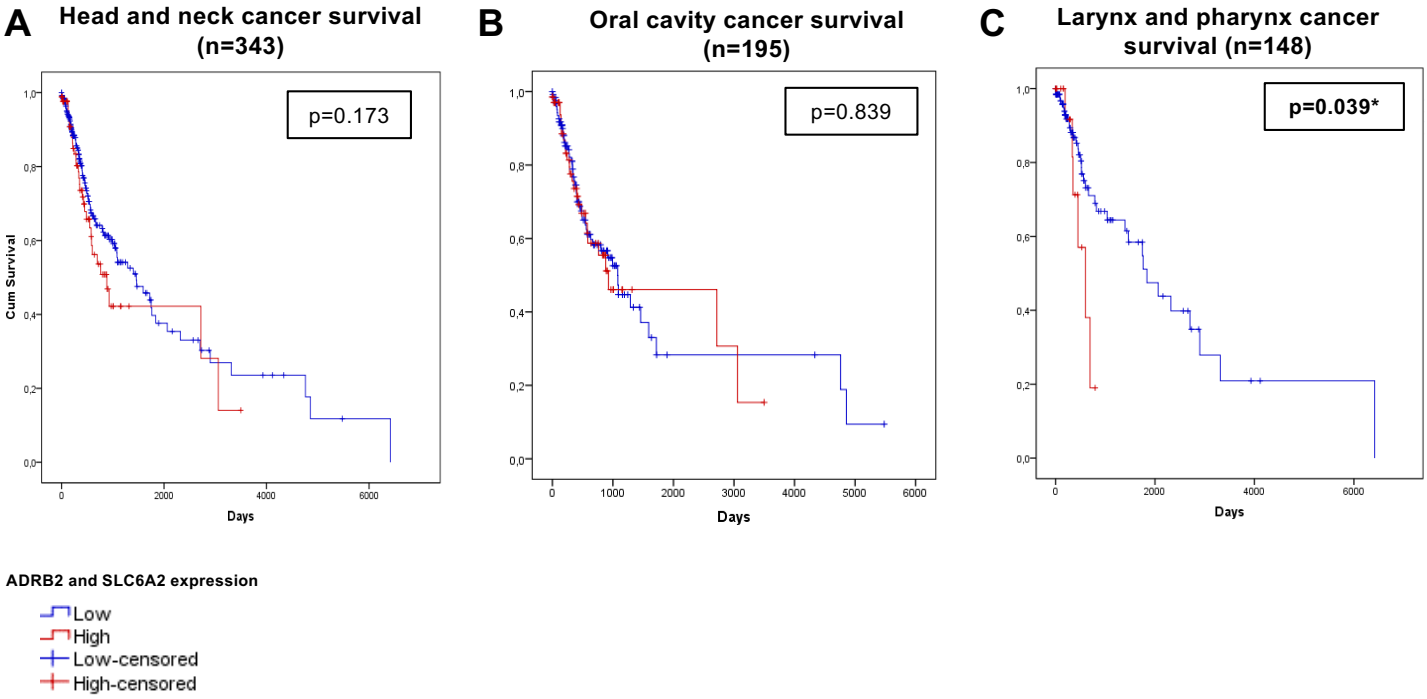


Figure 6. Overall survival analysis of the patients with HNSCC according to the ADRB2 and SLC6A2 expressions. A) Overall survival of all patients with HNSCC; B) Overall of patients with oral cavity SCC; C) Overall of patients with larynx and pharynx SCC. Survival curves were plotted by Kaplan- Meier method and the comparison of the survival rates was performed using log-rank test: *P<0.05.

4.7 Drug-gene interaction analysis reveals potential therapeutic options for HNSCC

The DEGs were inserted into the DGIdb database to explore the potential therapeutic options available for these genes. It was identified 56 FDA-approved antineoplastic and immunotherapeutic drugs that had 113 genes as targets (Supplementary file 3). In the Figure 7, drugs targeting two or more genes are displayed.

Among the listed drugs, docetaxel, fluorouracil, gemcitabine, and mitomycin are already used or in advanced phases of clinical trials for HNSCC therapy. Additionally, anakira, azacytidine, paclitaxel, sunitinib, and trichostatin are currently in pre-clinical or early clinical phases in studies of HNSCC therapy. Cyclophosphamide, lenalidomide, thalidomide, vinblastine, and vincristine have shown unsatisfactory results in HNSCC treatment in previous studies. Dactinomycin, mercaptopurine, mycophenolic acid, prednisone, procarbazine, streptozotocin, thiotepa, and tretinoin have not yet been tested as HNSCC therapy.

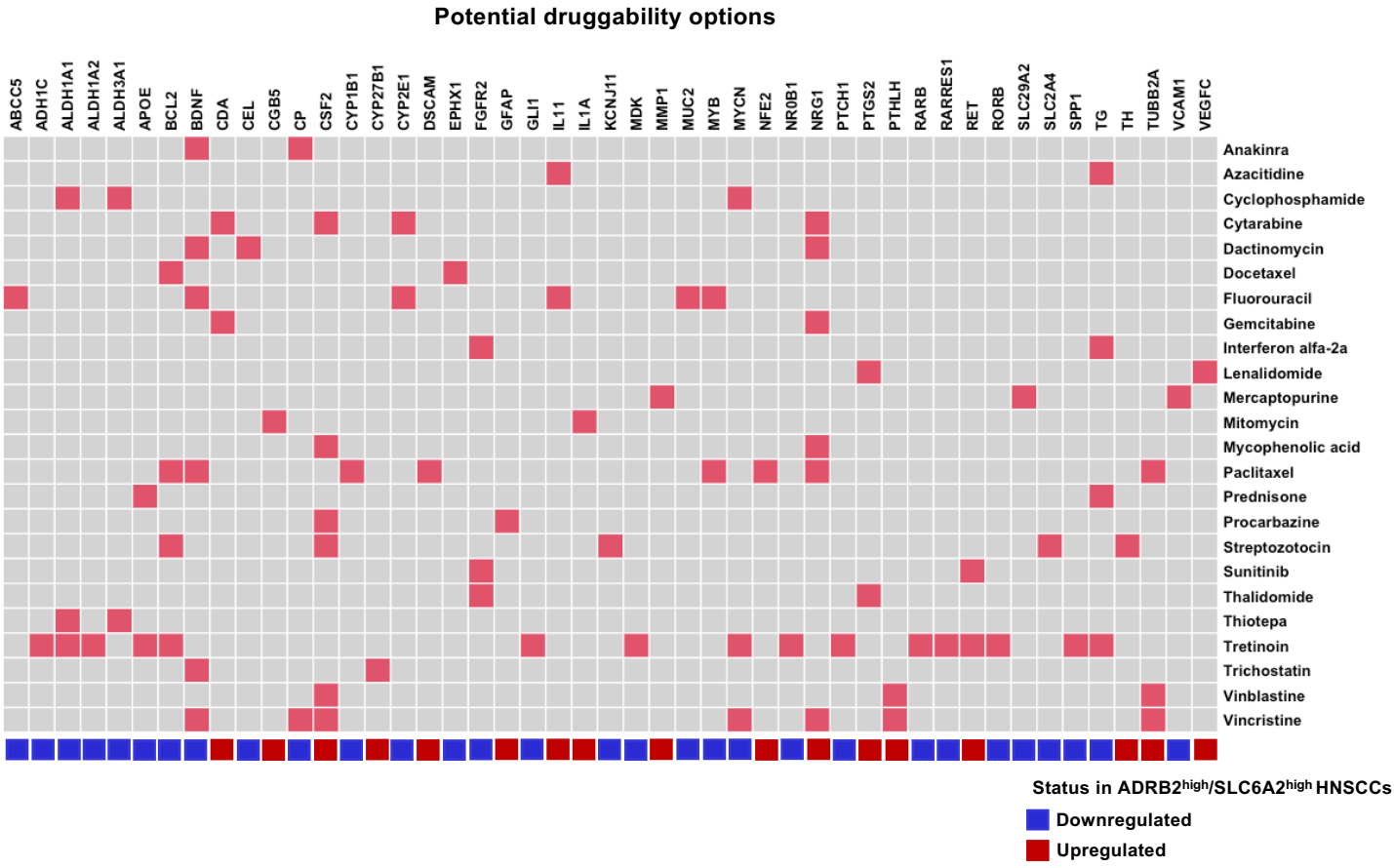


Figure 7. Drug-gene interaction analysis and potential therapeutics for HNSCC. Heatmap showing the top drugs and target-DEGs in HNSCC. Complete data in Supplementary file 3.

Discussion

4 DISCUSSION

Defining the role of chronic stress in HNSCC progression and outcome has been proven a challenging task. This might be explained by the heterogeneity among HNSCC from different anatomic sites and also by the complexity within the tumor bulk (34). In an attempt to overcome this last limitation, we performed an integrated analysis of the clinical and molecular aspects of 520 HNSCC patients based on the beta-adrenergic pathway activation. Applying machine-learning methods, we identified, for the first time, 898 DEGs between the $ADRB2^{low}$ / $SLC6A2^{low}$ and $ADRB2^{high}$ / $SLC6A2^{high}$ groups. By exploring these DEGs, several pathways related to cancer progression were shown to be altered and, ultimately, some DEGs were identified as potential targets for the personalized treatment of HNSCC. Furthermore, adrenergic pathway activation was shown to be a prognosis factor for HNSCC.

Here we identified a group of alterations in the microenvironment of $ADRB2^{high}$ / $SLC6A2^{high}$ HNSCCs that are pivotal to the tumoral progression. Beta-adrenergic signaling significantly led to the enhancement of metalloproteinases (MMP1, MMP3, MMP10, and MMP13) and laminins (LAMC2 and LAMA3) expression, corroborating others' findings (14). These molecules are directly implicated in the extracellular matrix (ECM) remodeling, facilitating tumor cell invasion, and contributing to the metastasis (35,36). Furthermore, we have observed decreased expression of cell adhesion molecules (EPCAM, VCAM1, and ICAM4), what might potentiate the motility of cells of the tumoral microenvironment.

Besides dysregulating the ECM components, the activation of the beta-adrenergic pathway was shown to significantly stimulate the angiogenesis by the overexpression of VEGFC, as shown previously (14). Additionally, $ADRB2^{high}$ / $SLC6A2^{high}$ HNSCCs presented higher expression of NGF, implicated in cancer cells dissemination and perineural invasion in HNSCC (37). Indeed, our clinicopathological findings confirmed the molecular data: more patients with beta-adrenergic pathway overactivation displayed perineural invasion than patients with $ADRB2^{low}$ / $SLC6A2^{low}$ expression ($p=0.026$, Table 1).

Inflammation has been shown to exert a dual role in HNSCC, and the activation of the beta-adrenergic receptors upregulated the expression of genes involved in inflammation (14,38). In this study, we also found higher expression of pro-

inflammatory genes (PTGS2/COX2 and IL1A), suggesting the close relationship between the beta-adrenergic pathway and inflammation. Notably, PTGS2 expression has been associated with poorer prognosis, and resistance to cisplatin in gastric cancer (39) and was significantly upregulated in ADRB2^{high} / SLC6A2^{high} HNSCCs.

Another notable facet of the activation of the beta-adrenergic pathway in HNSCC was that patients with ADRB2^{high} / SLC6A2^{high} expression presented underexpression of genes related to cancer cell stemness (SOX2, ALDH1A1, and EYA1) and lower stemness score. Accordingly, cancer stem cells are typically enriched in hypoxic environments and the expression of HIF3A, a marker of hypoxia, was also low in ADRB2^{high} / SLC6A2^{high} tumors. Interestingly, our pathological findings demonstrated that less patients of the ADRB2^{high} / SLC6A2^{high} group presented tumor graded as G3 or G4 (ADRB2^{low} / SLC6A2^{low}: 31.89% vs ADRB2^{high} / SLC6A2^{high}:14.94%, p=0.020, Table 1). These findings may seem contradictory to our data above, however the stemness is best defined as transitory rather permanent state (40). Thus, those tumors in frankly expansion might exhibit a different phenotype of those tumors in a dormant state. In this context, the plasticity of the cancer cells is essential to the success of the tumoral bulk to invade locally, metastasize, and be resistant to the therapy.

Finally, our results showed that the beta-adrenergic pathway activation did not influence the prognosis of HNSCC. However, when the lesions were split according to their anatomic location, patients with tumors arising in the larynx and pharynx that presented ADRB2^{high} / SLC6A2^{high} expression had lower survival rates than patients with ADRB2^{low} / SLC6A2^{low} HNSCCs. Curiously, the patients with ADRB2^{low} / SLC6A2^{low} expression showed greater number of patients with HPV p16 positive (35.48% vs 6.67%, p=0.031). One can hypothesize that the HPV status may have a relationship with the beta-adrenergic pathway activation but this issue needs to be further addressed.

As the concomitant high expression of ADRB2 and SLC6A2 was a prognostic factor for larynx and pharynx squamous cell carcinomas ($p = 0.039$), we identified some drugs that may be an interesting option to the management of these tumors. Interestingly, some drugs that are already used in the management of HNSCC (docetaxel, fluorouracil, and gemcitabine) came up as an option. This can explain the

high frequency of resistant tumors to these therapies: maybe the tumor heterogeneity among the patients may incite the drug resistance in some individuals and the successful treatment in others. Furthermore, we also identified other drugs that are currently under investigation and underscore that the results of these clinical trials should be analyzed carefully in the light of the personalized medicine: we may be missing drugs that would work properly in one patient but not in another.

This study has some limitations, as follows: 1) The lack of clinical information about the mental status of the patients. This study used the activation of the beta-adrenergic pathway as a read-out of for the chronic stress however, one cannot confirm if the patients were, indeed, with clinical chronic stress; 2) This study analyzed HNSCCs of different anatomic regions collectively. This may have masked individual features of the tumors as the behavior of HNSCC varies according to the where it arises. Thus, as future perspectives, we suggest a clinical study with information on the level of stress (psychological tests), and hormone dosage (plasma and/or saliva). Additionally, validation of our data in different databases may be interesting to verify if the DEGs identified in this study might be used as a molecular signature of a more aggressive HNSCC subtype.

In conclusion, this was the first study to provide a comprehensive panorama of the beta-adrenergic pathway activation repercussion in HNSCC. We have shown that beta-adrenergic pathway overexpression presents intimate relationship with the tumoral proliferation, invasion, migration, and angiogenesis. Finally, concomitant high expression of ADRB2 and SLC6A2 was a prognostic factor for larynx and pharynx squamous cell carcinomas.

ACKNOWLEDGMENTS

None to declare.

AUTHOR CONTRIBUTION

G.L.S Methodology, Data curation, Formal analysis, Investigation, and Writing the original draft. D.G.B Visualization, and Review and editing. G.I.M Visualization, and Review and editing. K.C.T Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Project administration, and Review and editing.

References

REFERENCES

1. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. *Am J Hypertens* 2015;**28**:1295-302.

2. Liu MY, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. *Neurol Res* 2017;**39**:573-80.

3. Labanski A, Langhorst J, Engler H, Elsenbruch S. Stress and the brain-gut axis in functional and chronic-inflammatory gastrointestinal diseases: a transdisciplinary challenge. *Psychoneuroendocrinology* 2020;**111**:104501.

4. Zhang X, Zhang Y, He Z, Yin K, Li B, Zhang L, *et al*. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. *Cell Death Dis* 2019;**10**:788.

5. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res* 2012;**18**:1201-6.

6. Takahashi K, Kaira K, Shimizu A, Sato T, Takahashi N, Ogawa H, et al. Clinical significance of β2-adrenergic receptor expression in patients with surgically resected gastric adenocarcinoma. *Tumor Biol* 2016;**37**:13885–92.

7. Ogawa H, Kaira K, Motegi Y, Yokobori T, Takada T, Kato R, *et al.* Prognostic significance of β2-adrenergic receptor expression in patients with surgically resected colorectal cancer. *Int J Clin Oncol* 2020;**25**:1137-44.

8. Zhang ZF, Feng XS, Chen H, Duan ZJ, Wang LX, Yang D, *et al.* Prognostic significance of synergistic hexokinase-2 and beta2-adrenergic receptor expression in human hepatocelluar carcinoma after curative resection. *BMC Gastroenterol* 2016;**16**:57.

9. Yang E V, Eubank TD. The impact of adrenergic signaling in skin cancer progression: possible repurposing of β-blockers for treatment of skin cancer. *Cancer Biomark* 2013;**13**:155-60.

10. Kim-Fuchs C, Le CP, Pimentel MA, Shackleford D, Ferrari D, Angst E, *et al.* Chronic stress accelerates pancreatic cancer growth and invasion: a critical

role for beta-adrenergic signaling in the pancreatic microenvironment. *Brain Behav Immun*. 2014;**40**:40-7.

11. He JJ, Zhang WH, Liu SL, Chen YF, Liao CX, Shen QQ, *et al*. Activation of β-adrenergic receptor promotes cellular proliferation in human glioblastoma. *Oncol Lett* 2017;**14**:3846–52.

12. Krizanova O, Babula P, Pacak K. Stress, catecholaminergic system and cancer. *Stress* 2016;**19**:419-28.

13. Zhao Y, Li W. Beta-adrenergic signaling on neuroendocrine differentiation, angiogenesis, and metastasis in prostate cancer progression. *Asian J Androl* 2019;**21**:253-9.

14. Bernabé DG, Tamae AC, Biasoli ÉR, Oliveira SH. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. *Brain Behav Immun* 2011;**25**:574-83.

15. Liu H, Wang C, Xie N, Zhuang Z, Liu X, Hou J, *et al*. Activation of adrenergic receptor β2 promotes tumor progression and epithelial mesenchymal transition in tongue squamous cell carcinoma. *Int J Mol Med* 2018;**41**:147–54.

16. Bravo-Calderón DM, Assao A, Garcia NG, Coutinho-Camillo CM, Roffé M, Germano JN, *et al.* Beta adrenergic receptor activation inhibits oral cancer migration and invasiveness. *Arch Oral Biol* 2020;**118**:104865.

17. Yamanaka Y, Mammoto T, Kirita T, Mukai M, Mashimo T, Sugimura M, *et al.* Epinephrine inhibits invasion of oral squamous carcinoma cells by modulating intracellular cAMP. *Cancer Lett* 2002;**176**:143–8.

18. Sakakitani S, Podyma-Inoue KA, Takayama R, Takahashi K, Ishigami-Yuasa M, Kagechika H, *et al*. Activation of β2-adrenergic receptor signals suppresses mesenchymal phenotypes of oral squamous cell carcinoma cells. *Cancer Sci*. 2020. doi: 10.1111/cas.14670

19. Dong H, Liao X-X, Mai H-M, Zhou N, Wang D-Y, Peng J-B, *et al*. Expression of beta adrenergic receptor in oral squamous cell carcinoma and its significance to the prognosis. International journal of clinical and experimental pathology. *Int J Clin Exp Pathol* 2017;**10**:10431–40.

20. Colaprico A, Silva TC, Olsen C, Garofano L, Cava C, Garolini D, *et al.* TCGAbiolinks: an R/Bioconductor package for integrative analysis of TCGA data. *Nucleic Acids Res* 2016;**44**:e71.

21. Risso D, Schwartz K, Sherlock G, Dudoit S. GC-Content Normalization for RNA-Seq Data. *BMC Bioinformatics* 2011;**12**:480.

22. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, *et al*. The cBio Cancer Genomics Portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012;**2**:401–4.

23. Malta TM, Sokolov A, Gentles AJ, Burzykowski T, Poisson L, Weinstein JN, *et al*. Machine learning identifies stemness features associated with oncogenic dedifferentiation. *Cell* 2018;**173**:338-54.e15.

24. Streby KA, Shah N, Ranalli MA, Kunkler A, Cripe TP. Nothing but NET: a review of norepinephrine transporter expression and efficacy of 131I-mIBG therapy. *Pediatr Blood Cancer* 2015;**62**:5-11.

25. Gu Z, Eils R, Schlesner M. Complex heatmaps reveal patterns and correlations in multidimensional genomic data. *Bioinformatics* 2016;**32**:2847–9.

26. The Gene Ontology Consortium. The Gene Ontology Resource: 20 years and still GOing strong. *Nucleic Acids Res*. 2019;**47**:D330-8.

27. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *OMICS* 2012;**16**:284-7.

28. Walter W, Sánchez-Cabo F, Ricote M. GOplot: an R package for visually combining expression data with functional analysis. *Bioinformatics* 2015;**31**:2912–4.

29. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, *et al.* STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res* 2019;**47**:D607-13.

30. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003;**13**:2498-504.

31. Cotto KC, Wagner AH, Feng YY, Kiwala S, Coffman AC, Spies G, *et al.* DGIdb 3.0: a redesign and expansion of the drug-gene interaction database. *Nucleic Acids Res* 2018;**46**:D1068-73.

32. Zhang H, Huang R, Cheung NKV, Guo H, Zanzonico PB, Thaler HT, *et al.* Imaging the norepinephrine transporter in neuroblastoma: a comparison of [18F]-MFBG and 123I-MIBG. *Clin Cancer Res*. 2014;**20**:2182-91.

33. Zhang H, Miao J, Li F, Xue W, Tang K, Zhao X, *et al.* Norepinephrine transporter promotes the invasion of human colon cancer cells. *Oncol Lett* 2020;**19**:824-32.

34. Leemans CR, Snijders PJF, Brakenhoff RH. The molecular landscape of head and neck cancer. *Nat Rev Cancer* 2018;**18**:269-82.

35. Gobin E, Bagwell K, Wagner J, Mysona D, Sandirasegarane S, Smith N, *et al.* A pan-cancer perspective of matrix metalloproteases (MMP) gene expression profile and their diagnostic/prognostic potential. *BMC Cancer* 2019;**19**:581.

36. Wang S, Liou G, Liu S, Chang JS, Hsiao J, Yen Y, *et a*l. Laminin γ2-enriched extracellular vesicles of oral squamous cell carcinoma cells enhance *in vitro* lymphangiogenesis *via* integrin α3-dependent uptake by lymphatic endothelial cells. *Int J Cancer* 2019;**144**:2795-810.

37. Lin C, Ren Z, Yang X, Yang R, Chen Y, Liu Z, *et al.* Nerve growth factor (NGF)-TrkA axis in head and neck squamous cell carcinoma triggers EMT and confers resistance to the EGFR inhibitor erlotinib. *Cancer Lett* 2020;**472**:81-96.

38. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 2005;**5**:243-51.

39. Lin X mian, Li S, Zhou C, Li R zhen, Wang H, Luo W, *et al.* Cisplatin induces chemoresistance through the PTGS2-mediated anti-apoptosis in gastric cancer. *Int J Biochem Cell Biol* 2019;**116**:105610.

40. Sánchez-Danés A, Blanpain C. Deciphering the cells of origin of squamous cell carcinomas. *Nat Rev Cancer* 2018;**18**:549-61.

Anexo

ANEXO A – Arquivos suplementares

Supplementary file 1. Key resources table used for methodology.

Supplementary file 2. DEGs based on ADRB2high / SLC6A2high expression and ADRB2low / SLC6A2low expression in head and neck squamous cell carcinomas

Supplementary file 3. Gene Ontology and pathway enrichment analysis of DEGs in head and neck squamous cell carcinomas

Supplementary file 4. Drug-gene interaction and potential therapeutics analysis for head and neck squamous cell carcinomas.

Supplementary file 1. Key resources table used for methodology.

REAGENT or RESOURCE Software and Algorithms	SOURCE	IDENTIFIER
Bioconductor 3.11	-	http://bioconductor.org/
cBioportal	Cerami *et al.,* 2012 (22)	http://cbioportal.org/
Cluster profile 3.16.1	Yu *et al.,* 2012 (26)	10.18129/B9.bioc.clusterProfiler
ComplexHeatmap 2.4.3	Gu, Eils and Schlesner, 2016 (25)	10.18129/B9.bioc.ComplexHeatmap
Cytoscape	Shannon *et al.,* 2003 (30)	https:// https://cytoscape.org/
DGIdb 3.0	Cotto *et al.,* 2018 (31)	https://www.dgidb.org/
EDASeq 2.22.0	Risso *et al.,* 2011 (21)	10.18129/B9.bioc.EDASeq
EdgeR 3.30.3	McCarthy, Chen, Symyth, 2012	10.18129/B9.bioc.edgeR
Gene Ontology Resource	Carbon *et al.,* 2019 (26)	http://geneontology.org/
Ggplot2 3.3.2	Wickham, 2016	https://cran.r-project.org/web/packages/ggplot2/index.html
GOPlot	Walter, Sanchez-Cabo and Ricote, 2015 (28)	https://wencke.github.io/
R 4.2.0	R Development Core Team, 2017	https://www.R-project.org
Search Tool for the Retrieval of Interacting Genes (STRING)	Szklarczyk *et al.,* 2019 (29)	https://string-db.org/
SPSS 20	-	https://www.ibm.com/products/spss-statistics
TCGA data	NIH Genomic Data Commons (GDC)	https://gdc.cancer.gov/
TCGAbiolinks 2.16.4	Colaprico *et al.,* 2016 (20)	10.18129/B9.bioc.TCGAbiolinks

Supplementary file 2. Complete list of DEGs between HNSCC with ADRB2^{high} / SLC6A2^{high} and ADRB2^{low} / SLC6A2^{low} expression.

RNA	logFC	FDR	Low	High	Delta
NTS	-5.439	0.000	13,024.133	175.920	70,840.707
WIF1	-4.628	0.000	907.043	16.609	4,197.520
PCP4	-4.553	0.000	59.996	1.207	273.177
CYP26A1	-4.466	0.000	438.887	16.690	1,960.198
IRS4	-4.284	0.000	72.910	0.218	312.378
KRT20	-4.010	0.000	71.793	1.310	287.886
ATP13A5	-3.940	0.000	513.984	30.885	2,025.027
MYO3A	-3.940	0.000	230.113	11.644	906.586
DLEC1	-3.878	0.000	73.797	3.368	286.209
EPHA7	-3.862	0.000	354.039	13.552	1,367.453
GSTA1	-3.856	0.000	2,250.055	145.655	8,675.942
GAGE2B	-3.824	0.004	155.352	0.138	594.105
NR0B1	-3.805	0.005	66.152	3.046	251.730
UGT1A7	-3.747	0.000	1,891.680	111.575	7,087.356
CEL	-3.694	0.000	2,466.441	159.287	9,111.209
MPPED1	-3.680	0.000	117.168	5.241	431.175
ZFR2	-3.668	0.000	106.414	2.575	390.322
GAGE4	-3.658	0.009	396.430	43.184	1,450.187
ODAM	-3.590	0.004	1,172.844	32.345	4,210.309
ALOX15	-3.530	0.000	292.055	54.724	1,030.929
ABCA17P	-3.423	0.000	78.508	6.241	268.771
FGFBP2	-3.361	0.000	1,520.133	63.149	5,108.838
STAG3	-3.304	0.000	619.324	32.034	2,046.138
ALDH1A1	-3.299	0.000	6,973.816	688.575	23,003.973
CLDN3	-3.261	0.000	371.379	33.874	1,211.004
ZNF541	-3.229	0.000	145.820	10.586	470.909
CES1	-3.213	0.000	7,496.363	1,507.057	24,085.944
FGF19	-3.199	0.000	593.777	17.149	1,899.258
FREM2	-3.188	0.000	723.402	81.989	2,306.001
SCN9A	-3.181	0.000	857.621	72.011	2,728.473
GPC3	-3.177	0.000	2,373.891	211.759	7,541.651
SCUBE3	-3.157	0.000	468.055	32.414	1,477.820
KIAA0319	-3.091	0.000	147.883	17.103	457.175
EPYC	-3.088	0.000	115.359	17.310	356.194
NTRK2	-3.079	0.000	14,457.527	1,519.287	44,518.613
SYCP2	-3.041	0.000	679.410	49.138	2,066.180
IL17REL	-3.039	0.000	105.891	3.908	321.759
KRT19	-3.035	0.000	102,546.648	10,519.000	311,187.407
CLGN	-3.030	0.000	207.395	16.011	628.499
FOXJ1	-2.967	0.000	232.836	31.126	690.896
MUC2	-2.949	0.000	118.348	10.920	348.984
KEL	-2.944	0.000	87.098	5.644	256.451
C16orf73	-2.898	0.002	70.238	13.138	203.529
SOX2	-2.891	0.000	6,270.582	767.908	18,128.843
NKX2-3	-2.855	0.000	84.840	9.644	242.181
HS3ST4	-2.851	0.000	79.051	6.977	225.350
ADH1C	-2.830	0.000	595.000	43.276	1,683.815
CR2	-2.825	0.000	155.461	13.552	439.100
CPLX2	-2.802	0.003	287.598	10.632	805.787
HIF3A	-2.795	0.000	82.250	11.149	229.893
LOC730101	-2.794	0.000	618.168	69.770	1,727.393
CLEC2L	-2.791	0.000	74.813	14.598	208.796
PPP1R1B	-2.781	0.000	433.355	48.897	1,205.139
SOX2OT	-2.780	0.000	224.586	22.621	624.354
MUC5B	-2.776	0.005	25,905.453	4,175.690	71,916.333
COCH	-2.737	0.000	542.078	68.609	1,483.797
SLC9A4	-2.644	0.000	110.484	10.356	292.066
PCDH19	-2.630	0.000	726.930	89.448	1,911.945
ALDH3A1	-2.613	0.000	19,693.715	2,919.552	51,466.024
DMRTA2	-2.607	0.000	219.859	35.000	573.179
CES4	-2.597	0.001	134.125	96.517	348.362

JAKMIP3	-2.596	0.000	84.559	14.345	219.489
UGT1A9	-2.594	0.000	320.594	72.460	831.597
WNK2	-2.584	0.000	2,081.094	312.195	5,376.546
SBK1	-2.575	0.000	582.852	92.149	1,500.958
PTPRT	-2.571	0.000	89.039	11.966	228.944
PLA2G2D	-2.558	0.000	186.617	25.540	477.356
VWDE	-2.523	0.000	56.887	9.839	143.500
GFRA3	-2.517	0.000	111.805	13.713	281.405
SPDYC	-2.511	0.001	45.336	6.943	113.858
C11orf92	-2.502	0.000	689.918	57.552	1,725.839
JAKMIP2	-2.496	0.000	270.977	31.448	676.353
SGEF	-2.491	0.000	760.270	126.816	1,893.699
SMC1B	-2.484	0.000	211.797	22.184	526.034
QRFPR	-2.462	0.000	164.148	31.517	404.208
GLT25D2	-2.460	0.000	344.629	48.207	847.954
FIBCD1	-2.457	0.000	558.758	76.115	1,373.022
KIAA2022	-2.450	0.000	81.902	9.494	200.693
MRAP2	-2.439	0.000	498.773	82.069	1,216.272
ADRA2B	-2.420	0.000	93.188	17.506	225.487
UPK1B	-2.412	0.000	6,277.828	1,092.000	15,143.902
PI16	-2.397	0.000	198.625	88.471	476.123
DMRT3	-2.392	0.000	88.773	14.471	212.320
NR5A1	-2.392	0.003	432.270	60.667	1,033.826
UGT1A8	-2.377	0.001	206.469	24.345	490.692
KRT15	-2.364	0.000	65,479.578	10,491.517	154,769.952
CYP4F3	-2.334	0.000	876.195	134.356	2,045.428
HS3ST6	-2.333	0.000	136.184	27.092	317.729
RBP4	-2.329	0.000	68.449	17.092	159.420
FOXA1	-2.317	0.000	1,221.102	220.402	2,829.436
AKR1C1	-2.317	0.000	39,398.977	8,051.678	91,286.591
KCNH1	-2.309	0.000	147.258	27.034	339.971
C19orf46	-2.303	0.000	95.797	18.115	220.649
KIAA1324	-2.296	0.000	1,347.672	262.115	3,094.003
UGT8	-2.290	0.000	367.664	73.368	842.019
PCSK2	-2.287	0.000	125.668	5.414	287.349
ABCA3	-2.274	0.000	1,348.176	194.954	3,065.563
FAM3B	-2.267	0.000	874.617	146.310	1,982.509
ADCY5	-2.266	0.000	95.082	20.172	215.435
GLS2	-2.263	0.000	355.301	66.678	804.183
PNCK	-2.249	0.000	506.004	110.678	1,138.209
KLHDC8A	-2.249	0.000	111.805	13.966	251.467
IRX6	-2.243	0.000	170.887	23.172	383.379
PTH2R	-2.237	0.000	137.668	36.034	307.934
SLC9A2	-2.235	0.000	460.727	89.517	1,029.627
MAP7D2	-2.232	0.000	398.559	69.552	889.595
LONRF2	-2.224	0.000	126.930	24.782	282.339
FBN3	-2.203	0.000	35.664	6.230	78.584
MSI1	-2.185	0.000	209.949	47.092	458.844
SPIB	-2.179	0.000	338.992	38.069	738.732
LGI3	-2.178	0.000	631.531	112.264	1,375.461
FMO3	-2.176	0.000	753.406	105.264	1,639.514
UGT2A1	-2.173	0.000	68.348	5.862	148.510
CSMD1	-2.172	0.000	125.086	30.759	271.728
SNX31	-2.164	0.000	134.262	33.391	290.478
AMY1A	-2.153	0.000	69.941	8.069	150.607
OGN	-2.153	0.000	277.418	63.310	597.255
NOS2	-2.151	0.000	663.813	44.770	1,427.625
CLDN10	-2.149	0.001	404.137	68.230	868.361
GDF15	-2.141	0.000	855.043	199.759	1,830.924
GLYATL2	-2.139	0.000	154.438	29.011	330.337
ICAM4	-2.133	0.000	194.609	45.874	415.016
GLB1L2	-2.127	0.000	383.992	91.448	816.901
FETUB	-2.123	0.000	497.039	96.287	1,055.244
INSM1	-2.122	0.000	164.004	4.989	347.983
VTCN1	-2.122	0.000	420.539	94.379	892.194
UGT1A6	-2.119	0.000	3,473.473	765.494	7,360.448
CNNM1	-2.117	0.000	166.762	49.345	353.019

C6orf223	-2.095	0.000	185.805	36.977	389.223
ABCA13	-2.080	0.000	2,379.113	544.563	4,949.204
CRB2	-2.076	0.000	91.238	17.126	189.415
SOX21	-2.075	0.000	895.848	207.655	1,858.443
C7	-2.068	0.000	236.855	56.057	489.771
FAM71E2	-2.059	0.002	48.988	10.069	100.869
PLAC8	-2.049	0.000	1,120.906	227.494	2,296.381
DIRAS2	-2.048	0.000	65.375	10.621	133.900
NEFH	-2.045	0.000	389.281	27.207	796.226
RORB	-2.036	0.000	75.363	10.655	153.476
PDE6B	-2.022	0.000	108.652	18.920	219.734
C4orf7	-2.018	0.001	14,309.340	1,913.322	28,869.236
MYB	-2.016	0.000	426.082	81.069	859.159
ST6GAL2	-2.008	0.000	299.547	64.425	601.626
TEX15	-1.997	0.002	74.945	18.184	149.640
AFF2	-1.997	0.000	238.734	54.575	476.638
OCA2	-1.995	0.000	73.637	14.356	146.890
PIPOX	-1.991	0.000	162.816	38.437	324.120
SCGB1A1	-1.988	0.007	145.879	33.529	290.028
LRRC4	-1.988	0.000	1,798.949	417.230	3,575.901
LTF	-1.986	0.002	10,690.391	3,095.678	21,233.829
HPN	-1.975	0.000	74.523	11.207	147.181
KRT36	-1.955	0.001	83.680	4.839	163.559
MGAT3	-1.952	0.000	612.844	105.678	1,196.032
TCAM1P	-1.950	0.000	141.238	19.103	275.468
TBX4	-1.947	0.000	70.070	13.379	136.454
ADH7	-1.943	0.000	4,952.785	1,192.356	9,624.967
C11orf93	-1.940	0.000	105.711	24.494	205.118
RAB6B	-1.932	0.000	1,045.496	231.632	2,019.598
ZDHHC2	-1.924	0.000	1,039.746	269.747	2,000.645
KRT8	-1.909	0.000	21,692.684	5,467.736	41,410.381
ALX1	-1.900	0.000	61.391	11.414	116.666
KCNE3	-1.899	0.000	829.117	186.701	1,574.567
CLDN8	-1.890	0.001	210.031	37.448	397.055
RIMKLA	-1.890	0.000	96.762	20.287	182.874
ARNT2	-1.888	0.000	836.641	174.195	1,579.160
PKDCC	-1.885	0.000	499.875	95.713	942.227
NCRNA00086	-1.876	0.000	107.508	27.287	201.690
AADAC	-1.868	0.000	187.344	42.506	349.901
GCNT2	-1.858	0.000	541.023	147.333	1,004.961
AKR1C3	-1.849	0.000	12,941.516	3,488.241	23,922.624
TRPV6	-1.841	0.000	79.055	21.632	145.558
psiTPTE22	-1.841	0.000	355.813	62.517	655.078
SUSD4	-1.837	0.000	1,920.375	509.598	3,528.453
B4GALNT4	-1.832	0.000	585.238	195.115	1,072.385
AKR1C2	-1.819	0.000	24,623.496	7,182.379	44,799.958
STOX1	-1.814	0.000	182.305	53.471	330.681
SV2B	-1.798	0.000	210.535	40.218	378.463
COL19A1	-1.796	0.003	48.902	8.460	87.819
CBS	-1.786	0.000	1,083.691	307.805	1,935.268
EPCAM	-1.785	0.000	6,007.855	1,595.402	10,723.733
SCGB2A1	-1.781	0.001	120.082	2.483	213.875
DSG4	-1.775	0.000	54.953	12.460	97.568
GPRC5D	-1.773	0.000	163.262	47.586	289.441
LOXL4	-1.773	0.000	829.242	228.034	1,470.013
CTTNBP2	-1.771	0.000	211.336	64.161	374.200
UBD	-1.767	0.000	4,778.766	1,235.552	8,444.833
MUC13	-1.764	0.001	110.762	26.494	195.418
HEY1	-1.763	0.000	1,487.074	361.207	2,621.539
CHIT1	-1.762	0.000	938.805	410.920	1,654.570
MUC6	-1.762	0.000	264.727	2.713	466.473
BTNL9	-1.761	0.000	340.203	59.184	599.069
CP	-1.760	0.000	2,270.758	545.287	3,997.313
SLC27A2	-1.760	0.000	243.723	69.943	428.834
PDIA2	-1.755	0.001	78.430	27.908	137.611
VCAM1	-1.754	0.000	3,774.059	661.678	6,619.393
TAF7L	-1.749	0.000	100.457	8.310	175.685

C6orf168	-1.747	0.000	412.578	117.690	720.731
EYA2	-1.747	0.000	972.758	260.138	1,699.050
MS4A1	-1.745	0.000	493.277	90.943	861.005
ISM2	-1.737	0.000	51.695	12.149	89.811
SOX5	-1.737	0.000	59.066	14.747	102.597
PCLO	-1.735	0.000	525.746	153.563	912.365
GPX2	-1.729	0.000	10,221.602	2,944.885	17,673.982
ALDH1L1	-1.720	0.000	355.965	93.414	612.168
NRXN3	-1.719	0.000	143.277	38.379	246.336
ADAM6	-1.714	0.000	235,030.426	86,567.655	402,839.734
RNF183	-1.712	0.000	42.109	12.885	72.098
CHDH	-1.712	0.000	152.863	37.241	261.682
CHST9	-1.707	0.009	209.730	66.172	358.012
BLK	-1.706	0.000	65.348	18.069	111.481
ZBTB7C	-1.700	0.000	2,241.969	669.621	3,810.261
TCP11	-1.694	0.000	74.324	12.529	125.895
FADS2	-1.694	0.000	4,530.852	1,450.632	7,674.363
FOXD3	-1.690	0.000	45.426	11.460	76.769
HLF	-1.689	0.000	677.742	193.529	1,144.514
UCHL1	-1.683	0.000	2,511.840	786.425	4,226.218
CACNA1B	-1.682	0.000	243.941	82.126	410.402
CCL26	-1.677	0.000	209.617	60.069	351.428
POMC	-1.676	0.000	189.262	45.747	317.193
ZG16B	-1.675	0.001	833.848	278.506	1,396.488
SLCO4C1	-1.672	0.000	101.844	18.885	170.328
INA	-1.670	0.001	181.832	50.563	303.671
SYNGR3	-1.665	0.000	303.199	81.966	504.889
FAM190A	-1.659	0.000	60.367	19.494	100.138
COLEC11	-1.656	0.000	84.383	21.299	139.774
CD19	-1.650	0.000	102.855	27.138	169.715
CTSE	-1.649	0.003	52.766	6.678	87.029
CHRDL1	-1.649	0.000	235.258	103.874	387.894
BEND5	-1.645	0.000	47.855	12.368	78.708
RPRM	-1.639	0.000	67.289	17.920	110.282
KIF1A	-1.628	0.004	170.891	53.276	278.190
TSPAN18	-1.626	0.000	1,692.703	531.793	2,753.128
LRRN1	-1.621	0.000	353.441	104.333	572.946
GRIN2A	-1.619	0.000	203.992	43.483	330.274
SERPINI1	-1.618	0.000	647.688	145.287	1,047.687
WSCD2	-1.617	0.000	120.832	37.966	195.439
OMD	-1.617	0.000	354.258	114.000	572.804
TMEM163	-1.613	0.000	108.109	31.885	174.355
TMSB15A	-1.612	0.000	111.758	16.195	180.098
ACTL8	-1.610	0.006	140.133	17.759	225.546
C6orf15	-1.609	0.000	630.621	160.126	1,014.439
KCNK2	-1.591	0.000	78.734	24.437	125.289
GABRB3	-1.590	0.001	159.629	50.943	253.750
LOC541473	-1.589	0.000	49.879	14.655	79.272
ZMAT1	-1.589	0.000	136.531	37.425	216.960
ADAM22	-1.584	0.000	57.965	15.931	91.830
FAM83E	-1.579	0.000	548.762	174.793	866.718
SAMD12	-1.579	0.000	1,407.824	448.644	2,223.318
AMOT	-1.579	0.000	822.621	331.747	1,298.890
LOC254559	-1.578	0.000	536.586	130.448	846.561
FZD7	-1.575	0.000	2,218.586	708.908	3,494.929
PRND	-1.574	0.000	53.309	16.310	83.925
NUP210	-1.573	0.000	4,057.473	1,393.506	6,381.090
MFSD4	-1.568	0.000	579.809	168.575	908.879
WISP2	-1.566	0.000	266.793	107.609	417.799
CYP2E1	-1.562	0.000	276.793	80.046	432.339
C1orf110	-1.560	0.002	442.574	149.149	690.449
MYEF2	-1.554	0.000	150.422	45.793	233.776
MIAT	-1.552	0.000	911.672	280.851	1,415.157
CCDC78	-1.550	0.000	82.492	28.218	127.889
PRG4	-1.549	0.000	214.484	71.241	332.278
FGF14	-1.547	0.000	102.105	31.621	157.981
GPAT2	-1.545	0.000	203.840	53.793	315.004

BTBD16	-1.542	0.001	50.789	13.057	78.334
SLC29A2	-1.539	0.000	599.906	211.046	923.302
ITGBL1	-1.539	0.000	770.883	243.701	1,186.028
CILP	-1.537	0.000	272.441	110.563	418.683
IGSF10	-1.535	0.000	251.828	105.345	386.614
ENPP6	-1.534	0.000	46.125	10.299	70.750
PTN	-1.533	0.000	1,406.387	354.552	2,156.394
TDRD10	-1.531	0.000	37.234	8.908	57.022
TMPRSS2	-1.529	0.000	836.695	258.724	1,279.686
KIAA1244	-1.528	0.000	270.738	91.184	413.817
MUC4	-1.526	0.001	6,439.035	1,680.345	9,824.663
MERTK	-1.525	0.000	796.230	271.678	1,214.194
RARB	-1.524	0.000	344.684	116.379	525.229
SIGLEC8	-1.524	0.000	46.855	15.460	71.388
KATNAL2	-1.523	0.000	81.887	27.793	124.702
STXBP6	-1.522	0.000	154.250	48.195	234.830
POU4F1	-1.522	0.002	58.848	22.172	89.589
SOSTDC1	-1.517	0.000	894.848	243.195	1,357.856
GPR160	-1.515	0.000	566.887	171.529	859.102
SOX30	-1.514	0.000	51.688	11.736	78.261
CES3	-1.514	0.000	126.730	39.264	191.832
SLAIN1	-1.511	0.000	114.129	38.425	172.424
KLHL23	-1.510	0.000	214.949	75.276	324.492
EPS8	-1.507	0.000	1,647.254	553.736	2,482.924
PIP5K1B	-1.506	0.000	127.938	38.782	192.634
PLIN4	-1.504	0.000	253.758	176.828	381.758
MCF2L	-1.501	0.000	769.719	263.149	1,155.380
SLIT2	-1.498	0.000	422.996	146.517	633.838
MYH11	-1.497	0.000	3,022.816	1,030.069	4,526.313
C8orf84	-1.488	0.000	275.371	73.218	409.839
SLC16A14	-1.488	0.000	500.277	168.851	744.361
SOST	-1.487	0.001	186.563	66.885	277.503
RNF150	-1.485	0.000	114.676	32.816	170.349
PLCH1	-1.485	0.000	126.875	44.287	188.415
PTGIS	-1.484	0.000	390.750	200.943	580.049
BEX2	-1.483	0.000	444.887	163.230	659.546
ANKLE1	-1.480	0.000	90.414	30.218	133.803
GULP1	-1.477	0.000	406.715	142.161	600.598
PNMA3	-1.471	0.000	47.594	11.322	70.033
PIWIL2	-1.471	0.001	132.863	54.494	195.381
C2orf65	-1.469	0.001	130.066	51.701	191.122
YBX2	-1.468	0.000	184.488	58.586	270.860
SPRR3	-1.467	0.001	72,948.148	25,783.632	106,981.348
NAALADL2	-1.465	0.000	152.559	54.345	223.533
C8G	-1.465	0.000	41.625	7.977	60.961
RANBP17	-1.464	0.000	97.133	30.816	142.192
ASRGL1	-1.464	0.000	228.145	73.828	333.968
TNFSF18	-1.462	0.000	52.574	17.000	76.876
CLIC6	-1.461	0.000	512.449	171.299	748.631
OXGR1	-1.456	0.000	70.488	23.908	102.622
RHBDL3	-1.451	0.000	122.688	50.057	177.975
PCDHA4	-1.449	0.001	58.250	17.103	84.405
TMEM90B	-1.449	0.000	147.023	50.391	213.021
PBX1	-1.449	0.000	2,669.461	995.069	3,867.323
BDNF	-1.443	0.000	172.367	62.724	248.662
PRSS21	-1.440	0.001	381.926	158.483	549.862
NWD1	-1.438	0.000	79.465	31.138	114.257
PENK	-1.436	0.000	95.250	37.207	136.761
ISYNA1	-1.435	0.000	1,791.582	675.908	2,571.747
GSTM2	-1.433	0.000	3,107.203	966.333	4,453.649
THSD7B	-1.432	0.000	102.141	23.724	146.311
PPM1H	-1.431	0.000	484.430	162.816	693.037
CACNA2D1	-1.430	0.000	357.180	137.586	510.740
SMOC2	-1.430	0.000	826.250	266.747	1,181.275
IGSF11	-1.429	0.000	185.727	60.517	265.491
CXCL17	-1.429	0.000	2,538.285	1,019.184	3,627.015
TG	-1.428	0.000	148.520	49.092	212.093

KCNJ11	-1.425	0.000	115.680	54.460	164.840
CYP4F11	-1.425	0.000	2,173.605	772.138	3,096.628
ARHGAP4	-1.423	0.000	2,016.379	688.862	2,868.719
MDK	-1.417	0.000	8,790.313	3,132.207	12,456.425
EYA1	-1.417	0.000	87.836	27.966	124.446
SLC6A4	-1.416	0.000	65.773	23.149	93.165
AP3B2	-1.415	0.000	112.027	48.713	158.517
FXYD6	-1.414	0.000	788.508	236.931	1,114.980
LOC96610	-1.412	0.000	123,065.762	53,975.218	173,735.122
CACNB4	-1.409	0.000	69.246	24.759	97.567
ATP12A	-1.408	0.001	796.078	267.966	1,120.742
MEI1	-1.407	0.000	396.961	92.207	558.494
NRCAM	-1.407	0.000	1,521.602	480.011	2,140.733
DLX6	-1.399	0.000	166.902	63.644	233.434
IGJ	-1.398	0.000	9,858.867	4,587.540	13,778.057
HOXA9	-1.396	0.000	215.047	62.885	300.289
BCL2	-1.395	0.000	850.621	295.046	1,186.947
CYP4X1	-1.395	0.000	627.563	186.379	875.513
DCHS2	-1.394	0.000	97.945	27.379	136.540
IGFBP5	-1.393	0.000	20,836.262	7,126.126	29,016.390
PEG10	-1.387	0.000	1,083.676	330.552	1,503.400
OTX1	-1.387	0.000	293.602	116.874	407.253
GABRP	-1.386	0.007	2,718.473	856.080	3,768.342
ACBD7	-1.386	0.000	136.977	37.931	189.845
SCN2A	-1.385	0.001	186.168	77.678	257.838
C12orf53	-1.384	0.000	72.000	21.609	99.624
CECR2	-1.382	0.000	190.938	71.023	263.848
RNF165	-1.382	0.000	221.219	75.299	305.636
LRIG1	-1.382	0.000	2,477.113	958.460	3,422.299
RNFT2	-1.380	0.000	143.215	49.322	197.700
SLC44A4	-1.376	0.000	428.773	172.000	589.829
RGMA	-1.373	0.000	2,950.297	1,069.149	4,051.823
CEACAM5	-1.372	0.000	10,848.184	4,421.471	14,887.387
CYP27A1	-1.370	0.000	1,025.754	367.517	1,405.346
LOC441869	-1.369	0.000	1,095.281	411.862	1,499.846
NRN1	-1.369	0.000	614.410	225.414	841.253
LUZP2	-1.368	0.000	50.227	19.172	68.700
THBS4	-1.365	0.001	3,006.602	1,162.736	4,103.141
TMEM116	-1.364	0.000	573.445	199.885	782.271
MYO5C	-1.355	0.000	784.910	271.402	1,063.255
MOSC1	-1.354	0.000	397.758	148.345	538.441
RASSF9	-1.350	0.000	534.699	194.632	721.795
TJP3	-1.349	0.000	569.012	204.851	767.851
TMPRSS11A	-1.347	0.000	2,263.438	796.322	3,048.627
HYDIN	-1.346	0.000	54.926	21.092	73.949
ATP2A1	-1.343	0.005	811.238	808.471	1,089.391
PAX1	-1.342	0.006	687.219	57.828	921.976
ADAMDEC1	-1.340	0.000	533.895	230.690	715.557
PRKAA2	-1.338	0.000	329.180	154.724	440.344
CAPN14	-1.336	0.000	654.629	207.034	874.616
FGF13	-1.334	0.000	227.695	85.299	303.657
FA2H	-1.333	0.000	273.832	102.333	364.919
CYP11A1	-1.332	0.005	87.102	32.287	116.035
FAM171A1	-1.327	0.000	806.730	285.655	1,070.459
ULBP1	-1.320	0.000	225.992	76.874	298.363
PRKX	-1.319	0.000	4,173.152	1,609.598	5,505.796
BZRAP1	-1.315	0.000	315.461	116.563	414.683
SVIP	-1.313	0.000	311.801	108.724	409.479
SFRP4	-1.312	0.000	3,059.898	1,431.989	4,015.823
MEGF10	-1.312	0.000	431.246	148.816	565.770
PYGM	-1.310	0.006	463.961	599.747	607.602
GSTM3	-1.309	0.000	4,380.684	1,495.575	5,736.112
GSTM5	-1.307	0.000	289.969	34.230	378.854
KIAA1683	-1.306	0.000	86.582	35.092	113.098
NR3C2	-1.305	0.000	139.480	52.287	181.984
MYH7B	-1.301	0.000	121.984	18.828	158.729
PARM1	-1.299	0.000	1,993.016	491.207	2,588.504

FBP1	-1.297	0.000	737.793	312.230	957.202
CGREF1	-1.293	0.000	271.223	121.046	350.728
ADAM23	-1.292	0.000	1,712.691	717.115	2,213.328
PODXL2	-1.291	0.000	1,343.070	516.092	1,733.732
ABCC5	-1.288	0.000	11,122.461	4,135.471	14,329.149
ELN	-1.288	0.000	1,905.391	763.862	2,454.628
MYH14	-1.286	0.000	10,940.840	4,408.057	14,072.049
IL34	-1.286	0.000	331.414	137.287	426.079
RASL11A	-1.286	0.000	259.586	92.885	333.720
KCNJ10	-1.285	0.000	48.699	15.471	62.588
ASPN	-1.285	0.000	3,497.105	1,366.759	4,493.870
SCIN	-1.284	0.000	373.691	135.609	479.732
NKAIN2	-1.284	0.000	124.910	51.644	160.341
LIPH	-1.282	0.000	622.105	258.230	797.513
PLA2G16	-1.282	0.000	593.727	237.690	760.964
SCUBE2	-1.281	0.000	261.473	96.897	334.992
TRIM2	-1.280	0.000	2,937.781	1,157.828	3,761.681
CTCFL	-1.280	0.000	210.500	49.954	269.436
SLC7A2	-1.279	0.000	1,195.469	482.540	1,528.990
SERPINB12	-1.279	0.005	135.148	57.034	172.799
DLGAP1	-1.277	0.002	71.891	20.379	91.839
PCP4L1	-1.276	0.000	406.664	175.989	518.768
ZNF667	-1.273	0.000	61.695	19.701	78.567
CR1	-1.273	0.000	116.082	51.793	147.767
IL17RB	-1.269	0.000	156.516	39.402	198.552
RND2	-1.265	0.000	144.133	59.931	182.310
GPRC5B	-1.265	0.000	791.750	332.931	1,001.356
APOC1	-1.265	0.000	1,523.133	637.851	1,926.268
ESPNL	-1.259	0.000	122.387	55.839	154.028
ZNF280B	-1.258	0.000	53.027	20.632	66.705
PCOLCE2	-1.253	0.000	266.230	106.471	333.600
COL11A1	-1.252	0.000	3,991.574	1,694.000	4,997.613
ATP6V0E2	-1.251	0.000	766.055	315.218	958.624
ADD2	-1.250	0.000	269.625	118.621	337.088
MUC20	-1.248	0.000	1,861.820	693.517	2,323.778
FTL	-1.247	0.000	117,011.586	49,170.770	145,918.695
ELF3	-1.245	0.000	9,876.191	4,037.989	12,294.336
C1QTNF3	-1.240	0.000	495.762	161.483	614.753
EPHX1	-1.239	0.000	4,974.125	2,046.253	6,162.759
GPLD1	-1.229	0.000	66.621	23.828	81.860
CLU	-1.226	0.000	11,219.828	4,297.011	13,756.578
SPOCK3	-1.225	0.007	170.570	208.207	208.903
SYT2	-1.223	0.000	72.156	16.805	88.230
FAT3	-1.222	0.000	61.898	15.483	75.666
PHGDH	-1.221	0.000	3,625.605	1,575.356	4,427.902
ETV1	-1.221	0.000	546.723	213.540	667.562
FGF12	-1.219	0.000	156.430	64.529	190.686
SHISA2	-1.219	0.000	1,232.574	412.391	1,502.145
LOC255167	-1.217	0.001	46.668	15.264	56.817
PIK3AP1	-1.215	0.000	1,285.266	551.897	1,562.035
CYP1B1	-1.215	0.000	1,466.129	607.345	1,781.547
KRT7	-1.213	0.001	5,103.605	1,714.103	6,192.288
KCNS3	-1.210	0.000	1,538.254	654.425	1,861.338
TMC4	-1.207	0.000	1,272.301	567.080	1,536.151
TSPYL5	-1.207	0.000	545.449	194.069	658.516
CCDC74A	-1.207	0.000	177.012	71.402	213.565
NSUN7	-1.206	0.000	115.227	47.356	138.974
CD22	-1.204	0.000	211.309	61.138	254.513
TFR2	-1.204	0.000	115.266	51.138	138.734
COL4A4	-1.203	0.000	233.578	74.805	281.037
MANSC1	-1.203	0.000	1,759.066	759.356	2,116.053
HLA-DQA1	-1.201	0.000	5,958.941	2,706.402	7,155.580
LGALS4	-1.199	0.007	58.641	20.736	70.328
CHST6	-1.199	0.000	250.227	107.943	299.952
OLFM1	-1.199	0.000	1,639.613	666.230	1,965.085
ALDH1A2	-1.196	0.000	59.539	23.885	71.189
C3orf58	-1.195	0.000	2,724.742	1,137.828	3,255.311

EMID1	-1.193	0.000	319.809	122.402	381.559
REPIN1	-1.193	0.000	3,362.531	1,430.483	4,010.243
COL21A1	-1.190	0.000	380.574	141.103	452.871
LRMP	-1.189	0.000	417.367	156.609	496.076
ZNF853	-1.187	0.000	305.383	125.908	362.547
RARRES1	-1.187	0.000	966.402	487.230	1,147.028
STK32B	-1.186	0.000	189.020	69.391	224.195
CACNA1D	-1.185	0.000	52.238	18.540	61.900
DSCR6	-1.184	0.001	68.859	35.586	81.563
KRT13	-1.184	0.004	150,534.430	67,880.253	178,279.274
PRELP	-1.184	0.000	1,216.559	525.218	1,440.309
CHPT1	-1.183	0.000	1,180.172	459.069	1,396.262
ROBO2	-1.178	0.000	181.277	74.690	213.610
GCLC	-1.178	0.000	7,669.172	3,360.782	9,031.487
FOXH1	-1.175	0.001	41.750	15.276	49.057
SCNN1A	-1.175	0.000	5,518.691	2,231.575	6,482.239
CRMP1	-1.175	0.000	755.105	327.517	886.929
ACPL2	-1.174	0.000	923.238	407.736	1,084.067
TMEM150C	-1.174	0.000	242.535	94.138	284.688
IKZF3	-1.174	0.000	105.496	44.080	123.829
APOE	-1.172	0.000	10,006.152	4,496.782	11,725.587
ILDR1	-1.171	0.000	434.098	192.414	508.238
RNF212	-1.170	0.001	229.473	91.368	268.597
LMO4	-1.168	0.000	4,712.695	1,957.161	5,502.943
LYZ	-1.166	0.000	23,641.582	13,682.655	27,576.398
TCL1A	-1.166	0.009	75.414	26.437	87.962
TFF3	-1.166	0.005	1,096.258	212.839	1,278.153
PRR15L	-1.161	0.000	179.555	69.805	208.412
C7orf46	-1.158	0.000	132.887	52.954	153.854
CAND2	-1.157	0.000	215.000	113.862	248.779
NUPR1	-1.157	0.000	3,760.926	1,893.736	4,349.841
NPTXR	-1.156	0.000	535.859	252.885	619.509
CMYA5	-1.155	0.004	2,827.879	1,881.621	3,264.916
CHST7	-1.153	0.000	614.703	266.701	708.585
CGN	-1.152	0.000	852.277	367.931	981.999
LEF1	-1.151	0.000	760.746	317.598	875.723
MLXIPL	-1.151	0.001	75.555	34.908	86.950
CD74	-1.151	0.000	101,640.887	46,349.483	116,960.889
BMP7	-1.150	0.000	3,198.180	1,392.471	3,677.772
SIX4	-1.149	0.000	706.012	316.011	811.068
KCNH2	-1.146	0.000	79.934	35.425	91.623
OXER1	-1.146	0.000	47.340	20.057	54.241
PLCB4	-1.145	0.000	258.699	114.126	296.131
TMEM20	-1.144	0.000	512.125	193.000	585.923
SYNPO2	-1.144	0.001	4,806.246	2,731.759	5,497.034
FLJ45445	-1.143	0.000	590.074	269.161	674.499
RAB42	-1.140	0.000	61.391	25.563	70.010
HAP1	-1.139	0.000	526.805	228.356	599.796
LOC100132215	-1.137	0.000	84.391	39.287	95.993
DACH1	-1.137	0.000	75.438	29.782	85.785
TNFAIP2	-1.136	0.000	9,413.836	4,073.529	10,691.818
CCDC136	-1.133	0.000	71.957	30.356	81.496
MAOB	-1.131	0.000	949.129	486.598	1,073.454
TCF15	-1.129	0.001	62.719	30.529	70.792
NCAM2	-1.129	0.001	53.832	25.655	60.751
TXNRD1	-1.128	0.000	10,105.652	4,576.920	11,401.629
LOC339535	-1.127	0.005	188.293	79.368	212.270
SLC29A4	-1.126	0.000	472.324	209.080	531.821
PRKD1	-1.125	0.000	209.602	92.126	235.815
ADM2	-1.124	0.000	500.879	221.230	563.216
CAPS	-1.124	0.000	448.391	197.540	504.194
PTCH1	-1.124	0.000	739.148	318.759	830.718
EPB41L1	-1.123	0.000	3,729.305	1,753.310	4,187.820
GPC4	-1.123	0.000	1,731.813	751.690	1,944.089
SLC4A11	-1.122	0.000	1,251.172	531.126	1,404.183
P4HTM	-1.122	0.000	537.859	243.690	603.390
CCL19	-1.119	0.001	765.660	295.253	856.925

STAP1	-1.118	0.000	47.730	20.149	53.373
ICA1	-1.117	0.000	331.863	130.920	370.838
GSTM4	-1.117	0.000	1,455.227	615.034	1,626.057
PLCE1	-1.117	0.000	343.250	147.678	383.508
GATM	-1.115	0.000	958.723	464.563	1,069.071
MORN3	-1.113	0.000	51.102	20.322	56.894
SPP1	-1.111	0.000	15,943.090	6,933.207	17,708.016
C11orf9	-1.110	0.000	268.227	117.563	297.804
SEPT3	-1.110	0.000	271.680	112.138	301.573
UCP2	-1.110	0.000	2,555.613	1,162.609	2,836.806
ITGA11	-1.109	0.000	1,162.648	502.333	1,289.854
TMEM119	-1.109	0.000	803.156	365.943	890.381
TMEM151B	-1.106	0.000	63.648	20.943	70.392
POU2AF1	-1.105	0.000	943.227	398.126	1,042.252
BANK1	-1.104	0.000	149.723	61.149	165.275
FNDC5	-1.103	0.000	80.406	79.195	88.722
PHYHD1	-1.103	0.000	482.270	214.598	531.915
KIAA1257	-1.101	0.000	64.586	26.989	71.095
DAPL1	-1.099	0.001	1,299.574	641.437	1,427.861
EGF	-1.097	0.000	123.793	68.253	135.742
DMRT2	-1.096	0.003	266.438	102.230	291.930
AOAH	-1.095	0.000	480.133	220.264	525.554
FAM184A	-1.094	0.000	54.840	21.885	59.987
LOC84856	-1.092	0.000	246.477	97.782	269.224
PPP1R9A	-1.092	0.002	88.570	30.793	96.677
MECOM	-1.091	0.000	1,111.410	477.322	1,212.907
GCHFR	-1.091	0.000	595.730	257.851	650.078
PPARG	-1.088	0.000	203.332	90.667	221.149
SALL2	-1.086	0.000	257.590	118.540	279.851
TSPAN7	-1.085	0.000	2,239.711	1,056.345	2,430.646
SV2A	-1.082	0.000	355.125	147.103	384.181
PLA1A	-1.081	0.000	95.801	46.586	103.597
PODN	-1.081	0.000	743.277	351.253	803.678
CXCR5	-1.080	0.001	76.699	28.920	82.849
GNAZ	-1.080	0.000	118.211	54.241	127.657
COMP	-1.080	0.001	1,541.801	634.253	1,664.432
MAP1B	-1.079	0.000	3,294.125	1,569.241	3,554.412
C3orf70	-1.076	0.000	257.074	114.023	276.705
TRIB2	-1.070	0.000	2,597.168	1,233.506	2,779.512
ARHGAP24	-1.068	0.000	672.547	321.011	718.215
CD79A	-1.065	0.001	896.332	445.402	954.559
PGD	-1.065	0.000	15,519.949	7,263.885	16,527.452
SLC2A4	-1.063	0.000	77.824	56.793	82.736
MMP11	-1.063	0.000	13,044.090	6,320.276	13,862.551
TTC28	-1.062	0.000	829.527	407.724	881.091
DNASE1L2	-1.061	0.000	51.863	23.402	55.042
PDGFRL	-1.060	0.000	426.789	203.598	452.603
FGFR2	-1.060	0.000	3,826.480	1,688.782	4,057.839
CPXM2	-1.060	0.000	1,082.941	518.931	1,147.716
NCRNA00176	-1.060	0.000	50.770	21.793	53.798
CELF6	-1.060	0.000	53.102	25.103	56.265
RHPN1	-1.058	0.000	381.828	196.816	403.838
DPT	-1.056	0.000	844.625	421.644	892.199
LILRB4	-1.056	0.000	803.309	402.713	848.495
PRR15	-1.056	0.000	152.145	75.954	160.703
AGR2	-1.055	0.001	2,156.305	906.839	2,275.298
ZNF238	-1.052	0.000	953.305	453.322	1,003.120
DYNC1I1	-1.051	0.000	274.637	123.828	288.612
SPEF2	-1.050	0.000	104.563	50.402	109.825
HSPB6	-1.050	0.003	1,396.891	1,276.621	1,466.168
CCDC85A	-1.049	0.000	50.402	22.793	52.877
CD200	-1.046	0.000	505.035	214.851	528.061
ZSCAN18	-1.045	0.000	586.871	290.943	613.334
HOXB3	-1.041	0.000	331.852	143.483	345.294
NRTN	-1.041	0.000	69.418	33.943	72.230
HCLS1	-1.039	0.000	2,440.840	1,179.011	2,537.012
NTN1	-1.039	0.000	2,664.395	1,278.713	2,768.385

ASB9	-1.038	0.000	100.914	43.356	104.766
PANX2	-1.038	0.000	918.941	440.506	953.449
CD79B	-1.036	0.000	254.047	112.966	263.223
MGST1	-1.035	0.004	3,357.289	1,767.425	3,474.581
HHEX	-1.035	0.000	311.941	149.816	322.830
C17orf28	-1.035	0.000	504.660	235.609	522.211
ICK	-1.034	0.000	2,158.613	1,039.402	2,230.990
CCDC74B	-1.031	0.000	68.820	32.816	70.964
PIK3R3	-1.031	0.000	2,003.770	935.678	2,066.049
SPIRE2	-1.029	0.000	345.445	180.816	355.499
PLLP	-1.028	0.000	396.941	196.471	407.994
TMEM35	-1.026	0.000	45.320	18.046	46.518
BCAT1	-1.024	0.000	3,140.723	1,521.529	3,217.327
SLC47A1	-1.023	0.000	267.746	126.115	273.878
SHC4	-1.021	0.000	117.875	39.299	120.383
MYCN	-1.020	0.000	93.453	36.276	95.347
GLI1	-1.020	0.000	233.641	97.563	238.261
ZAP70	-1.019	0.000	407.578	187.690	415.470
PDE3B	-1.019	0.000	413.816	201.966	421.622
FSTL4	-1.017	0.000	549.301	220.874	558.695
TCHH	-1.017	0.008	1,009.137	426.747	1,026.107
CX3CL1	-1.015	0.000	3,616.473	1,765.069	3,672.050
THEMIS	-1.014	0.000	110.445	51.851	111.958
CHI3L1	-1.014	0.000	3,769.684	2,108.529	3,820.898
MFAP4	-1.011	0.000	1,336.953	681.609	1,351.960
NKX3-2	-1.011	0.000	58.496	28.851	59.119
TMEM108	-1.010	0.000	94.309	41.782	95.298
BAI1	-1.010	0.001	175.320	81.517	177.030
SYTL5	-1.010	0.003	212.922	98.414	214.988
ABCA2	-1.009	0.000	2,056.016	1,083.678	2,074.043
DEPDC6	-1.008	0.000	510.164	262.586	514.262
GPR143	-1.008	0.000	148.508	69.782	149.683
PTCH2	-1.006	0.000	30.461	12.839	30.641
SKAP1	-1.005	0.000	224.301	99.322	225.528
MYLIP	-1.005	0.000	1,489.871	747.954	1,497.786
CABYR	-1.005	0.000	317.672	148.701	319.354
MEX3A	-1.004	0.000	590.504	251.184	592.773
DUSP2	-1.003	0.000	917.695	435.276	920.820
CD72	-1.003	0.000	143.941	68.368	144.431
SERPINF1	-1.003	0.000	5,790.863	2,775.483	5,806.488
SULF1	-1.002	0.000	9,526.531	4,655.563	9,549.293
PLEKHG4	-1.001	0.000	1,504.719	743.667	1,505.612
CTSS	-1.000	0.000	5,053.719	2,568.805	5,055.046
NR2E1	1.000	0.008	45.020	68.161	45.038
HSPA12A	1.001	0.000	536.598	1,064.494	536.969
FOSL1	1.001	0.000	3,296.031	6,600.828	3,299.991
MMP28	1.003	0.000	1,576.918	2,803.207	1,581.672
DIO3	1.004	0.000	51.258	87.747	51.475
NAV3	1.005	0.000	251.766	502.782	252.910
S100A12	1.006	0.000	1,080.695	2,197.046	1,086.801
HOXC13	1.006	0.000	330.375	626.736	332.466
DNER	1.009	0.000	151.934	240.989	153.296
CCRN4L	1.013	0.000	537.195	1,098.391	544.187
ISG15	1.013	0.000	11,528.723	24,037.494	11,682.050
COL4A6	1.014	0.000	1,732.465	2,921.701	1,756.714
MT1M	1.014	0.000	91.887	173.161	93.187
KRT14	1.015	0.000	553,666.504	1,042,337.678	561,704.470
RNF222	1.015	0.001	180.895	376.529	183.525
CDSN	1.015	0.004	3,917.117	8,564.207	3,977.389
TSKS	1.016	0.002	98.340	188.092	99.930
DKFZp434J0226	1.017	0.000	54.434	101.483	55.359
CPA4	1.019	0.000	1,709.125	3,337.402	1,741.420
PRSS23	1.019	0.000	6,341.973	12,673.023	6,463.697
DNAH5	1.020	0.000	172.316	348.908	175.685
HSF2BP	1.020	0.000	70.961	143.000	72.381
KRT6B	1.022	0.000	158,155.723	332,115.161	161,668.417
SLC47A2	1.029	0.000	234.441	457.793	241.333

APCDD1	1.031	0.000	2,366.223	4,259.529	2,438.657
LOC100216001	1.032	0.000	87.145	163.770	89.938
HES5	1.033	0.000	47.402	94.759	48.957
LCE3E	1.039	0.006	977.426	1,897.333	1,015.421
PROC	1.040	0.000	139.695	237.345	145.235
LIPG	1.042	0.000	616.773	1,345.540	642.639
VSIG1	1.042	0.000	69.992	136.092	72.964
SLC10A6	1.044	0.000	356.207	703.345	371.785
DLX1	1.045	0.000	135.820	251.345	141.960
UCA1	1.046	0.000	165.883	243.747	173.528
SORCS2	1.051	0.000	647.754	1,276.839	680.469
PLCD4	1.052	0.000	169.250	352.138	178.092
SLPI	1.057	0.000	17,787.637	38,247.092	18,792.810
LGALS7B	1.059	0.000	6,880.008	14,342.793	7,284.407
CYP27B1	1.060	0.000	416.852	828.644	441.979
SPRR2E	1.062	0.001	19,775.777	39,282.425	21,010.326
CD207	1.066	0.000	303.293	599.345	323.233
TMEM92	1.068	0.000	150.305	293.816	160.469
LOC554202	1.069	0.000	512.652	980.644	547.934
NLGN4X	1.071	0.000	279.742	633.598	299.558
ODF3L1	1.072	0.000	37.484	70.598	40.167
RAET1G	1.075	0.000	259.051	545.437	278.410
ITGA3	1.078	0.000	19,506.094	39,289.103	21,030.406
GRIN3B	1.082	0.000	39.219	83.287	42.441
HTR7	1.082	0.000	397.359	806.172	430.059
RNASE7	1.083	0.000	957.164	1,768.690	1,036.277
PLK2	1.083	0.000	3,994.414	8,623.563	4,327.027
IL1F10	1.084	0.004	52.203	102.391	56.575
KY	1.088	0.001	64.027	114.529	69.660
PGLYRP4	1.093	0.000	490.180	1,008.356	535.725
GJB2	1.093	0.000	40,188.875	86,219.517	43,923.287
S100A7	1.096	0.000	24,061.293	51,490.448	26,363.236
RHOD	1.096	0.000	4,156.910	8,960.287	4,557.802
PTHLH	1.099	0.000	8,271.551	16,801.115	9,086.801
FABP5	1.100	0.000	10,549.762	22,478.011	11,607.895
TUBB2A	1.104	0.000	4,978.031	10,697.736	5,497.029
APLN	1.105	0.000	416.496	850.494	460.358
HBA1	1.108	0.001	227.039	486.115	251.637
SLC35F3	1.118	0.000	162.492	326.494	181.617
SDR9C7	1.119	0.000	295.570	631.471	330.861
WISP3	1.121	0.002	151.133	300.552	169.414
GPR1	1.122	0.000	319.375	692.690	358.234
KIF12	1.124	0.000	59.801	115.103	67.202
DLX4	1.128	0.000	133.223	257.345	150.304
TTLL11	1.129	0.000	136.559	299.195	154.110
BIRC2	1.129	0.000	3,326.508	7,288.368	3,755.991
HAS1	1.138	0.000	75.145	165.759	85.501
FAM25A	1.139	0.002	1,073.637	2,047.115	1,222.402
ZBED2	1.140	0.000	1,134.711	2,427.897	1,293.653
NT5E	1.140	0.000	2,174.945	4,454.471	2,479.865
OTUD1	1.149	0.000	1,021.172	2,206.414	1,173.043
SLCO4A1	1.152	0.000	585.520	1,222.793	674.730
FAM83A	1.156	0.000	7,327.543	16,358.310	8,471.081
SPRR2B	1.159	0.005	2,251.820	4,118.345	2,610.779
CA2	1.160	0.000	4,464.574	8,068.690	5,179.793
KRT16	1.161	0.000	200,500.680	415,933.138	232,748.111
HCG4	1.163	0.000	160.371	352.069	186.544
TPPP3	1.165	0.000	2,149.582	4,539.920	2,504.885
LEPREL1	1.169	0.000	4,251.813	9,386.356	4,971.056
SCN2B	1.171	0.000	32.676	72.138	38.251
NHLH2	1.172	0.000	46.281	97.241	54.255
LAMC2	1.175	0.000	55,397.234	129,553.115	65,095.922
RAPGEF3	1.179	0.000	545.430	1,203.138	642.969
SFTPD	1.182	0.000	52.324	92.920	61.868
PCDH7	1.184	0.000	2,872.086	5,941.793	3,401.419
MYO3B	1.190	0.000	134.238	301.897	159.734
NIPAL4	1.192	0.000	2,401.820	5,681.034	2,863.438

LAMA3	1.194	0.000	18,737.039	40,901.506	22,366.604
GALNT6	1.197	0.000	2,624.422	5,781.506	3,140.457
SLITRK6	1.199	0.000	939.063	2,099.161	1,125.585
HTR1D	1.199	0.000	40.520	83.069	48.588
RIMS3	1.202	0.000	471.422	1,020.333	566.770
SLC22A1	1.203	0.000	48.066	94.805	57.803
FOSB	1.204	0.000	3,885.824	8,943.414	4,678.494
PPP2R2C	1.206	0.000	3,319.754	7,363.011	4,005.281
SLC5A10	1.211	0.000	51.516	122.724	62.365
FSTL3	1.215	0.000	2,627.160	5,568.690	3,193.027
SH3TC2	1.216	0.000	147.512	334.713	179.353
SPTLC3	1.218	0.000	543.621	1,234.506	662.027
D4S234E	1.219	0.000	919.922	2,053.989	1,121.013
C12orf70	1.219	0.000	33.531	76.379	40.862
C11orf63	1.220	0.000	173.332	382.080	211.419
FLRT2	1.222	0.000	1,951.133	4,093.828	2,383.519
PAQR5	1.226	0.000	925.125	2,100.736	1,133.853
LETM2	1.227	0.000	162.914	364.414	199.823
KLK5	1.233	0.000	3,788.430	7,735.874	4,669.260
CRCT1	1.233	0.000	1,678.801	3,586.839	2,069.662
FGFBP1	1.246	0.000	14,707.930	33,479.241	18,325.066
CSPG4	1.246	0.000	7,166.234	14,931.770	8,929.661
WNT7A	1.247	0.000	333.703	736.828	416.085
ODZ2	1.252	0.000	5,892.359	13,656.011	7,374.744
SLC16A2	1.256	0.000	746.051	1,744.356	937.405
ANO4	1.268	0.002	50.102	88.598	63.542
USP2	1.272	0.000	325.277	805.529	413.700
CXCL14	1.275	0.000	32,275.711	61,637.069	41,143.802
GNRHR	1.277	0.000	35.875	100.874	45.814
IFFO2	1.279	0.000	6,091.715	14,468.310	7,789.199
LCE3D	1.279	0.000	2,640.383	5,508.816	3,378.345
NFE2	1.282	0.000	46.348	102.379	59.409
KIAA1644	1.285	0.000	566.891	1,130.287	728.593
KRT6C	1.295	0.000	68,752.621	171,297.989	89,055.868
IL11	1.301	0.000	272.828	607.023	354.851
FAM178B	1.305	0.000	112.637	198.885	146.956
CYP27C1	1.305	0.000	484.367	1,072.747	632.221
WNT10A	1.309	0.000	961.988	2,140.299	1,259.116
GOLGA7B	1.311	0.000	1,042.883	2,552.897	1,367.605
VEGFC	1.312	0.000	800.090	1,926.103	1,049.601
EFR3B	1.313	0.000	129.738	334.908	170.376
CGB	1.314	0.000	115.320	60.345	151.576
FIGN	1.318	0.000	61.535	138.851	81.110
BMP2	1.319	0.000	1,326.816	3,126.092	1,750.017
PPP4R4	1.326	0.000	242.551	529.379	321.549
IGFBP6	1.327	0.000	5,585.871	13,594.920	7,411.669
CAV1	1.331	0.000	16,410.590	40,830.931	21,836.182
CGB5	1.335	0.001	64.723	40.828	86.428
RUNDC3A	1.336	0.000	118.238	328.782	157.936
FGF5	1.336	0.001	33.309	74.655	44.495
PLP1	1.336	0.000	36.219	89.310	48.397
TSPAN10	1.338	0.000	288.305	722.989	385.722
EREG	1.346	0.000	1,707.813	3,603.690	2,299.024
LHX1	1.346	0.001	32.219	71.356	43.382
CLVS1	1.351	0.000	35.273	111.713	47.647
THSD1	1.353	0.000	763.813	1,850.034	1,033.707
SLC38A4	1.359	0.000	182.563	476.690	248.059
TRIM58	1.360	0.000	85.324	193.885	116.078
BPIL2	1.361	0.001	128.996	387.345	175.545
DLX3	1.363	0.000	413.203	1,007.057	562.996
INHBA	1.363	0.000	1,945.164	4,266.552	2,651.955
KRT10	1.365	0.000	17,023.805	44,338.437	23,245.192
GUCY2C	1.367	0.000	90.852	81.931	124.199
RGS20	1.369	0.000	430.473	1,082.483	589.182
SLC22A3	1.381	0.000	522.996	1,243.701	722.463
STEAP4	1.388	0.000	1,682.719	3,885.345	2,335.370
CDA	1.394	0.000	924.121	2,395.563	1,288.292

ENKUR	1.395	0.000	36.387	87.931	50.755
GJB6	1.403	0.000	13,299.574	33,256.678	18,665.407
IRX1	1.405	0.000	97.520	208.115	137.011
PTGS1	1.415	0.000	2,650.844	6,882.115	3,751.651
GRIA3	1.418	0.000	65.098	134.448	92.322
CCBE1	1.418	0.000	69.855	183.690	99.085
CASP14	1.421	0.002	574.586	1,378.667	816.384
EPGN	1.436	0.000	218.313	536.471	313.423
LOC100131726	1.439	0.000	129.578	345.897	186.427
VSIG8	1.446	0.000	441.688	1,015.713	638.476
TRIML2	1.448	0.001	82.164	170.103	118.954
MT1L	1.450	0.000	148.813	262.805	215.767
TRHDE	1.459	0.000	38.598	71.575	56.330
CYP26B1	1.485	0.000	799.379	1,960.770	1,187.371
PTGS2	1.487	0.000	2,473.750	5,849.782	3,679.206
DHRS2	1.492	0.000	2,007.410	587.000	2,994.850
FAM46B	1.493	0.000	2,163.184	5,803.011	3,229.374
F3	1.493	0.000	6,836.051	19,174.586	10,208.048
CYP39A1	1.495	0.000	225.395	595.218	336.948
RET	1.500	0.000	157.340	387.816	236.030
LIPC	1.502	0.000	32.461	81.839	48.741
PNLIPRP3	1.502	0.000	360.625	1,027.552	541.512
VIT	1.508	0.000	97.793	221.253	147.481
KANK4	1.515	0.000	344.008	806.207	521.095
MMP1	1.522	0.000	25,217.391	65,474.069	38,390.673
ELAVL2	1.534	0.000	148.793	344.276	228.312
C1orf68	1.537	0.000	51.012	128.299	78.408
KCNK10	1.538	0.000	245.887	578.437	378.211
DSCAM	1.546	0.000	47.941	128.172	74.094
DSC1	1.549	0.000	1,075.938	2,756.494	1,667.046
POU3F1	1.550	0.000	500.012	1,236.816	775.026
NRG1	1.551	0.000	876.332	2,654.253	1,359.038
DEFB4A	1.557	0.000	721.246	1,585.690	1,122.651
CXCR1	1.563	0.000	93.285	223.609	145.765
PAEP	1.564	0.000	59.141	113.989	92.520
NTSR1	1.568	0.000	63.813	153.276	100.070
KRT2	1.580	0.002	292.598	946.920	462.373
COL17A1	1.581	0.000	40,059.832	114,941.138	63,338.073
MICALCL	1.588	0.000	262.180	704.402	416.277
SPRR2G	1.589	0.000	4,703.199	12,046.678	7,471.820
SFTPA2	1.592	0.000	28.387	121.080	45.183
TLL1	1.600	0.000	287.469	756.621	459.854
CDH16	1.601	0.000	182.219	488.414	291.675
MMP13	1.615	0.000	8,421.043	24,863.874	13,601.992
AREG	1.625	0.000	1,884.480	5,066.667	3,061.754
PPBP	1.636	0.000	42.105	112.851	68.886
DSG1	1.637	0.000	10,348.375	29,314.046	16,941.012
CDHR1	1.652	0.000	865.148	2,350.724	1,428.815
KRT3	1.655	0.000	150.488	677.678	249.087
L1CAM	1.658	0.000	572.051	1,409.391	948.566
CWH43	1.666	0.000	494.336	1,282.816	823.547
ZNF474	1.672	0.000	42.406	142.931	70.917
AJAP1	1.673	0.000	234.387	661.299	392.157
IL1A	1.690	0.000	1,490.746	4,739.621	2,519.618
IGFL2	1.702	0.000	321.863	891.046	547.931
HEPHL1	1.724	0.000	3,466.359	11,140.897	5,976.193
NCRNA00162	1.732	0.000	93.762	220.310	162.412
IGFL1	1.735	0.000	1,300.738	4,490.414	2,256.610
SH2D5	1.738	0.000	497.063	1,606.517	863.954
ANXA13	1.770	0.000	20.766	60.517	36.759
IL1RL1	1.777	0.000	125.945	457.023	223.821
MMP10	1.792	0.000	5,618.688	20,958.011	10,070.004
PCDHGC5	1.798	0.000	184.480	547.908	331.623
DLX2	1.806	0.000	71.652	195.310	129.381
LGALS9C	1.808	0.000	268.949	928.770	486.276
NGF	1.812	0.000	64.906	217.977	117.605
KRT1	1.840	0.000	17,243.148	59,864.333	31,732.729

ARL14	1.859	0.000	108.816	375.103	202.267
SCN4B	1.868	0.000	241.129	871.506	450.384
SLC6A11	1.906	0.000	271.781	950.092	518.078
CCDC147	1.937	0.000	21.875	102.092	42.381
FLRT3	1.952	0.000	1,023.293	3,450.310	1,997.566
MMP3	1.960	0.000	3,947.957	14,005.034	7,737.255
XIST	1.961	0.004	1,663.695	2,640.678	3,262.140
KRT75	2.008	0.000	1,730.867	7,326.655	3,474.932
LGALS9B	2.018	0.000	56.535	225.494	114.083
PSORS1C1	2.021	0.000	33.145	128.425	66.986
C10orf67	2.108	0.000	21.723	80.437	45.788
LAMB4	2.152	0.000	30.551	103.667	65.760
IL20	2.167	0.000	66.738	306.080	144.639
MYO7B	2.170	0.000	99.180	288.713	215.259
C11orf70	2.189	0.000	69.281	184.276	151.651
IL24	2.191	0.000	591.477	2,302.069	1,296.166
CSF2	2.228	0.000	91.785	372.678	204.455
DEFB103B	2.243	0.000	498.387	1,937.161	1,117.776
CNGB1	2.282	0.000	403.754	1,737.517	921.477
ALPP	2.297	0.000	21.582	58.828	49.568
SPINK6	2.346	0.000	518.195	1,445.759	1,215.546
ADRB2	2.435	0.000	411.270	2,224.575	1,001.637
MYO16	2.466	0.000	23.727	109.632	58.506
ZFP42	2.475	0.000	109.352	168.793	270.593
GDPD2	2.476	0.000	293.141	1,467.011	725.753
GFAP	2.576	0.000	36.281	200.908	93.470
PSG4	2.594	0.000	65.945	450.655	171.043
SFTA1P	2.650	0.000	23.020	92.092	61.008
TH	3.021	0.000	64.680	299.080	195.388
PSG5	3.044	0.000	35.188	54.782	107.116
FOLR3	3.090	0.000	53.559	389.414	165.499
SLC6A2	3.695	0.000	63.535	724.379	234.791
IFNK	3.777	0.000	11.938	114.080	45.083

Supplementary file 3. Complete list of the upregulated and downregulated processes in HNSCC with ADRB2^{high} / SLC6A2^{high} expression according to GO analysis.

Upregulated processes in ADRB2^{high} / SLC6A2^{high} HNSCCs

GO	ID	Description	Gene Ratio	p.adjust	Count	geneID
BP	GO:0008544	epidermis development	38/225	5.67E-21	38	COL17A1/CYP26B1/APCDD1/KRT75/IL20/KRT6C/POU3F1/LAMA3/WNT10A/LAMC2/CYP27B1/KRT16/INHBA/KRT6B/SPINK6/FABP5/HOXC13/PTHLH/KRT14/DSG1/KRT10/KRT1/SPRR2G/EREG/SLITRK6/HES5/DSC1/C1orf68/KLK5/LCE3D/KRT3/S100A7/SPRR2E/KRT2/CASP14/CDSN/SPRR2B/LCE3E
BP	GO:0043588	skin development	32/225	7.12E-17	32	CYP26B1/ITGA3/APCDD1/KRT75/IL20/KRT6C/POU3F1/WNT10A/CYP27B1/KRT16/INHBA/KRT6B/SPINK6/HOXC13/KRT14/DSG1/KRT10/KRT1/SPRR2G/EREG/DSC1/C1orf68/KLK5/LCE3D/KRT3/S100A7/SPRR2E/KRT2/CASP14/CDSN/SPRR2B/LCE3E
BP	GO:0009913	epidermal cell differentiation	29/225	4.80E-16	29	CYP26B1/KRT75/IL20/KRT6C/POU3F1/CYP27B1/KRT16/KRT6B/SPINK6/KRT14/DSG1/KRT10/KRT1/SPRR2G/EREG/SLITRK6/HES5/DSC1/C1orf68/KLK5/LCE3D/KRT3/S100A7/SPRR2E/KRT2/CASP14/CDSN/SPRR2B/LCE3E
MF	GO:0048018	receptor ligand activity	28/225	2.04E-11	28	NRG1/BMP2/IL24/CSF2/NGF/IL1A/FLRT3/AREG/IL20/IFNK/VEGFC/IL11/APLN/WNT10A/FLRT2/DEFB103B/INHBA/CXCL14/PTHLH/WNT7A/PPBP/EREG/EPGN/CGB3/DEFB4A/FGF5/CCN6/IL1F10
MF	GO:0030546	signaling receptor activator activity	28/225	2.59E-11	28	NRG1/BMP2/IL24/CSF2/NGF/IL1A/FLRT3/AREG/IL20/IFNK/VEGFC/IL11/APLN/WNT10A/FLRT2/DEFB103B/INHBA/CXCL14/PTHLH/WNT7A/PPBP/EREG/EPGN/CGB3/DEFB4A/FGF5/CCN6/IL1F10
BP	GO:0030216	keratinocyte differentiation	27/225	5.82E-16	27	CYP26B1/KRT75/IL20/KRT6C/POU3F1/CYP27B1/KRT16/KRT6B/SPINK6/KRT14/DSG1/KRT10/KRT1/SPRR2G/EREG/DSC1/C1orf68/KLK5/LCE3D/KRT3/S100A7/SPRR2E/KRT2/CASP14/CDSN/SPRR2B/LCE3E
BP	GO:0031424	keratinization	21/225	3.86E-13	21	CYP26B1/KRT75/KRT6C/KRT16/KRT6B/SPINK6/KRT14/DSG1/KRT10/KRT1/SPRR2G/DSC1/KLK5/LCE3D/KRT3/SPRR2E/KRT2/CASP14/CDSN/SPRR2B/LCE3E
BP	GO:0070268	cornification	20/225	4.37E-18	20	CYP26B1/KRT75/KRT6C/KRT16/KRT6B/SPINK6/KRT14/DSG1/KRT10/KRT1/SPRR2G/DSC1/KLK5/LCE3D/KRT3/SPRR2E/KRT2/CASP14/CDSN/SPRR2B
BP	GO:0030198	extracellular matrix organization	17/225	2.51E-06	17	COL17A1/MMP3/ITGA3/LAMB4/TLL1/LAMA3/FLRT2/VIT/MMP1/LAMC2/MMP10/MMP28/MMP13/COL4A6/HAS1/KLK5/NR2E1
BP	GO:0043062	extracellular structure organization	17/225	2.60E-06	17	COL17A1/MMP3/ITGA3/LAMB4/TLL1/LAMA3/FLRT2/VIT/MMP1/LAMC2/MMP10/MMP28/MMP13/COL4A6/HAS1/KLK5/NR2E1
BP	GO:0034329	cell junction assembly	16/225	3.88E-05	16	COL17A1/NRG1/CAV1/FLRT3/RHOD/LAMA3/FLRT2/LAMC2/GJB2/KRT14/WNT7A/DSG1/SLITRK6/NLGN4X/DNER/DSCAM
BP	GO:0048871	multicellular organismal homeostasis	16/225	0.00028	16	ADRB2/CYP26B1/CAV1/CNGB1/CDHR1/IL1A/VSIG1/APLN/PTGS2/SFTPD/KRT16/CA2/FABP5/KRT1/NTSR1/SFTPA2

BP	GO:00 50900	leukocyte migration	14/225	0.00303	14	CAV1/RET/ITGA3/VEGFC/L1CAM/CXCR1/SFTPD/ MMP1/CXCL14/PPBP/MMP28/S100A12/S100A7/IL 1F10
CC	GO:00 62023	collagen-containing extracellular matrix	14/234	0.00037	14	COL17A1/F3/LAMB4/L1CAM/LAMA3/CSPG4/VIT/L AMC2/P3H2/SLPI/MMP28/KRT1/COL4A6/S100A7
MF	GO:00 05125	cytokine activity	14/225	8.95E-07	14	NRG1/BMP2/IL24/CSF2/IL1A/AREG/IL20/IFNK/IL11 /INHBA/CXCL14/WNT7A/PPBP/IL1F10
MF	GO:00 05126	cytokine receptor binding	14/225	1.86E-05	14	BMP2/CSF2/NGF/IL1A/IL20/IFNK/VEGFC/IL11/DEF B103B/INHBA/CXCL14/PPBP/DEFB4A/IL1F10
BP	GO:00 98742	cell-cell adhesion via plasma-membrane adhesion molecules	13/225	2.86E-05	13	BMP2/CDHR1/RET/FLRT3/TENM2/L1CAM/PCDH7/ PCDHGC5/DSG1/CDH16/DSC1/LGALS7B/DSCAM
BP	GO:00 42063	gliogenesis	13/225	5.33E-05	13	NRG1/BMP2/DLX2/AREG/SH3TC2/POU3F1/CSPG 4/DLX1/HES5/PLP1/DNER/FGF5/NR2E1
BP	GO:00 48608	reproductive structure development	13/225	0.00228	13	BIRC2/CSF2/FSTL3/DLX3/FOSL1/PTGS2/CYP27B 1/GJB2/INHBA/WNT7A/EREG/ZFP42/LHX1
BP	GO:00 61458	reproductive system development	13/225	0.00242	13	BIRC2/CSF2/FSTL3/DLX3/FOSL1/PTGS2/CYP27B 1/GJB2/INHBA/WNT7A/EREG/ZFP42/LHX1
BP	GO:00 99177	regulation of trans-synaptic signaling	13/225	0.00257	13	ADRB2/PLK2/NGF/RIMS3/NSG1/PTGS2/CA2/FABP 5/SORCS2/WNT7A/NTSR1/NLGN4X/NR2E1
CC	GO:00 97060	synaptic membrane	13/234	0.00205	13	SLC6A2/SH2D5/FLRT3/ITGA3/SLC6A11/RIMS3/NS G1/FOSL1/TENM2/GRIA3/FABP5/NLGN4X/GRIN3B
MF	GO:00 08083	growth factor activity	13/225	1.68E-07	13	NRG1/BMP2/CSF2/NGF/AREG/VEGFC/IL11/INHBA /PPBP/EREG/EPGN/FGF5/CCN6
BP	GO:00 43010	camera-type eye development	12/225	0.00051	12	TH/DLX2/RET/INHBA/DLX1/WNT7A/SLITRK6/HES 5/DIO3/DSCAM/LHX1/NR2E1
BP	GO:00 32496	response to lipopolysaccharide	12/225	0.00069	12	NOCT/TH/IL24/CSF2/GJB6/PTGS2/CYP27B1/GJB2 /SLPI/PPBP/S100A7/IL1F10
BP	GO:00 02237	response to molecule of bacterial origin	12/225	0.00097	12	NOCT/TH/IL24/CSF2/GJB6/PTGS2/CYP27B1/GJB2 /SLPI/PPBP/S100A7/IL1F10
BP	GO:00 06959	humoral immune response	12/225	0.00133	12	IFNK/SFTPD/DEFB103B/SLPI/PPBP/PGLYRP4/RN ASE7/KRT1/KLK5/S100A12/S100A7/DEFB4A
BP	GO:00 01654	eye development	12/225	0.00153	12	TH/DLX2/RET/INHBA/DLX1/WNT7A/SLITRK6/HES 5/DIO3/DSCAM/LHX1/NR2E1
BP	GO:00 18108	peptidyl-tyrosine phosphorylation	12/225	0.00157	12	NRG1/CAV1/IL24/CSF2/RET/AREG/IL20/IL11/CSP G4/EREG/EPGN/HES5
BP	GO:00 18212	peptidyl-tyrosine modification	12/225	0.00168	12	NRG1/CAV1/IL24/CSF2/RET/AREG/IL20/IL11/CSP G4/EREG/EPGN/HES5
BP	GO:01 50063	visual system development	12/225	0.00168	12	TH/DLX2/RET/INHBA/DLX1/WNT7A/SLITRK6/HES 5/DIO3/DSCAM/LHX1/NR2E1
BP	GO:00 48880	sensory system development	12/225	0.00188	12	TH/DLX2/RET/INHBA/DLX1/WNT7A/SLITRK6/HES 5/DIO3/DSCAM/LHX1/NR2E1
BP	GO:00 30900	forebrain development	12/225	0.00234	12	NRG1/BMP2/TH/DLX2/POU3F1/INHBA/DLX1/WNT 7A/DNAH5/HES5/LHX1/NR2E1
BP	GO:00 50673	epithelial cell proliferation	12/225	0.00658	12	CAV1/F3/BMP2/AREG/VEGFC/FGFBP1/APLN/WN T7A/EREG/EPGN/HES5/KRT2

BP	GO:0050804	modulation of chemical synaptic transmission	12/225	0.00681	12	ADRB2/PLK2/NGF/RIMS3/NSG1/PTGS2/CA2/SORCS2/WNT7A/NTSR1/NLGN4X/NR2E1
BP	GO:0001667	ameboidal-type cell migration	12/225	0.01051	12	PLK2/RET/ITGA3/VEGFC/FGFBP1/PTGS2/KRT16/CCBE1/WNT7A/HAS1/KRT2/NR2E1
BP	GO:0001819	positive regulation of cytokine production	12/225	0.01085	12	LGALS9C/BIRC2/LGALS9B/CSF2/IL1A/IL1RL1/RAET1G/PTGS2/CCBE1/EREG/PAEP/IL1F10
CC	GO:0001533	cornified envelope	12/234	1.36E-11	12	DSG1/KRT10/KRT1/SPRR2G/DSC1/C1orf68/LCE3D/SPRR2E/KRT2/CDSN/SPRR2B/LCE3E
CC	GO:0005882	intermediate filament	12/234	1.01E-05	12	IFFO2/KRT75/KRT6C/KRT16/KRT6B/KRT14/KRT10/GFAP/KRT1/KRT3/KRT2/CASP14
CC	GO:0045111	intermediate filament cytoskeleton	12/234	4.87E-05	12	IFFO2/KRT75/KRT6C/KRT16/KRT6B/KRT14/KRT10/GFAP/KRT1/KRT3/KRT2/CASP14
MF	GO:0004175	endopeptidase activity	12/225	0.0087	12	F3/MMP3/PRSS23/USP2/TLL1/MMP1/MMP10/MMP28/PROC/MMP13/KLK5/CASP14
BP	GO:0010001	glial cell differentiation	11/225	7.06E-05	11	NRG1/BMP2/DLX2/SH3TC2/POU3F1/DLX1/HES5/PLP1/DNER/FGF5/NR2E1
BP	GO:0050730	regulation of peptidyl-tyrosine phosphorylation	11/225	0.00029	11	NRG1/CAV1/IL24/CSF2/AREG/IL20/IL11/CSPG4/EREG/EPGN/HES5
BP	GO:0060326	cell chemotaxis	11/225	0.0012	11	VEGFC/CXCR1/SFTPD/DEFB103B/CXCL14/PPBP/MMP28/S100A12/S100A7/DEFB4A/IL1F10
BP	GO:0042742	defense response to bacterium	11/225	0.00229	11	SFTPD/DEFB103B/ISG15/SLPI/PPBP/PGLYRP4/RNASE7/KLK5/S100A12/S100A7/DEFB4A
BP	GO:0050678	regulation of epithelial cell proliferation	11/225	0.00632	11	CAV1/F3/BMP2/AREG/VEGFC/FGFBP1/APLN/WNT7A/EREG/EPGN/HES5
BP	GO:0001503	ossification	11/225	0.00913	11	ADRB2/GDPD2/NOCT/BMP2/AREG/FSTL3/PTGS2/CYP27B1/ISG15/PTHLH/MMP13
BP	GO:0050808	synapse organization	11/225	0.01085	11	NRG1/FLRT3/ITGA3/L1CAM/FLRT2/PCDHGC5/WNT7A/SLITRK6/NLGN4X/DNER/DSCAM
BP	GO:0042391	regulation of membrane potential	11/225	0.01651	11	ADRB2/SCN4B/CAV1/RIMS3/GRIA3/KCNK10/WNT7A/SCN2B/NTSR1/NLGN4X/CCN6
BP	GO:1903706	regulation of hemopoiesis	11/225	0.02956	11	CYP26B1/CSF2/FSTL3/IL20/NFE2/INHBA/CA2/ISG15/PGLYRP4/HES5/TRIM58
CC	GO:0005769	early endosome	11/234	0.00321	11	ADRB2/CAV1/RET/RHOD/NSG1/STEAP4/SORCS2/LIPG/CD207/CLVS1/DNER
CC	GO:0098793	presynapse	11/234	0.03309	11	SLC6A2/TH/CNGB1/NGF/FLRT3/SLC6A11/RIMS3/FOSL1/WNT7A/NTSR1/NLGN4X
MF	GO:0070851	growth factor receptor binding	11/225	1.15E-06	11	CSF2/IL1A/FLRT3/AREG/VEGFC/IL11/FLRT2/EREG/EPGN/FGF5/IL1F10
MF	GO:0046873	metal ion transmembrane transporter activity	11/225	0.02517	11	SLC6A2/SCN4B/SLC6A11/SLC5A10/SLC22A3/NIPAL4/KCNK10/SCN2B/SLC10A6/SLC22A1/GRIN3B
BP	GO:0019730	antimicrobial humoral response	10/225	2.25E-06	10	SFTPD/DEFB103B/SLPI/PPBP/PGLYRP4/RNASE7/KLK5/S100A12/S100A7/DEFB4A
BP	GO:0007565	female pregnancy	10/225	0.00012	10	PSG4/ITGA3/PSG5/FOSL1/PTGS2/CYP27B1/GJB2/FOSB/PTHLH/DSG1

BP	GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	10/225	0.00012	10	NRG1/IL24/CSF2/AREG/IL20/IL11/CSPG4/EREG/EPGN/HES5
BP	GO:0015893	drug transport	10/225	0.0002	10	SLC6A2/FOLR3/SLC22A3/INHBA/CA2/SLC35F3/SLC47A2/NTSR1/SLC22A1/HBA1
BP	GO:0044706	multi-multicellular organism process	10/225	0.00037	10	PSG4/ITGA3/PSG5/FOSL1/PTGS2/CYP27B1/GJB2/FOSB/PTHLH/DSG1
BP	GO:0021537	telencephalon development	10/225	0.00091	10	NRG1/BMP2/TH/DLX2/INHBA/DLX1/DNAH5/HES5/LHX1/NR2E1
BP	GO:0006836	neurotransmitter transport	10/225	0.00167	10	SLC6A2/TH/CSF2/SLC6A11/RIMS3/APLN/SLC22A3/WNT7A/NTSR1/SLC22A1
BP	GO:0010721	negative regulation of cell development	10/225	0.00911	10	PLK2/NRG1/DLX2/DLX1/PTHLH/WNT7A/PAEP/HES5/DIO3/NR2E1
BP	GO:0010631	epithelial cell migration	10/225	0.01059	10	PLK2/ITGA3/VEGFC/FGFBP1/PTGS2/KRT16/CCBE1/WNT7A/KRT2/NR2E1
BP	GO:0090132	epithelium migration	10/225	0.01119	10	PLK2/ITGA3/VEGFC/FGFBP1/PTGS2/KRT16/CCBE1/WNT7A/KRT2/NR2E1
BP	GO:0090130	tissue migration	10/225	0.01247	10	PLK2/ITGA3/VEGFC/FGFBP1/PTGS2/KRT16/CCBE1/WNT7A/KRT2/NR2E1
BP	GO:0045765	regulation of angiogenesis	10/225	0.01811	10	RAPGEF3/PLK2/F3/IL1A/VEGFC/FGFBP1/PTGS2/CCBE1/KRT1/NR2E1
BP	GO:0048545	response to steroid hormone	10/225	0.01811	10	CAV1/TH/AREG/FOSL1/PTGS2/GJB2/CA2/FOSB/DSG1/NR2E1
BP	GO:0030099	myeloid cell differentiation	10/225	0.02983	10	CSF2/FSTL3/IL20/IL11/NFE2/INHBA/CA2/ISG15/DHRS2/TRIM58
CC	GO:0005911	cell-cell junction	10/234	0.02732	10	SCN4B/COL17A1/FLRT3/GJB6/FLRT2/AJAP1/GJB2/DSG1/DSC1/CDSN
MF	GO:0015291	secondary active transmembrane transporter activity	10/225	0.00094	10	SLC6A2/SLC16A2/SLC6A11/SLCO4A1/SLC5A10/SLC38A4/SLC22A3/SLC10A6/SLC47A2/SLC22A1
MF	GO:0022804	active transmembrane transporter activity	10/225	0.01411	10	SLC6A2/SLC16A2/SLC6A11/SLCO4A1/SLC5A10/SLC38A4/SLC22A3/SLC10A6/SLC47A2/SLC22A1
BP	GO:0007156	homophilic cell adhesion via plasma membrane adhesion molecules	9/225	0.00021	9	CDHR1/RET/L1CAM/PCDH7/PCDHGC5/DSG1/CDH16/DSC1/DSCAM
BP	GO:0050806	positive regulation of synaptic transmission	9/225	0.00021	9	ADRB2/PLK2/RIMS3/NSG1/PTGS2/CA2/WNT7A/NTSR1/NR2E1
BP	GO:0045766	positive regulation of angiogenesis	9/225	0.00085	9	RAPGEF3/PLK2/F3/IL1A/VEGFC/FGFBP1/PTGS2/CCBE1/NR2E1
BP	GO:0030595	leukocyte chemotaxis	9/225	0.00163	9	VEGFC/CXCR1/SFTPD/CXCL14/PPBP/MMP28/S100A12/S100A7/IL1F10
BP	GO:0001894	tissue homeostasis	9/225	0.00189	9	ADRB2/CNGB1/CDHR1/VSIG1/PTGS2/SFTPD/CA2/KRT1/SFTPA2
BP	GO:1904018	positive regulation of vasculature development	9/225	0.00195	9	RAPGEF3/PLK2/F3/IL1A/VEGFC/FGFBP1/PTGS2/CCBE1/NR2E1
BP	GO:0007611	learning or memory	9/225	0.00398	9	PLK2/TH/NGF/ITGA3/FOSL1/PTGS2/KCNK10/NTSR1/NLGN4X

BP	GO:0090596	sensory organ morphogenesis	9/225	0.00398	9	CYP26B1/TH/GJB6/HOXC13/SLITRK6/MYO3B/DIO3/DSCAM/LHX1
BP	GO:0045165	cell fate commitment	9/225	0.00574	9	NRG1/CYP26B1/BMP2/DLX2/WNT10A/DLX1/WNT7A/HES5/NR2E1
BP	GO:0001822	kidney development	9/225	0.00674	9	CYP26B1/BMP2/RET/FSTL3/ITGA3/CA2/HES5/IRX1/LHX1
BP	GO:0090287	regulation of cellular response to growth factor stimulus	9/225	0.00915	9	CAV1/FSTL3/ITGA3/VEGFC/FGFBP1/APLN/DLX1/CCBE1/HES5
BP	GO:0072001	renal system development	9/225	0.00935	9	CYP26B1/BMP2/RET/FSTL3/ITGA3/CA2/HES5/IRX1/LHX1
BP	GO:0048511	rhythmic process	9/225	0.00975	9	NOCT/TH/CSF2/USP2/INHBA/HTR7/EREG/HAS1/NHLH2
BP	GO:0050890	cognition	9/225	0.00995	9	PLK2/TH/NGF/ITGA3/FOSL1/PTGS2/KCNK10/NTSR1/NLGN4X
BP	GO:0001655	urogenital system development	9/225	0.01897	9	CYP26B1/BMP2/RET/FSTL3/ITGA3/CA2/HES5/IRX1/LHX1
BP	GO:0003002	regionalization	9/225	0.0269	9	CYP26B1/BMP2/DLX2/DLX1/HOXC13/WNT7A/HES5/IRX1/LHX1
BP	GO:0001505	regulation of neurotransmitter levels	9/225	0.02864	9	SLC6A2/CAV1/TH/SLC6A11/RIMS3/PTGS2/SLC22A3/WNT7A/NTSR1
BP	GO:0046394	carboxylic acid biosynthetic process	9/225	0.02864	9	PTGS1/CYP39A1/PTGS2/CSPG4/FABP5/LIPC/LIPG/PLP1/HAS1
BP	GO:0016053	organic acid biosynthetic process	9/225	0.02909	9	PTGS1/CYP39A1/PTGS2/CSPG4/FABP5/LIPC/LIPG/PLP1/HAS1
CC	GO:0005788	endoplasmic reticulum lumen	9/234	0.0118	9	COL17A1/FSTL3/PRSS23/PTGS2/P3H2/LIPC/WNT7A/PROC/COL4A6
CC	GO:0045211	postsynaptic membrane	9/234	0.01536	9	SH2D5/FLRT3/SLC6A11/NSG1/TENM2/GRIA3/FABP5/NLGN4X/GRIN3B
MF	GO:0030246	carbohydrate binding	9/225	0.00802	9	LGALS9C/LGALS9B/GALNT6/SFTPD/P3H2/KRT1/CD207/LGALS7B/SFTPA2
MF	GO:0008509	anion transmembrane transporter activity	9/225	0.02837	9	SLC6A2/SLC16A2/SLC6A11/SLCO4A1/SLC38A4/SLC22A3/SLC10A6/SLC22A1/ANO4
BP	GO:0018149	peptide cross-linking	8/225	5.86E-07	8	KRT10/KRT1/C1orf68/LCE3D/SPRR2E/KRT2/SPRR2B/LCE3E
BP	GO:0042476	odontogenesis	8/225	0.0002	8	BMP2/DLX2/DLX3/WNT10A/INHBA/CA2/DLX1/KLK5
BP	GO:0030856	regulation of epithelial cell differentiation	8/225	0.00062	8	CAV1/IL20/AJAP1/CYP27B1/PROC/HES5/LHX1/CDSN
BP	GO:0007416	synapse assembly	8/225	0.0014	8	NRG1/FLRT3/FLRT2/WNT7A/SLITRK6/NLGN4X/DNER/DSCAM
BP	GO:0050679	positive regulation of epithelial cell proliferation	8/225	0.00359	8	F3/BMP2/AREG/VEGFC/FGFBP1/APLN/WNT7A/EPGN
BP	GO:0097529	myeloid leukocyte migration	8/225	0.00403	8	VEGFC/CXCR1/SFTPD/PPBP/MMP28/S100A12/S100A7/IL1F10

BP	GO:00 42445	hormone metabolic process	8/225	0.00744	8	CYP26B1/BMP2/NGF/CYP27C1/CYP27B1/DHRS2/ DIO3/CGB3
BP	GO:00 72330	monocarboxylic acid biosynthetic process	8/225	0.0082	8	PTGS1/CYP39A1/PTGS2/CSPG4/FABP5/LIPC/LIP G/PLP1
BP	GO:00 45637	regulation of myeloid cell differentiation	8/225	0.01134	8	CSF2/FSTL3/IL20/NFE2/INHBA/CA2/ISG15/TRIM58
BP	GO:00 10632	regulation of epithelial cell migration	8/225	0.02515	8	PLK2/ITGA3/VEGFC/FGFBP1/PTGS2/CCBE1/WNT 7A/NR2E1
BP	GO:00 50768	negative regulation of neurogenesis	8/225	0.02699	8	PLK2/NRG1/DLX2/DLX1/WNT7A/HES5/DIO3/NR2E 1
BP	GO:00 01818	negative regulation of cytokine production	8/225	0.02746	8	LGALS9C/LGALS9B/IL1RL1/SFTPD/INHBA/ISG15/ NAV3/PGLYRP4
BP	GO:00 18105	peptidyl-serine phosphorylation	8/225	0.02892	8	RAPGEF3/PLK2/CAV1/IL24/RET/IFNK/IL11/PTGS2
CC	GO:00 45095	keratin filament	8/234	1.75E-05	8	KRT75/KRT6C/KRT6B/KRT14/KRT1/KRT3/KRT2/C ASP14
CC	GO:00 30136	clathrin-coated vesicle	8/234	0.00187	8	ADRB2/AREG/SFTPD/EREG/EPGN/CD207/CLVS1/ SFTPA2
CC	GO:01 50034	distal axon	8/234	0.02086	8	TH/CNGB1/FLRT3/ITGA3/TENM2/L1CAM/NTSR1/D SCAM
CC	GO:00 30135	coated vesicle	8/234	0.02245	8	ADRB2/AREG/SFTPD/EREG/EPGN/CD207/CLVS1/ SFTPA2
MF	GO:00 20037	heme binding	8/225	0.00033	8	PTGS1/CYP26B1/CYP39A1/CYP27C1/STEAP4/PT GS2/CYP27B1/HBA1
MF	GO:00 15293	symporter activity	8/225	0.00052	8	SLC6A2/SLC16A2/SLC6A11/SLC5A10/SLC38A4/S LC22A3/SLC10A6/SLC22A1
MF	GO:00 46906	tetrapyrrole binding	8/225	0.00054	8	PTGS1/CYP26B1/CYP39A1/CYP27C1/STEAP4/PT GS2/CYP27B1/HBA1
MF	GO:00 15081	sodium ion transmembrane transporter activity	8/225	0.00068	8	SLC6A2/SCN4B/SLC6A11/SLC5A10/SLC22A3/SCN 2B/SLC10A6/SLC22A1
MF	GO:00 16705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	8/225	0.00099	8	PTGS1/CYP26B1/TH/CYP39A1/CYP27C1/PTGS2/ CYP27B1/P3H2
MF	GO:00 08237	metallopeptidase activity	8/225	0.00225	8	MMP3/TLL1/MMP1/MMP10/MMP28/MMP13/CPA4/ TRHDE
MF	GO:00 43177	organic acid binding	8/225	0.00479	8	FOLR3/CYP26B1/TH/CYP27C1/P3H2/FABP5/GRIN 3B/HBA1
MF	GO:00 05539	glycosaminoglycan binding	8/225	0.00913	8	FGFBP1/VIT/LAMC2/LIPC/PGLYRP4/RNASE7/LIP G/CCN6
BP	GO:00 46530	photoreceptor cell differentiation	7/225	1.05E-05	7	TH/CNGB1/DLX2/CDHR1/DLX1/DIO3/DSCAM
BP	GO:00 61844	antimicrobial humoral immune response mediated by antimicrobial peptide	7/225	2.79E-05	7	PPBP/PGLYRP4/RNASE7/KLK5/S100A12/S100A7/ DEFB4A

BP	GO:00 42475	odontogenesis of dentin-containing tooth	7/225	0.00011	7	BMP2/DLX2/DLX3/WNT10A/CA2/DLX1/KLK5
BP	GO:00 42303	molting cycle	7/225	0.00042	7	APCDD1/WNT10A/PTGS2/KRT16/INHBA/HOXC13/ KRT14
BP	GO:00 42633	hair cycle	7/225	0.00042	7	APCDD1/WNT10A/PTGS2/KRT16/INHBA/HOXC13/ KRT14
BP	GO:00 30282	bone mineralization	7/225	0.00046	7	ADRB2/BMP2/PTGS2/CYP27B1/ISG15/PTHLH/MM P13
BP	GO:00 46425	regulation of receptor signaling pathway via JAK-STAT	7/225	0.00138	7	CAV1/IL24/CSF2/RET/IL20/IFNK/HES5
BP	GO:19 04892	regulation of receptor signaling pathway via STAT	7/225	0.00198	7	CAV1/IL24/CSF2/RET/IL20/IFNK/HES5
BP	GO:00 60041	retina development in camera-type eye	7/225	0.00222	7	DLX2/RET/DLX1/DIO3/DSCAM/LHX1/NR2E1
BP	GO:00 01890	placenta development	7/225	0.00249	7	BIRC2/CSF2/DLX3/FOSL1/PTGS2/CYP27B1/GJB2
BP	GO:00 07259	receptor signaling pathway via JAK-STAT	7/225	0.0032	7	CAV1/IL24/CSF2/RET/IL20/IFNK/HES5
BP	GO:00 31214	biomineral tissue development	7/225	0.00367	7	ADRB2/BMP2/PTGS2/CYP27B1/ISG15/PTHLH/MM P13
BP	GO:01 10148	biomineralization	7/225	0.00367	7	ADRB2/BMP2/PTGS2/CYP27B1/ISG15/PTHLH/MM P13
BP	GO:00 97696	receptor signaling pathway via STAT	7/225	0.00447	7	CAV1/IL24/CSF2/RET/IL20/IFNK/HES5
BP	GO:00 10634	positive regulation of epithelial cell migration	7/225	0.00476	7	PLK2/ITGA3/VEGFC/FGFBP1/PTGS2/CCBE1/WNT 7A
BP	GO:00 01659	temperature homeostasis	7/225	0.00507	7	ADRB2/CAV1/IL1A/APLN/PTGS2/FABP5/NTSR1
BP	GO:00 51897	positive regulation of protein kinase B signaling	7/225	0.00556	7	NRG1/F3/RET/AREG/EREG/EPGN/FGF5
BP	GO:00 21953	central nervous system neuron differentiation	7/225	0.00684	7	DLX2/INHBA/DLX1/WNT7A/HES5/LHX1/NR2E1
BP	GO:00 48839	inner ear development	7/225	0.0088	7	BMP2/GJB6/GJB2/CXCL14/SLITRK6/HES5/MYO3B
BP	GO:00 30278	regulation of ossification	7/225	0.01172	7	ADRB2/GDPD2/NOCT/BMP2/AREG/CYP27B1/ISG 15
BP	GO:00 02064	epithelial cell development	7/225	0.01294	7	RAPGEF3/VSIG1/WNT7A/PROC/SLITRK6/KRT2/C DSN
BP	GO:00 51216	cartilage development	7/225	0.01358	7	BMP2/DLX2/VIT/PTHLH/WNT7A/HES5/MMP13
BP	GO:00 43583	ear development	7/225	0.01713	7	BMP2/GJB6/GJB2/CXCL14/SLITRK6/HES5/MYO3B

BP	GO:00 10594	regulation of endothelial cell migration	7/225	0.0213	7	PLK2/VEGFC/FGFBP1/PTGS2/CCBE1/WNT7A/NR 2E1
BP	GO:00 50663	cytokine secretion	7/225	0.02664	7	LGALS9C/LGALS9B/IL1A/IL1RL1/ISG15/PAEP/S10 0A12
BP	GO:00 90092	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	7/225	0.02717	7	CAV1/BMP2/FSTL3/ITGA3/INHBA/DLX1/HES5
BP	GO:00 51896	regulation of protein kinase B signaling	7/225	0.02879	7	NRG1/F3/RET/AREG/EREG/EPGN/FGF5
MF	GO:00 05506	iron ion binding	7/225	0.00334	7	CYP26B1/TH/CYP39A1/CYP27C1/CYP27B1/P3H2/ HBA1
MF	GO:00 31406	carboxylic acid binding	7/225	0.01187	7	FOLR3/CYP26B1/TH/CYP27C1/P3H2/FABP5/GRIN 3B
MF	GO:00 22853	active ion transmembrane transporter activity	7/225	0.03158	7	SLC6A2/SLC6A11/SLCO4A1/SLC5A10/SLC22A3/S LC10A6/SLC22A1
BP	GO:00 45104	intermediate filament cytoskeleton organization	6/225	2.92E-05	6	KRT6C/KRT16/KRT14/GFAP/KRT3/KRT2
BP	GO:00 45103	intermediate filament-based process	6/225	3.28E-05	6	KRT6C/KRT16/KRT14/GFAP/KRT3/KRT2
BP	GO:00 22617	extracellular matrix disassembly	6/225	0.00044	6	MMP3/TLL1/MMP1/MMP10/MMP13/KLK5
BP	GO:00 45682	regulation of epidermis development	6/225	0.00057	6	IL20/CYP27B1/KRT10/HES5/KRT2/CDSN
BP	GO:00 32649	regulation of interferon-gamma production	6/225	0.0014	6	LGALS9C/LGALS9B/IL1RL1/INHBA/ISG15/PGLYR P4
BP	GO:00 33138	positive regulation of peptidyl-serine phosphorylation	6/225	0.00171	6	RAPGEF3/CAV1/RET/IFNK/IL11/PTGS2
BP	GO:00 32609	interferon-gamma production	6/225	0.00248	6	LGALS9C/LGALS9B/IL1RL1/INHBA/ISG15/PGLYR P4
BP	GO:00 32963	collagen metabolic process	6/225	0.00271	6	MMP3/MMP1/P3H2/MMP10/MMP28/MMP13
BP	GO:00 07613	memory	6/225	0.00295	6	PLK2/TH/NGF/ITGA3/PTGS2/KCNK10
BP	GO:00 10595	positive regulation of endothelial cell migration	6/225	0.00459	6	PLK2/VEGFC/FGFBP1/PTGS2/CCBE1/WNT7A
BP	GO:00 46683	response to organophosphorus	6/225	0.00573	6	RAPGEF3/BIRC2/AREG/FOSL1/PTGS2/FOSB
BP	GO:00 07292	female gamete generation	6/225	0.00615	6	FOSL1/PAQR5/PTGS2/INHBA/EREG/CGB3
BP	GO:00 33135	regulation of peptidyl-serine phosphorylation	6/225	0.00682	6	RAPGEF3/CAV1/RET/IFNK/IL11/PTGS2

BP	GO:0038127	ERBB signaling pathway	6/225	0.00755	6	NRG1/AREG/SH3TC2/FAM83A/EREG/EPGN
BP	GO:0072006	nephron development	6/225	0.00755	6	BMP2/RET/ITGA3/HES5/IRX1/LHX1
BP	GO:0035296	regulation of tube diameter	6/225	0.0078	6	ADRB2/CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0044344	cellular response to fibroblast growth factor stimulus	6/225	0.0078	6	FLRT3/FGFBP1/APLN/FLRT2/LHX1/FGF5
BP	GO:0097746	regulation of blood vessel diameter	6/225	0.0078	6	ADRB2/CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0035150	regulation of tube size	6/225	0.00806	6	ADRB2/CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0051384	response to glucocorticoid	6/225	0.0086	6	TH/AREG/FOSL1/PTGS2/GJB2/FOSB
BP	GO:0014074	response to purine-containing compound	6/225	0.00945	6	RAPGEF3/BIRC2/AREG/FOSL1/PTGS2/FOSB
BP	GO:0071774	response to fibroblast growth factor	6/225	0.00975	6	FLRT3/FGFBP1/APLN/FLRT2/LHX1/FGF5
BP	GO:0031960	response to corticosteroid	6/225	0.01386	6	TH/AREG/FOSL1/PTGS2/GJB2/FOSB
BP	GO:0006633	fatty acid biosynthetic process	6/225	0.01465	6	PTGS1/PTGS2/FABP5/LIPC/LIPG/PLP1
BP	GO:0051302	regulation of cell division	6/225	0.01631	6	PLK2/IL1A/VEGFC/PPBP/EREG/FGF5
BP	GO:0003018	vascular process in circulatory system	6/225	0.01953	6	ADRB2/CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0001936	regulation of endothelial cell proliferation	6/225	0.02003	6	CAV1/F3/BMP2/VEGFC/FGFBP1/APLN
BP	GO:0008217	regulation of blood pressure	6/225	0.02316	6	ADRB2/PTGS1/VEGFC/APLN/PTGS2/NTSR1
BP	GO:0002040	sprouting angiogenesis	6/225	0.02372	6	PLK2/VEGFC/FGFBP1/PTGS2/CCBE1/NR2E1
BP	GO:0048167	regulation of synaptic plasticity	6/225	0.02602	6	PLK2/RIMS3/NSG1/PTGS2/SORCS2/NR2E1
BP	GO:0001935	endothelial cell proliferation	6/225	0.02846	6	CAV1/F3/BMP2/VEGFC/FGFBP1/APLN
BP	GO:1901888	regulation of cell junction assembly	6/225	0.0291	6	CAV1/FLRT3/RHOD/FLRT2/WNT7A/SLITRK6
BP	GO:1901654	response to ketone	6/225	0.02974	6	CAV1/TH/FOSL1/GJB2/FOSB/DSG1
CC	GO:0005604	basement membrane	6/234	0.00095	6	COL17A1/LAMB4/LAMA3/LAMC2/P3H2/COL4A6
CC	GO:0005796	Golgi lumen	6/234	0.00137	6	NGF/CSPG4/DEFB103B/WNT7A/PROC/DEFB4A
CC	GO:0031901	early endosome membrane	6/234	0.00882	6	CAV1/NSG1/STEAP4/SORCS2/CD207/CLVS1

MF	GO:0015370	solute:sodium symporter activity	6/225	0.00033	6	SLC6A2/SLC6A11/SLC5A10/SLC22A3/SLC10A6/SLC22A1
MF	GO:0005200	structural constituent of cytoskeleton	6/225	0.00193	6	TUBB2A/KRT16/KRT6B/KRT14/GFAP/KRT2
MF	GO:0004222	metalloendopeptidase activity	6/225	0.00203	6	MMP3/TLL1/MMP1/MMP10/MMP28/MMP13
MF	GO:0015294	solute:cation symporter activity	6/225	0.00203	6	SLC6A2/SLC6A11/SLC5A10/SLC22A3/SLC10A6/SLC22A1
MF	GO:0004252	serine-type endopeptidase activity	6/225	0.01663	6	F3/MMP3/PRSS23/MMP1/PROC/KLK5
MF	GO:0008236	serine-type peptidase activity	6/225	0.02906	6	F3/MMP3/PRSS23/MMP1/PROC/KLK5
MF	GO:0016825	hydrolase activity, acting on acid phosphorus-nitrogen bonds	6/225	0.03184	6	F3/MMP3/PRSS23/MMP1/PROC/KLK5
MF	GO:0017171	serine hydrolase activity	6/225	0.03184	6	F3/MMP3/PRSS23/MMP1/PROC/KLK5
BP	GO:0009954	proximal/distal pattern formation	5/225	3.20E-05	5	CYP26B1/DLX2/DLX1/HES5/IRX1
BP	GO:0032689	negative regulation of interferon-gamma production	5/225	5.88E-05	5	LGALS9C/LGALS9B/IL1RL1/INHBA/PGLYRP4
BP	GO:0032570	response to progesterone	5/225	0.0002	5	CAV1/FOSL1/GJB2/FOSB/DSG1
BP	GO:0030574	collagen catabolic process	5/225	0.00025	5	MMP3/MMP1/MMP10/MMP28/MMP13
BP	GO:0021872	forebrain generation of neurons	5/225	0.00072	5	DLX2/INHBA/DLX1/HES5/NR2E1
BP	GO:0007585	respiratory gaseous exchange by respiratory system	5/225	0.0009	5	APLN/SFTPD/CCBE1/NTSR1/SFTPA2
BP	GO:0060135	maternal process involved in female pregnancy	5/225	0.00104	5	ITGA3/PTGS2/CYP27B1/GJB2/DSG1
BP	GO:0003407	neural retina development	5/225	0.00137	5	DLX2/DLX1/DIO3/DSCAM/LHX1
BP	GO:0045685	regulation of glial cell differentiation	5/225	0.00188	5	BMP2/DLX2/DLX1/HES5/NR2E1
BP	GO:0042310	vasoconstriction	5/225	0.00224	5	CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0042509	regulation of tyrosine phosphorylation of STAT protein	5/225	0.00329	5	CAV1/IL24/CSF2/IL20/HES5
BP	GO:0097756	negative regulation of blood vessel diameter	5/225	0.00347	5	CAV1/APLN/PTGS2/HTR7/HTR1D
BP	GO:0007260	tyrosine phosphorylation of STAT protein	5/225	0.00384	5	CAV1/IL24/CSF2/IL20/HES5

BP	GO:00 51781	positive regulation of cell division	5/225	0.00403	5	IL1A/VEGFC/PPBP/EREG/FGF5
BP	GO:00 45639	positive regulation of myeloid cell differentiation	5/225	0.00488	5	IL20/INHBA/CA2/ISG15/TRIM58
BP	GO:00 32755	positive regulation of interleukin-6 production	5/225	0.00612	5	LGALS9C/LGALS9B/EREG/PAEP/IL1F10
BP	GO:00 07044	cell-substrate junction assembly	5/225	0.00639	5	COL17A1/RHOD/LAMA3/LAMC2/KRT14
BP	GO:00 48709	oligodendrocyte differentiation	5/225	0.00639	5	NRG1/DLX2/DLX1/HES5/PLP1
BP	GO:00 51591	response to cAMP	5/225	0.00639	5	RAPGEF3/BIRC2/AREG/FOSL1/FOSB
BP	GO:01 50115	cell-substrate junction organization	5/225	0.00639	5	COL17A1/RHOD/LAMA3/LAMC2/KRT14
BP	GO:19 01890	positive regulation of cell junction assembly	5/225	0.00756	5	CAV1/FLRT3/FLRT2/WNT7A/SLITRK6
BP	GO:00 06939	smooth muscle contraction	5/225	0.01071	5	ADRB2/CAV1/PTGS2/HTR7/HTR1D
BP	GO:00 01938	positive regulation of endothelial cell proliferation	5/225	0.01152	5	F3/BMP2/VEGFC/FGFBP1/APLN
BP	GO:00 08543	fibroblast growth factor receptor signaling pathway	5/225	0.01236	5	FLRT3/FGFBP1/APLN/FLRT2/FGF5
BP	GO:00 21782	glial cell development	5/225	0.01325	5	NRG1/SH3TC2/POU3F1/HES5/PLP1
BP	GO:00 71621	granulocyte chemotaxis	5/225	0.01669	5	CXCR1/PPBP/S100A12/S100A7/IL1F10
BP	GO:00 14013	regulation of gliogenesis	5/225	0.01723	5	BMP2/DLX2/DLX1/HES5/NR2E1
BP	GO:00 51291	protein heterooligomerizatio n	5/225	0.01949	5	BIRC2/CNGB1/KRT10/KRT1/HBA1
BP	GO:00 42552	myelination	5/225	0.02193	5	NRG1/SH3TC2/POU3F1/HES5/PLP1
BP	GO:00 07272	ensheathment of neurons	5/225	0.02323	5	NRG1/SH3TC2/POU3F1/HES5/PLP1
BP	GO:00 08366	axon ensheathment	5/225	0.02323	5	NRG1/SH3TC2/POU3F1/HES5/PLP1
BP	GO:00 32355	response to estradiol	5/225	0.02323	5	TH/AREG/PTGS2/GJB2/WNT7A
BP	GO:00 50921	positive regulation of chemotaxis	5/225	0.02389	5	F3/VEGFC/CXCL14/S100A7/DSCAM
BP	GO:00 31644	regulation of nervous system process	5/225	0.02526	5	ADRB2/FABP5/WNT7A/NTSR1/NLGN4X
BP	GO:00 50715	positive regulation of cytokine secretion	5/225	0.02667	5	LGALS9C/LGALS9B/IL1A/IL1RL1/PAEP

BP	GO:00 60078	regulation of postsynaptic membrane potential	5/225	0.0274	5	ADRB2/GRIA3/WNT7A/NTSR1/NLGN4X
BP	GO:00 72073	kidney epithelium development	5/225	0.0274	5	BMP2/RET/HES5/IRX1/LHX1
BP	GO:00 97530	granulocyte migration	5/225	0.02814	5	CXCR1/PPBP/S100A12/S100A7/IL1F10
BP	GO:00 08277	regulation of G protein-coupled receptor signaling pathway	5/225	0.02889	5	ADRB2/CNGB1/RGS20/APLN/KLK5
BP	GO:00 07605	sensory perception of sound	5/225	0.03122	5	TH/GJB6/GJB2/SLITRK6/MYO3B
BP	GO:00 07612	learning	5/225	0.03122	5	TH/FOSL1/PTGS2/NTSR1/NLGN4X
CC	GO:00 05581	collagen trimer	5/234	0.00379	5	COL17A1/SFTPD/CCBE1/COL4A6/SFTPA2
CC	GO:00 30665	clathrin-coated vesicle membrane	5/234	0.01206	5	ADRB2/AREG/EREG/EPGN/CD207
CC	GO:00 44306	neuron projection terminus	5/234	0.02453	5	TH/CNGB1/FLRT3/FSTL3/NTSR1
MF	GO:00 04497	monooxygenase activity	5/225	0.00865	5	CYP26B1/TH/CYP39A1/CYP27C1/CYP27B1
MF	GO:00 05178	integrin binding	5/225	0.02682	5	NRG1/ITGA3/LAMA3/ISG15/CCN6
MF	GO:00 03774	motor activity	5/225	0.02998	5	MYO16/MYO7B/KIF12/DNAH5/MYO3B

Downregulated processes in ADRB2^{high} / SLC6A2^{high} HNSCCs

GO	ID	Description	Gene Ratio	p.adjust	Count	geneID
CC	GO:00 62023	collagen-containing extracellular matrix	38/590	5.66E-10	38	MDK/GPC3/COCH/GDF15/SMOC2/FGFR2/FREM2/CTSS/SERPINF1/PTN/NTN1/BMP7/OGN/OMD/APOE/SBSPON/ADAMDEC1/MUC2/PODN/ASPN/DPT/CLU/SULF1/GPC4/PRELP/ELN/CILP/MFAP4/COL4A4/PRG4/COL21A1/COL11A1/SOST/THBS4/COMP/COL19A1/SERPINB12/LGALS4
CC	GO:00 98793	presynapse	34/590	5.60E-06	34	CEL/NTRK2/SLC29A2/NTS/SYNGR3/TMEM163/RAB6B/KCNH1/TSPOAP1/FXYD6/BDNF/PCLO/CTTNBP2/LGI3/ICA1/PTN/SV2B/SYNDIG1/SV2A/KCNK2/CACNA1D/HAP1/GPC4/ADAM23/SLC2A4/SYT2/KCNJ10/PENK/CACNA1B/SLC6A4/GRIN2A/SCN2A/CPLX2/KIF1A
BP	GO:00 48732	gland development	32/572	4.63E-06	32	SOX2/MDK/BCL2/LMO4/LEF1/PBX1/FOXA1/RARB/SIX4/PTCH1/FGFR2/SERPINF1/PTN/IGFBP5/NTN1/BMP7/ELF3/NKX2-3/TG/FA2H/HPN/INSM1/SULF1/HOXB3/HOXA9/ALDH1A2/EGF/SOSTDC1/GLI1/NR5A1/NR0B1/PAX1
BP	GO:00 09410	response to xenobiotic stimulus	30/572	7.50E-09	30	CYP26A1/EPHX1/ARNT2/ALDH3A1/FMO3/GCLC/MARC1/PHGDH/AKR1C1/CES1/GSTM4/CES3/UGT1A7/SERPINF1/UGT1A6/GSTA1/PPP1R1B/UGT1A9/CYP2E1/GSTM3/GSTM2/PPARG/CYP1B1/AADAC/GSTM5/PENK/GRIN2A/UGT1A8/MGST1/SCGB1A1

BP	GO:0007409	axonogenesis	30/572	0.00012	30	NTRK2/EPHA7/BCL2/ARHGAP4/GFRA3/PTCH1/ETV1/FGFR2/BDNF/SLIT2/KEL/NRXN3/RNF165/NTN1/BMP7/NEFH/CRMP1/APOE/MAP1B/UCHL1/RND2/FGF13/NRCAM/NRTN/OLFM1/SPP1/FSTL4/ROBO2/ADGRB1/POU4F1
BP	GO:0001503	ossification	29/572	1.61E-05	29	SOX2/MDK/BCL2/GPC3/LEF1/PBX1/PTCH1/ALOX15/FGFR2/PRKD1/PKDCC/PTN/IGFBP5/BMP7/RORB/OMD/TMEM119/IGSF10/ASPN/ITGA11/GPLD1/CHRDL1/SPP1/PENK/GLI1/COL11A1/SOST/COMP/LTF
BP	GO:0060537	muscle tissue development	29/572	2.56E-05	29	ZBTB18/BCL2/DIPK2A/FZD7/LEF1/RARB/SIX4/HLF/NUPR1/FGFR2/KEL/EYA2/MYH14/IGFBP5/BMP7/PI16/KCNK2/DMRTA2/RBP4/MYH11/ELN/MEGF10/EYA1/ALDH1A2/GLI1/COL11A1/FOXH1/POU4F1/COL19A1
BP	GO:0048568	embryonic organ development	29/572	6.07E-05	29	LRIG1/HEY1/MYO3A/LEF1/PBX1/RARB/SIX4/KRT19/KRT8/PTCH1/FGFR2/OTX1/STOX1/PKDCC/NTN1/BMP7/DLX6/HPN/RBP4/CRB2/HOXB3/EYA1/NKX3-2/ALDH1A2/SLC44A4/GLI1/ALX1/COL11A1/FOXH1
BP	GO:0042391	regulation of membrane potential	29/572	7.76E-05	29	NTRK2/BCL2/SCN9A/KCNE3/KCNH1/GCLC/FGF14/STOX1/PTN/MYH14/KCNJ11/CACNB4/KCNK2/FGF13/CACNA2D1/CACNA1D/NRCAM/KCNH2/FGF12/IGSF11/TMEM108/KCNJ10/CACNA1B/GRIN2A/SCN2A/GABRB3/PPP1R9A/GABRP/TCL1A
BP	GO:0050769	positive regulation of neurogenesis	29/572	0.00035	29	NTRK2/MDK/BCL2/MYB/FOXA1/GPRC5B/IL34/RARB/ADRA2B/PRKD1/BDNF/SERPINI1/SLIT2/SERPINF1/PTN/NTN1/BMP7/APOE/MAP1B/RND2/NRCAM/DMRTA2/CX3CL1/HAP1/PPARG/SYT2/PCP4/ROBO2/PPP1R9A
BP	GO:0010975	regulation of neuron projection development	29/572	0.00079	29	NTRK2/EPHA7/MDK/ARHGAP4/KIAA0319/MYLIP/RGMA/PRKD1/BDNF/SERPINI1/SLIT2/KEL/SERPINF1/PTN/NTN1/BMP7/CRMP1/APOE/MAP1B/RND2/FGF13/NRCAM/CX3CL1/OLFM1/SYT2/SPP1/FSTL4/ROBO2/PPP1R9A
BP	GO:0014706	striated muscle tissue development	28/572	2.94E-05	28	ZBTB18/BCL2/DIPK2A/FZD7/LEF1/RARB/SIX4/HLF/NUPR1/FGFR2/KEL/EYA2/MYH14/BMP7/PI16/KCNK2/DMRTA2/RBP4/MYH11/ELN/MEGF10/EYA1/ALDH1A2/GLI1/COL11A1/FOXH1/POU4F1/COL19A1
BP	GO:0048608	reproductive structure development	28/572	0.00016	28	SYCP2/MERTK/HEY1/BCL2/LEF1/FOXA1/SIX4/KRT19/KRT8/PTCH1/NUPR1/FGFR2/SLIT2/SERPINF1/PTN/AKR1C3/BMP7/PTGIS/SULF1/PPARG/RBP4/HOXA9/SPP1/ROBO2/GLI1/NR5A1/MGST1/NR0B1
BP	GO:0061458	reproductive system development	28/572	0.00018	28	SYCP2/MERTK/HEY1/BCL2/LEF1/FOXA1/SIX4/KRT19/KRT8/PTCH1/NUPR1/FGFR2/SLIT2/SERPINF1/PTN/AKR1C3/BMP7/PTGIS/SULF1/PPARG/RBP4/HOXA9/SPP1/ROBO2/GLI1/NR5A1/MGST1/NR0B1
BP	GO:0007389	pattern specification process	28/572	0.00029	28	HEY1/GPC3/LEF1/PBX1/FOXA1/HHEX/PTCH1/DMRT3/FGFR2/OTX1/BMP7/FOXJ1/DMRTA2/CRB2/HOXB3/HOXA9/EYA1/NKX3-2/ALDH1A2/SOSTDC1/ROBO2/GLI1/ALX1/RIPPLY3/TCF15/FOXH1/DMRT2/PAX1
BP	GO:0050808	synapse organization	27/572	0.00016	27	CEL/NTRK2/EPHA7/SIX4/LRRC4/BDNF/PCLO/CTTNBP2/PTN/NTN1/CACNB4/NEFH/SYNDIG1/APOE/MAP1B/LRRN1/NRCAM/CX3CL1/GPC4/TMEM108/ROBO2/ADD2/INA/ADGRB1/GABRB3/PPP1R9A/POU4F1
BP	GO:0016049	cell growth	27/572	0.00212	27	EPHA7/BCL2/ARHGAP4/LEF1/CHPT1/IL17RB/BDNF/PLCE1/SLIT2/IGFBP5/NTN1/PI16/APOE/MAP1B/

						RND2/PTCH2/FGF13/HPN/NRCAM/PPARG/FBP1/TMEM108/OLFM1/SYT2/SLC44A4/SPP1/FSTL4
MF	GO:0048018	receptor ligand activity	27/559	0.00303	27	EPHA7/MDK/NTS/IL34/GDF15/FGF14/ADM2/BDNF/POMC/PTN/FAM3B/BMP7/OGN/CCL26/TG/FGF13/CX3CL1/FGF12/NRTN/TNFSF18/EGF/FNDC5/SPP1/PENK/FGF19/THBS4/CCL19
MF	GO:0030546	signaling receptor activator activity	27/559	0.00349	27	EPHA7/MDK/NTS/IL34/GDF15/FGF14/ADM2/BDNF/POMC/PTN/FAM3B/BMP7/OGN/CCL26/TG/FGF13/CX3CL1/FGF12/NRTN/TNFSF18/EGF/FNDC5/SPP1/PENK/FGF19/THBS4/CCL19
BP	GO:0006631	fatty acid metabolic process	26/572	0.00014	26	CEL/FADS2/SLC27A2/ALOX15/CYP4F3/CES1/GSTM4/AOAH/AKR1C3/GSTA1/CD74/AKR1C2/GPAT2/ADH7/APOC1/FA2H/CYP2E1/PTGIS/GSTM2/PPARG/GLYATL2/CYP1B1/PRKAA2/CYP4F11/UGT1A8/MLXIPL
BP	GO:0001558	regulation of cell growth	26/572	0.0005	26	EPHA7/BCL2/ARHGAP4/LEF1/CHPT1/IL17RB/BDNF/PLCE1/SLIT2/IGFBP5/NTN1/PI16/APOE/MAP1B/RND2/PTCH2/FGF13/HPN/NRCAM/PPARG/FBP1/OLFM1/SYT2/SLC44A4/SPP1/FSTL4
BP	GO:0048871	multicellular organismal homeostasis	26/572	0.00442	26	ALDH1A1/BCL2/GCNT2/MRAP2/UCP2/ADCY5/PLAC8/GATM/TMEM119/MUC2/FA2H/SCNN1A/RBP4/YBX2/LYZ/JCHAIN/MUC6/PRKAA2/SPP1/PTH2R/ZG16B/MLXIPL/MUC4/MUC13/LTF/TFF3
CC	GO:0043025	neuronal cell body	26/590	0.00439	26	EPHA7/KCNE3/KCNH1/SERPINI1/CD200/SERPINF1/KCNJ11/CNNM1/PPP1R1B/APOE/SV2A/MAP1B/UCHL1/KCNK2/HPN/NPTXR/CX3CL1/OLFM1/PRKAA2/CD22/PENK/CACNA1B/PCSK2/PPP1R9A/CPLX2/KIF1A
MF	GO:0001228	DNA-binding transcription activator activity, RNA polymerase II-specific	26/559	0.00169	26	SOX2/MYB/LEF1/ARNT2/PBX1/FOXA1/SIX4/HLF/SOX21/ETV1/OTX1/SALL2/RORB/SPIB/ELF3/FOXJ1/TBX4/IKZF3/CTCFL/HOXB3/MYCN/ALX1/TCF15/FOXH1/POU4F1/PAX1
MF	GO:0001216	DNA-binding transcription activator activity	26/559	0.00174	26	SOX2/MYB/LEF1/ARNT2/PBX1/FOXA1/SIX4/HLF/SOX21/ETV1/OTX1/SALL2/RORB/SPIB/ELF3/FOXJ1/TBX4/IKZF3/CTCFL/HOXB3/MYCN/ALX1/TCF15/FOXH1/POU4F1/PAX1
MF	GO:0015267	channel activity	26/559	0.00472	26	BCL2/SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/TMC4/TMEM150C/SLC4A11/CLIC6/KCNJ11/TRPV6/CACNB4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/PANX2/KCNJ10/CACNA1B/GRIN2A/SCN2A/GABRB3/GABRP
MF	GO:0022803	passive transmembrane transporter activity	26/559	0.00485	26	BCL2/SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/TMC4/TMEM150C/SLC4A11/CLIC6/KCNJ11/TRPV6/CACNB4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/PANX2/KCNJ10/CACNA1B/GRIN2A/SCN2A/GABRB3/GABRP
BP	GO:0042445	hormone metabolic process	25/572	5.76E-08	25	ALDH1A1/CYP26A1/FOXA1/TSPOAP1/AKR1C1/CES1/CYP27A1/UGT1A7/AKR1C3/AKR1C2/ADH7/TG/UGT1A9/HPN/ADH1C/RBP4/CYP1B1/ALDH1A2/SLC44A4/SPP1/PCSK2/UGT1A8/NR5A1/CYP11A1/CHST9
BP	GO:0016042	lipid catabolic process	25/572	3.77E-05	25	CEL/CYP26A1/SLC27A2/PDE3B/CYP4F3/PLCE1/CES1/CES3/PLAAT3/CYP27A1/AOAH/PLCH1/AKR1C3/PLA2G2D/APOE/APOC1/PLA1A/LIPH/PLCB4/GLYATL2/GPLD1/CYP1B1/AADAC/ENPP6/SPP1

BP	GO:00 48638	regulation of developmental growth	25/572	7.35E-05	25	EPHA7/BCL2/ARHGAP4/SIX4/PTCH1/GDF15/PLAC8/FGFR2/BDNF/NTN1/PI16/APOE/MAP1B/KCNK2/RND2/FGF13/NRCAM/RBP4/OLFM1/SYT2/SPP1/FSTL4/SLC6A4/GLI1/AGR2
BP	GO:00 32535	regulation of cellular component size	25/572	0.0002	25	EPS8/EPHA7/ARHGAP4/ALOX15/HCLS1/BDNF/SLIT2/KEL/TMSB15A/SCIN/NTN1/APOE/CCL26/MAP1B/SPIRE2/RND2/FGF13/DEPTOR/NRCAM/ELN/OLFM1/SPP1/FSTL4/ADD2/PPP1R9A
BP	GO:00 07517	muscle organ development	25/572	0.00091	25	ZBTB18/BCL2/FZD7/LEF1/SIX4/HLF/NUPR1/ETV1/FGFR2/KEL/MYH14/PI16/KCNK2/DMRTA2/RBP4/ELN/ITGA11/MEGF10/GLI1/COL11A1/TCF15/FOXH1/ADGRB1/POU4F1/COL19A1
BP	GO:00 50673	epithelial cell proliferation	25/572	0.002	25	SOX2/PRKX/MDK/GPC3/FZD7/SIX4/PTCH1/NUPR1/FGFR2/STOX1/PRKD1/SERPINF1/PTN/IGFBP5/DLX6/APOE/CCL26/HPN/SULF1/PPARG/EYA1/ALDH1A2/GLI1/THBS4/ODAM
BP	GO:00 34765	regulation of ion transmembrane transport	25/572	0.00778	25	SCN9A/KCNE3/WNK2/KCNS3/KCNH1/FGF14/FXYD6/KEL/CTSS/CLIC6/KCNJ11/CACNB4/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/KCNH2/FGF12/CD19/KCNJ10/CACNA1B/GRIN2A/SCN2A/ATP2A1
BP	GO:00 22604	regulation of cell morphogenesis	25/572	0.00798	25	NTRK2/EPS8/EPHA7/MDK/ARHGAP4/COCH/FAM171A1/BDNF/SLIT2/KEL/PTN/MYH14/NTN1/APOE/MAP1B/RND2/FGF13/HPN/NRCAM/OLFM1/SYT2/SPP1/FSTL4/ROBO2/PPP1R9A
MF	GO:19 01681	sulfur compound binding	25/559	3.95E-07	25	CEL/MDK/CBS/PTCH1/SMOC2/FGFR2/SLIT2/GSTM4/PTN/PLA2G2D/BMP7/ACBD7/APOE/CCN5/LIPH/GSTM3/GSTM2/PRELP/PCOLCE2/COL11A1/SOST/THBS4/COMP/LTF/MGST1
BP	GO:00 71466	cellular response to xenobiotic stimulus	24/572	1.45E-09	24	CYP26A1/EPHX1/ARNT2/ALDH3A1/FMO3/MARC1/PHGDH/AKR1C1/CES1/GSTM4/CES3/UGT1A7/SERPINF1/UGT1A6/GSTA1/UGT1A9/CYP2E1/GSTM3/GSTM2/CYP1B1/AADAC/GSTM5/UGT1A8/MGST1
BP	GO:00 01655	urogenital system development	24/572	8.82E-05	24	PRKX/EPHA7/BCL2/GPC3/EPCAM/CYP26A1/PBX1/FOXA1/RARB/SIX4/PTCH1/FGFR2/PLCE1/SLIT2/SERPINF1/BMP7/FOXJ1/SULF1/RBP4/COL4A4/EYA1/ALDH1A2/ROBO2/GLI1
BP	GO:00 10721	negative regulation of cell development	24/572	0.00017	24	SOX2/HEY1/EPHA7/BCL2/ARHGAP4/KIAA0319/PBX1/MYLIP/RGMA/NEXMIF/SLIT2/PTN/NTN1/BMP7/PI16/CRMP1/APOE/FGF13/CX3CL1/STAP1/SPP1/FSTL4/SLC6A4/LTF
BP	GO:00 03002	regionalization	24/572	0.00022	24	HEY1/GPC3/LEF1/PBX1/FOXA1/HHEX/PTCH1/DMRT3/FGFR2/OTX1/FOXJ1/DMRTA2/CRB2/HOXB3/HOXA9/ALDH1A2/SOSTDC1/ROBO2/GLI1/ALX1/TCF15/FOXH1/DMRT2/PAX1
BP	GO:00 30098	lymphocyte differentiation	24/572	0.00024	24	MERTK/MDK/BCL2/MYB/FZD7/LEF1/HHEX/VCAM1/PLA2G2D/CD74/NKX2-3/FOXJ1/ZAP70/CR2/CR1/LILRB4/IKZF3/THEMIS/CD79B/CD19/MS4A1/CCL19/CD79A/PAX1
BP	GO:00 01505	regulation of neurotransmitter levels	24/572	0.00027	24	SLC29A2/SYNGR3/GCHFR/CHDH/TSPOAP1/PHGDH/PCLO/NOS2/SV2A/SLC7A2/PTGIS/CACNA1D/CLU/CYP1B1/SYT2/ENPP6/MAOB/KCNJ10/SLC44A4/CACNA1B/SLC6A4/GRIN2A/PPP1R9A/CPLX2
BP	GO:00 45666	positive regulation of neuron differentiation	24/572	0.0005	24	NTRK2/MDK/BCL2/FOXA1/GPRC5B/RARB/ADRA2B/PRKD1/BDNF/SERPINI1/SLIT2/SERPINF1/PTN/NTN1/BMP7/APOE/MAP1B/RND2/NRCAM/CX3CL1/SYT2/PCP4/ROBO2/PPP1R9A

BP	GO:0048545	response to steroid hormone	24/572	0.00079	24	MDK/BCL2/ABCA3/LEF1/FOXA1/ALDH3A1/RARB/ABCA2/SLIT2/SERPINF1/PTN/AKR1C3/BMP7/RORB/NR3C2/SOX30/PPARG/MAOB/SPP1/FOXH1/SCGB2A1/NR5A1/NR0B1/SCGB1A1
BP	GO:0008544	epidermis development	24/572	0.00907	24	BCL2/KRT15/KRT19/KRT8/PTCH1/SOX21/FGFR2/AKR1C3/IGFBP5/ELF3/PTCH2/FA2H/KRT20/DNASE1L2/DSG4/SLC44A4/SFRP4/SOSTDC1/GLI1/SPRR3/KRT7/KRT36/KRT13/TCHH
BP	GO:0002429	immune response-activating cell surface receptor signaling pathway	24/572	0.0113	24	BCL2/VTCN1/HLA-DQA1/BTNL9/MUC2/SKAP1/ZAP70/CR2/CR1/LILRB4/THEMIS/GPLD1/CD79B/BLK/CD19/MUC6/MUC20/STAP1/CD22/MS4A1/MUC4/CD79A/MUC13/MUC5B
BP	GO:0002757	immune response-activating signal transduction	24/572	0.0113	24	BCL2/VTCN1/HLA-DQA1/BTNL9/MUC2/SKAP1/ZAP70/CR2/CR1/LILRB4/THEMIS/GPLD1/CD79B/BLK/CD19/MUC6/MUC20/STAP1/CD22/MS4A1/MUC4/CD79A/MUC13/MUC5B
BP	GO:0050900	leukocyte migration	24/572	0.02028	24	MERTK/EPS8/MDK/EPCAM/SLIT2/CD200/VCAM1/PTN/CD74/NKX2-3/FOXJ1/CCL26/PODXL2/ZAP70/CX3CL1/CXCL17/TNFSF18/JCHAIN/STAP1/CEACAM5/ADD2/CXCR5/THBS4/CCL19
BP	GO:0002791	regulation of peptide secretion	24/572	0.02071	24	MDK/ADCY5/KCNS3/IL17RB/CD200/VTCN1/ICA1/ILDR1/TFR2/KCNJ11/NOS2/CD74/APOE/C1QTNF3/CACNA1D/BANK1/CX3CL1/RBP4/KRT20/GPLD1/BLK/PANX2/CD22/CCL19
MF	GO:0005539	glycosaminoglycan binding	24/559	2.84E-07	24	CEL/MDK/PTCH1/SMOC2/FGFR2/SLIT2/PTN/PLA2G2D/BMP7/EPYC/APOE/CCN5/PODXL2/LIPH/SULF1/PRELP/JCHAIN/PCOLCE2/COL11A1/SOST/THBS4/COMP/LTF/SPOCK3
MF	GO:0005216	ion channel activity	24/559	0.00605	24	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/TMC4/TMEM150C/SLC4A11/CLIC6/KCNJ11/TRPV6/CACNB4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A/SCN2A/GABRB3/GABRP
MF	GO:0046873	metal ion transmembrane transporter activity	24/559	0.00675	24	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/SLC9A2/SLC4A11/KCNJ11/TRPV6/CACNB4/SLC9A4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/SLC6A4/GRIN2A/SCN2A/ATP12A/ATP2A1
BP	GO:0006805	xenobiotic metabolic process	23/572	4.04E-12	23	CYP26A1/EPHX1/ARNT2/ALDH3A1/FMO3/MARC1/PHGDH/AKR1C1/CES1/GSTM4/CES3/UGT1A7/UGT1A6/GSTA1/UGT1A9/CYP2E1/GSTM3/GSTM2/CYP1B1/AADAC/GSTM5/UGT1A8/MGST1
BP	GO:0001101	response to acid chemical	23/572	0.0004	23	NTRK2/MYB/FZD7/CYP26A1/RARB/KRT8/PTCH1/GCLC/FGFR2/AKR1C1/SERPINF1/PTN/AKR1C3/RORB/AKR1C2/CYP2E1/PPARG/RBP4/PRKAA2/ALDH1A2/SLC6A4/CCL19/SCGB1A1
BP	GO:0046394	carboxylic acid biosynthetic process	23/572	0.00064	23	GLS2/FADS2/CBS/SLC27A2/ABCC5/ALOX15/RIMKLA/PHGDH/GSTM4/CYP27A1/AKR1C3/GATM/CD74/APOC1/FA2H/CYP2E1/PTGIS/BCAT1/PRKAA2/ALDH1A2/EGF/FGF19/MLXIPL
BP	GO:0016053	organic acid biosynthetic process	23/572	0.00067	23	GLS2/FADS2/CBS/SLC27A2/ABCC5/ALOX15/RIMKLA/PHGDH/GSTM4/CYP27A1/AKR1C3/GATM/CD74/APOC1/FA2H/CYP2E1/PTGIS/BCAT1/PRKAA2/ALDH1A2/EGF/FGF19/MLXIPL

BP	GO:0050678	regulation of epithelial cell proliferation	23/572	0.00148	23	SOX2/MDK/GPC3/FZD7/SIX4/PTCH1/NUPR1/FGFR2/STOX1/PRKD1/SERPINF1/PTN/DLX6/APOE/CCL26/HPN/SULF1/PPARG/EYA1/ALDH1A2/GLI1/THBS4/ODAM
BP	GO:0006874	cellular calcium ion homeostasis	23/572	0.01448	23	PDE6B/BCL2/ADCY5/TSPOAP1/PLCE1/KEL/PLCH1/ATP13A5/SLC35G1/TRPV6/APOE/SV2A/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CXCR5/CCL19/ATP2A1
BP	GO:0055074	calcium ion homeostasis	23/572	0.01945	23	PDE6B/BCL2/ADCY5/TSPOAP1/PLCE1/KEL/PLCH1/ATP13A5/SLC35G1/TRPV6/APOE/SV2A/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CXCR5/CCL19/ATP2A1
BP	GO:0072503	cellular divalent inorganic cation homeostasis	23/572	0.03079	23	PDE6B/BCL2/ADCY5/TSPOAP1/PLCE1/KEL/PLCH1/ATP13A5/SLC35G1/TRPV6/APOE/SV2A/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CXCR5/CCL19/ATP2A1
BP	GO:0031667	response to nutrient levels	23/572	0.03461	23	BCL2/CYP26A1/KIAA1324/ALDH3A1/GDF15/GCLC/PRKD1/VCAM1/POMC/PTN/AKR1C3/BMP7/KCNJ11/APOE/MAP1B/PPARG/KRT20/PRKAA2/ALDH1A2/SPP1/PENK/SLC6A4/DAPL1
BP	GO:0072001	renal system development	22/572	0.00011	22	PRKX/EPHA7/BCL2/GPC3/EPCAM/CYP26A1/PBX1/RARB/SIX4/PTCH1/FGFR2/PLCE1/SLIT2/SERPINF1/BMP7/FOXJ1/SULF1/RBP4/COL4A4/EYA1/ALDH1A2/ROBO2
BP	GO:0051961	negative regulation of nervous system development	22/572	0.00032	22	SOX2/HEY1/EPHA7/ARHGAP4/KIAA0319/PBX1/MYLIP/RGMA/NEXMIF/SLIT2/PTN/NTN1/BMP7/CRMP1/APOE/FGF13/CX3CL1/STAP1/SPP1/FSTL4/SLC6A4/ROBO2
BP	GO:0030198	extracellular matrix organization	22/572	0.00231	22	ICAM4/SCUBE3/SMOC2/VCAM1/CTSS/LOXL4/ELF3/HPN/DPT/SULF1/MYH11/ELN/ITGA11/CYP1B1/MFAP4/COL4A4/MMP11/SPP1/COL11A1/TCF15/COMP/COL19A1
BP	GO:0043062	extracellular structure organization	22/572	0.00239	22	ICAM4/SCUBE3/SMOC2/VCAM1/CTSS/LOXL4/ELF3/HPN/DPT/SULF1/MYH11/ELN/ITGA11/CYP1B1/MFAP4/COL4A4/MMP11/SPP1/COL11A1/TCF15/COMP/COL19A1
BP	GO:0042692	muscle cell differentiation	22/572	0.00398	22	HEY1/BCL2/FZD7/RARB/SIX4/KCNH1/KRT19/KRT8/GDF15/MYEF2/FGFR2/BDNF/KEL/IGFBP5/PI16/TMEM119/UCHL1/MYH11/MEGF10/CEACAM5/COMP/ADGRB1
BP	GO:0022407	regulation of cell-cell adhesion	22/572	0.00654	22	SOX2/EPHA7/MDK/MYB/GCNT2/EPCAM/LEF1/FOXA1/ALOX15/NEXMIF/VCAM1/VTCN1/PLA2G2D/BMP7/CD74/FOXJ1/SKAP1/ZAP70/LILRB4/CX3CL1/CCL19/SCGB1A1
BP	GO:0034329	cell junction assembly	22/572	0.00794	22	CEL/NTRK2/EPHA7/BCL2/SIX4/LRRC4/CLDN3/UGT8/BDNF/PCLO/NTN1/SYNDIG1/MAP1B/LRRN1/NRCAM/GPC4/ROBO2/ADD2/ADGRB1/GABRB3/PPP1R9A/POU4F1
BP	GO:0043254	regulation of protein-containing complex assembly	22/572	0.0133	22	EPS8/LMO4/SVIP/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/APOE/CCL26/MAP1B/SPIRE2/SKAP1/STXBP6/INSM1/CLU/ELN/JCHAIN/ADD2/SOST/PPP1R9A/TCL1A
BP	GO:0050804	modulation of chemical synaptic transmission	22/572	0.01575	22	CEL/NTRK2/LRRC4/FGF14/BDNF/PTN/APOE/MAP1B/CACNA1D/NPTXR/CX3CL1/HAP1/PLCB4/IGSF11/TMEM108/KCNJ10/CACNA1B/SLC6A4/GRIN2A/ADGRB1/PPP1R9A/CPLX2

BP	GO:0099177	regulation of trans-synaptic signaling	22/572	0.01613	22	CEL/NTRK2/LRRC4/FGF14/BDNF/PTN/APOE/MAP1B/CACNA1D/NPTXR/CX3CL1/HAP1/PLCB4/IGSF11/TMEM108/KCNJ10/CACNA1B/SLC6A4/GRIN2A/ADGRB1/PPP1R9A/CPLX2
MF	GO:0022836	gated channel activity	22/559	0.00139	22	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/TMC4/TMEM150C/CLIC6/KCNJ11/CACNB4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A/SCN2A/GABRB3/GABRP
BP	GO:0097305	response to alcohol	21/572	1.07E-05	21	EPS8/ADCY5/PTCH1/CLDN3/ABCA2/FGFR2/SLIT2/VCAM1/AKR1C3/AKR1C2/ADH7/CYP2E1/PPARG/RBP4/GPLD1/SLC2A4/PRKAA2/MAOB/PENK/GRIN2A/CCL19
BP	GO:0001822	kidney development	21/572	0.00014	21	PRKX/EPHA7/BCL2/GPC3/EPCAM/CYP26A1/PBX1/RARB/SIX4/PTCH1/FGFR2/PLCE1/SLIT2/SERPINF1/BMP7/FOXJ1/SULF1/COL4A4/EYA1/ALDH1A2/ROBO2
BP	GO:0048562	embryonic organ morphogenesis	21/572	0.00023	21	LRIG1/MYO3A/RARB/SIX4/FGFR2/OTX1/STOX1/NTN1/BMP7/DLX6/HPN/RBP4/CRB2/HOXB3/EYA1/NKX3-2/SLC44A4/GLI1/ALX1/COL11A1/FOXH1
BP	GO:0050768	negative regulation of neurogenesis	21/572	0.00032	21	SOX2/HEY1/EPHA7/ARHGAP4/KIAA0319/PBX1/MYLIP/RGMA/NEXMIF/SLIT2/PTN/NTN1/BMP7/CRMP1/APOE/FGF13/CX3CL1/STAP1/SPP1/FSTL4/SLC6A4
BP	GO:0070661	leukocyte proliferation	21/572	0.00037	21	BCL2/LEF1/HHEX/IL34/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP70/CR2/CX3CL1/CLU/IKZF3/TNFSF18/CD19/CD22/MS4A1/CCL19/CD79A/SCGB1A1
BP	GO:0060562	epithelial tube morphogenesis	21/572	0.001	21	PRKX/EPHA7/MDK/BCL2/LMO4/GPC3/LEF1/PBX1/FOXA1/SIX4/PTCH1/FGFR2/STOX1/SLIT2/NTN1/BMP7/EYA1/EGF/SOSTDC1/ALX1/FOXH1
BP	GO:0008202	steroid metabolic process	21/572	0.00141	21	CEL/CYP26A1/PBX1/SLC27A2/TSPOAP1/AKR1C1/CES1/CYP27A1/AKR1C3/AKR1C2/APOE/APOC1/CYP2E1/CYP1B1/PRKAA2/SPP1/FGF19/UGT1A8/NR5A1/CYP11A1/NR0B1
BP	GO:0006869	lipid transport	21/572	0.007	21	CEL/MYB/ABCA3/ABCA13/GULP1/PTCH1/SLC27A2/ABCA2/AKR1C1/CES1/POMC/PLA2G2D/NOS2/APOE/APOC1/CLU/PPARG/RBP4/PRKAA2/EGF/SPP1
BP	GO:0040013	negative regulation of locomotion	21/572	0.0072	21	BCL2/ARHGAP4/NEXMIF/SLIT2/CD200/SERPINF1/PTN/IGFBP5/CD74/DACH1/APOE/PODN/PTPRT/CX3CL1/SULF1/PPARG/CYP1B1/STAP1/ROBO2/ADGRB1/SPOCK3
BP	GO:0051271	negative regulation of cellular component movement	21/572	0.00784	21	BCL2/ARHGAP4/KCNE3/NEXMIF/SLIT2/CD200/SERPINF1/PTN/IGFBP5/CD74/DACH1/APOE/PODN/PTPRT/CX3CL1/SULF1/PPARG/CYP1B1/STAP1/ADGRB1/SPOCK3
BP	GO:0010876	lipid localization	21/572	0.01753	21	CEL/MYB/ABCA3/ABCA13/GULP1/PTCH1/SLC27A2/ABCA2/AKR1C1/CES1/POMC/PLA2G2D/NOS2/APOE/APOC1/CLU/PPARG/RBP4/PRKAA2/EGF/SPP1
BP	GO:0043588	skin development	21/572	0.01927	21	BCL2/KRT15/KRT19/KRT8/SOX21/FGFR2/AKR1C3/IGFBP5/PTCH2/FA2H/KRT20/DNASE1L2/DSG4/SOSTDC1/SPRR3/TCF15/KRT7/COMP/KRT36/KRT13/TCHH
BP	GO:0019932	second-messenger-mediated signaling	21/572	0.03008	21	MRAP2/ADCY5/ADRA2B/ADM2/PDE3B/PCLO/PLCE1/VCAM1/NOS2/APOE/ZAP70/GSTM2/HAP1/GPR143/CD22/TCP11/GRIN2A/CXCR5/ADGRB1/PPP1R9A/NR5A1

CC	GO:1902495	transmembrane transporter complex	21/590	0.00081	21	EPS8/SCN9A/KCNE3/KCNS3/KCNH1/ABCA2/CLIC6/KCNJ11/CACNB4/KCNK2/SCNN1A/CACNA2D1/CACNA1D/KCNH2/CACNA1B/GRIN2A/SCN2A/ATP12A/GABRB3/ATP2A1/GABRP
CC	GO:1990351	transporter complex	21/590	0.0011	21	EPS8/SCN9A/KCNE3/KCNS3/KCNH1/ABCA2/CLIC6/KCNJ11/CACNB4/KCNK2/SCNN1A/CACNA2D1/CACNA1D/KCNH2/CACNA1B/GRIN2A/SCN2A/ATP12A/GABRB3/ATP2A1/GABRP
CC	GO:0098984	neuron to neuron synapse	21/590	0.00209	21	NTRK2/EPS8/EPHA7/KCNH1/LRRC4/PTCH1/PCLO/ADAM22/NEFH/SYNDIG1/MAP1B/NRCAM/PLCB4/IGSF11/TMEM108/PENK/GRIN2A/ADD2/ADGRB1/DLGAP1/PPP1R9A
CC	GO:0030133	transport vesicle	21/590	0.00763	21	NTS/SYNGR3/TMEM163/BDNF/CTTNBP2/LGI3/ICA1/ARFGEF3/HLA-DQA1/RASSF9/SV2B/CD74/SV2A/HAP1/SLC2A4/SYT2/PENK/PCSK2/GRIN2A/SYTL5/KIF1A
BP	GO:0090596	sensory organ morphogenesis	20/572	0.00013	20	LRIG1/NTRK2/BCL2/MYO3A/RARB/SIX4/FGFR2/OTX1/STOX1/PTN/NTN1/BMP7/RORB/DLX6/HPN/RBP4/EYA1/NKX3-2/SLC44A4/COL11A1
BP	GO:0043491	protein kinase B signaling	20/572	0.00025	20	MERTK/NTRK2/GCNT2/PIK3R3/PIK3AP1/GDF15/FGFR2/HCLS1/STOX1/AKR1C3/IGFBP5/AKR1C2/TSPYL5/BANK1/CX3CL1/CD19/EGF/FGF19/CHI3L1/CCL19
BP	GO:0060485	mesenchyme development	20/572	0.0004	20	HEY1/MDK/BCL2/GCNT2/LEF1/FOXA1/SIX4/FGFR2/BMP7/HPN/CRB2/NRTN/OLFM1/ALDH1A2/FGF19/ROBO2/ALX1/TCF15/FOXH1/PAX1
BP	GO:0007178	transmembrane receptor protein serine/threonine kinase signaling pathway	20/572	0.00569	20	GPC3/GCNT2/LEF1/GDF15/RGMA/CGN/RNF165/BMP7/ASPN/SULF1/CRB2/CILP/PEG10/CHRDL1/DSG4/SFRP4/SOSTDC1/SOST/FOXH1/COMP
BP	GO:2000146	negative regulation of cell motility	20/572	0.00569	20	BCL2/ARHGAP4/NEXMIF/SLIT2/CD200/SERPINF1/PTN/IGFBP5/CD74/DACH1/APOE/PODN/PTPRT/CX3CL1/SULF1/PPARG/CYP1B1/STAP1/ADGRB1/SPOCK3
BP	GO:0006066	alcohol metabolic process	20/572	0.0105	20	ALDH1A1/CEL/ISYNA1/PLCE1/AKR1C1/CES1/CYP27A1/PLCH1/AKR1C3/AKR1C2/APOE/ADH7/APOC1/ADH1C/RBP4/PLCB4/CYP1B1/PRKAA2/ALDH1A2/CYP11A1
BP	GO:0031346	positive regulation of cell projection organization	20/572	0.01484	20	NTRK2/EPS8/MDK/PRKD1/BDNF/SERPINI1/SLIT2/SERPINF1/PTN/NTN1/BMP7/APOE/MAP1B/RND2/CX3CL1/HAP1/SYT2/ROBO2/CCL19/PPP1R9A
BP	GO:0032970	regulation of actin filament-based process	20/572	0.01684	20	EPS8/MDK/KCNE3/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/RND2/FGF13/CX3CL1/ELN/STAP1/ADD2/SYNPO2/PPP1R9A/ODAM/ATP2A1
BP	GO:0045785	positive regulation of cell adhesion	20/572	0.02413	20	SOX2/MDK/MYB/GCNT2/FOXA1/SMOC2/ALOX15/VCAM1/VTCN1/PTN/BMP7/CD74/EMID1/SKAP1/ZAP70/LILRB4/CX3CL1/TNFSF18/AGR2/CCL19
CC	GO:0014069	postsynaptic density	20/590	0.0019	20	NTRK2/EPS8/EPHA7/KCNH1/LRRC4/PTCH1/PCLO/ADAM22/NEFH/SYNDIG1/MAP1B/NRCAM/PLCB4/IGSF11/TMEM108/GRIN2A/ADD2/ADGRB1/DLGAP1/PPP1R9A
CC	GO:0032279	asymmetric synapse	20/590	0.0022	20	NTRK2/EPS8/EPHA7/KCNH1/LRRC4/PTCH1/PCLO/ADAM22/NEFH/SYNDIG1/MAP1B/NRCAM/PLCB4/IGSF11/TMEM108/GRIN2A/ADD2/ADGRB1/DLGAP1/PPP1R9A

CC	GO:0099572	postsynaptic specialization	20/590	0.00429	20	NTRK2/EPS8/EPHA7/KCNH1/LRRC4/PTCH1/PCLO/ADAM22/NEFH/SYNDIG1/MAP1B/NRCAM/PLCB4/IGSF11/TMEM108/GRIN2A/ADD2/ADGRB1/DLGAP1/PPP1R9A
CC	GO:0098978	glutamatergic synapse	20/590	0.00443	20	EPS8/EPHA7/LRRC4/PPM1H/TSPOAP1/FXYD6/CTTNBP2/ADAM22/PPP1R1B/APOE/SV2A/NPTXR/NRCAM/GPC4/ADAM23/PLCB4/GRIN2A/SCN2A/PPP1R9A/CPLX2
MF	GO:0004857	enzyme inhibitor activity	20/559	0.01621	20	TRIB2/GPC3/LEF1/GCHFR/SERPINI1/SLIT2/UGT1A7/SERPINF1/PTN/PPP1R1B/PI16/APOC1/FETUB/RARRES1/CRB2/UGT1A8/LTF/SERPINB12/SPOCK3/SCGB1A1
BP	GO:0007416	synapse assembly	19/572	2.23E-06	19	CEL/NTRK2/EPHA7/SIX4/LRRC4/BDNF/PCLO/NTN1/SYNDIG1/MAP1B/LRRN1/NRCAM/GPC4/ROBO2/ADD2/ADGRB1/GABRB3/PPP1R9A/POU4F1
BP	GO:0043583	ear development	19/572	4.71E-05	19	SOX2/LRIG1/BCL2/MYO3A/SIX4/FGFR2/OTX1/STOX1/FREM2/NTN1/DLX6/KCNK2/HPN/EYA1/NKX3-2/SLC44A4/COL11A1/TCF15/GABRB3
BP	GO:0045926	negative regulation of growth	19/572	0.00026	19	EPHA7/BCL2/ARHGAP4/GPC3/PTCH1/GDF15/PLAC8/SLIT2/IGFBP5/NTN1/PI16/KCNK2/FGF13/PPARG/FBP1/RBP4/SPP1/FSTL4/SLC6A4
BP	GO:0045165	cell fate commitment	19/572	0.00073	19	SOX2/BCL2/LMO4/FZD7/MIAT/FOXA1/PTCH1/DMRT3/FGFR2/SOX5/EYA2/TBX4/PTCH2/FGF13/DMRTA2/PPARG/EYA1/SOSTDC1/POU4F1
BP	GO:0051146	striated muscle cell differentiation	19/572	0.00182	19	BCL2/FZD7/RARB/SIX4/KCNH1/KRT19/KRT8/GDF15/MYEF2/BDNF/KEL/IGFBP5/PI16/TMEM119/UCHL1/MYH11/CEACAM5/COMP/ADGRB1
BP	GO:0030336	negative regulation of cell migration	19/572	0.00747	19	BCL2/ARHGAP4/NEXMIF/SLIT2/CD200/SERPINF1/PTN/IGFBP5/CD74/DACH1/APOE/PODN/PTPRT/CX3CL1/SULF1/PPARG/CYP1B1/STAP1/ADGRB1
BP	GO:0022412	cellular process involved in reproduction in multicellular organism	19/572	0.01604	19	SYCP2/MDK/BCL2/SLIT2/CCDC136/PTN/MEI1/TMEM119/SPIRE2/OCA2/CABYR/CTCFL/YBX2/ROBO2/TCP11/PIWIL2/M1AP/TEX15/MEIOB
BP	GO:0030900	forebrain development	19/572	0.02631	19	SOX2/NTRK2/MDK/LEF1/RARB/FGFR2/OTX1/SLIT2/PTN/FGF13/DMRTA2/HAP1/TMEM108/ALDH1A2/ROBO2/GLI1/POU4F1/KIF1A/NR0B1
BP	GO:0010959	regulation of metal ion transport	19/572	0.03525	19	BCL2/KCNE3/WNK2/FGF14/FXYD6/KEL/CACNB4/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/KCNH2/FGF12/CD19/EGF/CACNA1B/NKAIN2/ATP2A1
BP	GO:0070482	response to oxygen levels	19/572	0.03525	19	BCL2/MYB/ARNT2/ALDH3A1/UCP2/CLDN3/HIF3A/STOX1/VCAM1/PTN/BMP7/NOS2/KCNK2/PTGIS/PPARG/SLC2A4/PENK/SLC6A4/SCN2A
CC	GO:0034702	ion channel complex	19/590	0.0019	19	EPS8/SCN9A/KCNE3/KCNS3/KCNH1/CLIC6/KCNJ11/CACNB4/KCNK2/SCNN1A/CACNA2D1/CACNA1D/KCNH2/CACNA1B/GRIN2A/SCN2A/GABRB3/ATP2A1/GABRP
MF	GO:0005201	extracellular matrix structural constituent	19/559	9.91E-07	19	OGN/SBSPON/PODN/ASPN/DPT/PRELP/ELN/CILP/MFAP4/COL4A4/PRG4/MUC6/COL21A1/CHI3L1/FBN3/COL11A1/MUC4/COMP/COL19A1
MF	GO:0008201	heparin binding	19/559	1.72E-06	19	CEL/MDK/PTCH1/SMOC2/FGFR2/SLIT2/PTN/PLA2G2D/BMP7/APOE/CCN5/LIPH/PRELP/PCOLCE2/COL11A1/SOST/THBS4/COMP/LTF

MF	GO:0005261	cation channel activity	19/559	0.01105	19	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/SLC4A11/KCNJ11/TRPV6/CACNB4/KCNK2/SCNN1A/HPN/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A/SCN2A
BP	GO:0048705	skeletal system morphogenesis	18/572	0.00043	18	COCH/RARB/SIX4/FGFR2/BMP7/TBX4/TMEM119/HOXB3/EYA1/NKX3-2/SFRP4/COL21A1/ALX1/COL11A1/TCF15/COMP/LTF/PAX1
BP	GO:0051896	regulation of protein kinase B signaling	18/572	0.00055	18	NTRK2/GCNT2/PIK3AP1/GDF15/FGFR2/HCLS1/STOX1/AKR1C3/IGFBP5/AKR1C2/TSPYL5/BANK1/CX3CL1/CD19/EGF/FGF19/CHI3L1/CCL19
BP	GO:0015850	organic hydroxy compound transport	18/572	0.00125	18	CEL/MYB/PTCH1/ABCA2/ADRA2B/AKR1C1/CES1/POMC/APOE/APOC1/CLU/PPARG/RBP4/SYT2/MAOB/EGF/SPP1/SLC6A4
BP	GO:0061448	connective tissue development	18/572	0.00198	18	MDK/COCH/FOXA1/RARB/SOX5/PLAAT3/PKDCC/SCIN/BMP7/SULF1/HOXB3/GPLD1/NKX3-2/COL21A1/CHI3L1/ALX1/COL11A1/COMP
BP	GO:0098742	cell-cell adhesion via plasma-membrane adhesion molecules	18/572	0.00198	18	EPCAM/PCDH19/LRRC4/CLDN3/VCAM1/PTPRT/CX3CL1/GPC4/DCHS2/CRB2/IGSF11/DSG4/ROBO2/CEACAM5/FAT3/CLDN8/CLDN10/PCDHA4
BP	GO:0010769	regulation of cell morphogenesis involved in differentiation	18/572	0.00553	18	NTRK2/EPHA7/MDK/ARHGAP4/BDNF/SLIT2/KEL/NTN1/APOE/MAP1B/RND2/FGF13/NRCAM/OLFM1/SPP1/FSTL4/ROBO2/PPP1R9A
BP	GO:1904062	regulation of cation transmembrane transport	18/572	0.01875	18	KCNE3/WNK2/FGF14/FXYD6/KEL/CTSS/KCNJ11/CACNB4/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/KCNH2/FGF12/CD19/GRIN2A/ATP2A1
BP	GO:0070997	neuron death	18/572	0.02189	18	NTRK2/EPHA7/MDK/BCL2/MYB/TRIM2/SIX4/GCLC/NUPR1/BDNF/CD200/SERPINF1/APOE/CX3CL1/CLU/SCN2A/GABRB3/POU4F1
BP	GO:0031589	cell-substrate adhesion	18/572	0.02541	18	MERTK/PRKX/MDK/BCL2/GCNT2/FZD7/SMOC2/ALOX15/NEXMIF/ITGBL1/VCAM1/PTN/EMID1/SKAP1/CX3CL1/ITGA11/AGR2/MUC4
BP	GO:0051480	regulation of cytosolic calcium ion concentration	18/572	0.02733	18	PDE6B/BCL2/ADCY5/TSPOAP1/PLCE1/PLCH1/SLC35G1/TRPV6/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CXCR5/CCL19
BP	GO:0009913	epidermal cell differentiation	18/572	0.02799	18	KRT15/KRT19/KRT8/PTCH1/AKR1C3/PTCH2/FA2H/KRT20/DNASE1L2/DSG4/SLC44A4/SFRP4/GLI1/SPRR3/KRT7/KRT36/KRT13/TCHH
BP	GO:0001666	response to hypoxia	18/572	0.02867	18	BCL2/MYB/ARNT2/ALDH3A1/UCP2/CLDN3/HIF3A/STOX1/VCAM1/PTN/BMP7/NOS2/KCNK2/PTGIS/SLC2A4/PENK/SLC6A4/SCN2A
BP	GO:0030111	regulation of Wnt signaling pathway	18/572	0.03149	18	SOX2/MDK/GPC3/WNK2/FZD7/LEF1/GPRC5B/HHEX/FGFR2/WIF1/APOE/SULF1/SHISA2/EGF/SFRP4/SOSTDC1/GLI1/SOST
BP	GO:0030278	regulation of ossification	17/572	0.00018	17	MDK/BCL2/PBX1/PTCH1/FGFR2/PRKD1/PKDCC/PTN/IGFBP5/BMP7/RORB/OMD/TMEM119/GLI1/SOST/COMP/LTF
BP	GO:0045665	negative regulation of neuron differentiation	17/572	0.00059	17	SOX2/HEY1/EPHA7/ARHGAP4/KIAA0319/PBX1/MYLIP/RGMA/SLIT2/NTN1/BMP7/CRMP1/APOE/FGF13/SPP1/FSTL4/SLC6A4
BP	GO:0060560	developmental growth involved in morphogenesis	17/572	0.00097	17	EPHA7/ARHGAP4/SIX4/FGFR2/BDNF/SLIT2/NTN1/APOE/MAP1B/RND2/FGF13/NRCAM/TMEM108/OLFM1/SYT2/SPP1/FSTL4

BP	GO:2000027	regulation of animal organ morphogenesis	17/572	0.00214	17	MDK/BCL2/GPC3/FZD7/SIX4/DMRT3/FGFR2/STOX1/PTN/BMP7/HPN/ASPN/SULF1/GPC4/EYA1/ROBO2/GLI1
BP	GO:0046651	lymphocyte proliferation	17/572	0.00448	17	BCL2/LEF1/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP70/CR2/IKZF3/TNFSF18/CD19/CD22/MS4A1/CCL19/CD79A/SCGB1A1
BP	GO:0032943	mononuclear cell proliferation	17/572	0.00482	17	BCL2/LEF1/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP70/CR2/IKZF3/TNFSF18/CD19/CD22/MS4A1/CCL19/CD79A/SCGB1A1
BP	GO:0010976	positive regulation of neuron projection development	17/572	0.00616	17	NTRK2/MDK/PRKD1/BDNF/SERPINI1/SLIT2/SERPINF1/PTN/NTN1/BMP7/APOE/MAP1B/RND2/CX3CL1/SYT2/ROBO2/PPP1R9A
BP	GO:0032409	regulation of transporter activity	17/572	0.0066	17	BCL2/KCNE3/WNK2/SYNGR3/FGF14/FXYD6/CTSS/KCNJ11/CACNB4/CACNA2D1/CACNA1D/GSTM2/HAP1/PPARG/FGF12/GRIN2A/ATP2A1
BP	GO:0042063	gliogenesis	17/572	0.00833	17	SOX2/NTRK2/MDK/MYB/LEF1/IL34/PHGDH/PTN/ADAM22/FA2H/CX3CL1/CLU/PPARG/MYRF/STAP1/KCNJ10/PENK
BP	GO:0046879	hormone secretion	17/572	0.01448	17	MYB/ADCY5/KCNS3/PCLO/POMC/ICA1/FAM3B/ILDR1/TFR2/KCNJ11/NOS2/C1QTNF3/CACNA1D/RBP4/GPLD1/BLK/SPP1
BP	GO:0042113	B cell activation	17/572	0.01534	17	BCL2/LEF1/HHEX/VCAM1/CD74/NKX2-3/FOXJ1/ZAP70/CR2/BANK1/IKZF3/CD79B/CD19/CD22/MS4A1/CXCR5/CD79A
BP	GO:1901214	regulation of neuron death	17/572	0.01671	17	NTRK2/EPHA7/MDK/BCL2/MYB/TRIM2/SIX4/GCLC/NUPR1/BDNF/CD200/SERPINF1/APOE/CX3CL1/CLU/GABRB3/POU4F1
BP	GO:0009914	hormone transport	17/572	0.01867	17	MYB/ADCY5/KCNS3/PCLO/POMC/ICA1/FAM3B/ILDR1/TFR2/KCNJ11/NOS2/C1QTNF3/CACNA1D/RBP4/GPLD1/BLK/SPP1
BP	GO:0070588	calcium ion transmembrane transport	17/572	0.01971	17	KCNE3/FGF14/PLCE1/PLCH1/SLC35G1/TRPV6/CACNB4/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/CACNA1B/GRIN2A/CCL19/ATP2A1
BP	GO:0046677	response to antibiotic	17/572	0.02434	17	EPS8/BCL2/MYB/ADCY5/CLDN3/FGFR2/VCAM1/ADH7/CYP2E1/CLU/RBP4/CYP1B1/SLC2A4/MAOB/PENK/GRIN2A/SCGB1A1
BP	GO:0032956	regulation of actin cytoskeleton organization	17/572	0.03601	17	EPS8/MDK/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/RND2/CX3CL1/ELN/STAP1/ADD2/SYNPO2/PPP1R9A/ODAM
BP	GO:0006721	terpenoid metabolic process	16/572	7.98E-07	16	ALDH1A1/GPC3/CYP26A1/AKR1C1/UGT1A7/AKR1C3/APOE/ADH7/UGT1A9/CYP2E1/ADH1C/GPC4/RBP4/CYP1B1/ALDH1A2/UGT1A8
BP	GO:0034754	cellular hormone metabolic process	16/572	2.12E-06	16	ALDH1A1/CYP26A1/TSPOAP1/AKR1C1/UGT1A7/AKR1C3/AKR1C2/ADH7/UGT1A9/ADH1C/RBP4/CYP1B1/ALDH1A2/SPP1/UGT1A8/CYP11A1
BP	GO:0006720	isoprenoid metabolic process	16/572	5.69E-06	16	ALDH1A1/GPC3/CYP26A1/AKR1C1/UGT1A7/AKR1C3/APOE/ADH7/UGT1A9/CYP2E1/ADH1C/GPC4/RBP4/CYP1B1/ALDH1A2/UGT1A8
BP	GO:0051897	positive regulation of protein kinase B signaling	16/572	0.00011	16	GCNT2/PIK3AP1/GDF15/FGFR2/HCLS1/STOX1/AKR1C3/IGFBP5/AKR1C2/TSPYL5/CX3CL1/CD19/EGF/FGF19/CHI3L1/CCL19
BP	GO:0048736	appendage development	16/572	0.00013	16	GPC3/LEF1/PBX1/RARB/PTCH1/FGFR2/FREM2/PKDCC/RNF165/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1/COMP

BP	GO:00 60173	limb development	16/572	0.00013	16	GPC3/LEF1/PBX1/RARB/PTCH1/FGFR2/FREM2/PKDCC/RNF165/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1/COMP
BP	GO:00 50770	regulation of axonogenesis	16/572	0.00017	16	NTRK2/EPHA7/ARHGAP4/BDNF/SLIT2/KEL/NTN1/APOE/MAP1B/RND2/FGF13/NRCAM/OLFM1/SPP1/FSTL4/ROBO2
BP	GO:00 06575	cellular modified amino acid metabolic process	16/572	0.00023	16	PIPOX/CHDH/GCLC/GSTM4/PLAAT3/PLA2G2D/GATM/GSTA1/ALDH1L1/TG/PLA1A/HPN/GSTM3/GSTM2/GSTM5/MGST1
BP	GO:00 48839	inner ear development	16/572	0.00029	16	SOX2/LRIG1/MYO3A/SIX4/FGFR2/OTX1/STOX1/FREM2/NTN1/DLX6/KCNK2/HPN/EYA1/SLC44A4/COL11A1/GABRB3
BP	GO:00 60541	respiratory system development	16/572	0.00041	16	GPC3/LEF1/FOXA1/SIX4/FGFR2/PKDCC/PTN/IGFBP5/FOXJ1/TBX4/HYDIN/RBP4/ALDH1A2/CHI3L1/GLI1/AGR2
BP	GO:00 51216	cartilage development	16/572	0.00074	16	MDK/COCH/RARB/SOX5/PKDCC/SCIN/BMP7/SULF1/HOXB3/GPLD1/NKX3-2/COL21A1/CHI3L1/ALX1/COL11A1/COMP
BP	GO:00 48588	developmental cell growth	16/572	0.00239	16	EPHA7/ARHGAP4/BDNF/SLIT2/NTN1/PI16/APOE/MAP1B/RND2/FGF13/NRCAM/TMEM108/OLFM1/SYT2/SPP1/FSTL4
BP	GO:00 72330	monocarboxylic acid biosynthetic process	16/572	0.00272	16	FADS2/SLC27A2/ALOX15/GSTM4/CYP27A1/AKR1C3/GATM/CD74/APOC1/FA2H/CYP2E1/PTGIS/PRKAA2/ALDH1A2/FGF19/MLXIPL
BP	GO:00 42593	glucose homeostasis	16/572	0.00321	16	FOXA1/ADCY5/PTCH1/GCLC/POMC/SERPINF1/FAM3B/IGFBP5/KCNJ11/PPARG/RBP4/GPLD1/SLC2A4/CSMD1/PRKAA2/MLXIPL
BP	GO:00 33500	carbohydrate homeostasis	16/572	0.00334	16	FOXA1/ADCY5/PTCH1/GCLC/POMC/SERPINF1/FAM3B/IGFBP5/KCNJ11/PPARG/RBP4/GPLD1/SLC2A4/CSMD1/PRKAA2/MLXIPL
BP	GO:00 06836	neurotransmitter transport	16/572	0.00934	16	SLC29A2/SYNGR3/TSPOAP1/PCLO/ICA1/SV2B/SV2A/CACNA1D/SYT2/MAOB/KCNJ10/SLC44A4/CACNA1B/SLC6A4/PPP1R9A/CPLX2
BP	GO:00 07548	sex differentiation	16/572	0.00934	16	SYCP2/MERTK/BCL2/PBX1/SIX4/DMRT3/NUPR1/SLIT2/AKR1C3/DACH1/RBP4/HOXA9/ROBO2/NR5A1/MGST1/NR0B1
BP	GO:00 43270	positive regulation of ion transport	16/572	0.011	16	KCNE3/WNK2/FGF14/CTSS/KCNJ11/APOE/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/KCNH2/FGF12/CD19/SLC6A4/ATP2A1
BP	GO:00 50890	cognition	16/572	0.02066	16	NTRK2/MDK/MGAT3/BDNF/AFF2/NRXN3/SERPINF1/PTN/GATM/PPP1R1B/APOE/KCNK2/FGF13/SLC6A4/GRIN2A/SCN2A
BP	GO:00 51235	maintenance of location	16/572	0.03401	16	FTL/PLCE1/TMSB15A/PLCH1/SCIN/APOE/GSTM2/CX3CL1/HAP1/PPARG/IGSF11/CD19/PDIA2/CCL19/NR5A1/ATP2A1
CC	GO:00 34703	cation channel complex	16/590	0.001	16	EPS8/SCN9A/KCNE3/KCNS3/KCNH1/KCNJ11/CACNB4/KCNK2/SCNN1A/CACNA2D1/CACNA1D/KCNH2/CACNA1B/GRIN2A/SCN2A/ATP2A1
MF	GO:00 16705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	16/559	4.48E-05	16	P4HTM/FADS2/CYP26A1/FMO3/CYP4F3/AKR1C1/CYP27A1/AKR1C3/NOS2/AKR1C2/CYP2E1/PTGIS/CYP4X1/CYP1B1/CYP4F11/CYP11A1

MF	GO:0031406	carboxylic acid binding	16/559	0.00043	16	P4HTM/CYP26A1/GCHFR/GCLC/AKR1C1/OXER1/UGT1A7/NOS2/AKR1C2/APOC1/UGT1A9/PPARG/GPR143/CD22/CYP4F11/UGT1A8
MF	GO:0005244	voltage-gated ion channel activity	16/559	0.00054	16	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/CLIC6/KCNJ11/CACNB4/KCNK2/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A/SCN2A
MF	GO:0022832	voltage-gated channel activity	16/559	0.00054	16	SCN9A/KCNE3/KCNS3/KCNH1/TSPOAP1/CLIC6/KCNJ11/CACNB4/KCNK2/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A/SCN2A
MF	GO:0043177	organic acid binding	16/559	0.00083	16	P4HTM/CYP26A1/GCHFR/GCLC/AKR1C1/OXER1/UGT1A7/NOS2/AKR1C2/APOC1/UGT1A9/PPARG/GPR143/CD22/CYP4F11/UGT1A8
BP	GO:0001523	retinoid metabolic process	15/572	6.32E-07	15	ALDH1A1/GPC3/CYP26A1/AKR1C1/UGT1A7/AKR1C3/APOE/ADH7/UGT1A9/ADH1C/GPC4/RBP4/CYP1B1/ALDH1A2/UGT1A8
BP	GO:0016101	diterpenoid metabolic process	15/572	1.32E-06	15	ALDH1A1/GPC3/CYP26A1/AKR1C1/UGT1A7/AKR1C3/APOE/ADH7/UGT1A9/ADH1C/GPC4/RBP4/CYP1B1/ALDH1A2/UGT1A8
BP	GO:0022612	gland morphogenesis	15/572	3.99E-06	15	MDK/BCL2/FOXA1/PTCH1/FGFR2/PTN/IGFBP5/NTN1/BMP7/ELF3/NKX2-3/HPN/SULF1/SOSTDC1/GLI1
BP	GO:0035107	appendage morphogenesis	15/572	5.05E-05	15	GPC3/LEF1/PBX1/RARB/PTCH1/FGFR2/FREM2/PKDCC/RNF165/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1
BP	GO:0035108	limb morphogenesis	15/572	5.05E-05	15	GPC3/LEF1/PBX1/RARB/PTCH1/FGFR2/FREM2/PKDCC/RNF165/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1
BP	GO:0006022	aminoglycan metabolic process	15/572	0.00024	15	GPC3/GCNT2/PXYLP1/CHST7/ABCC5/OGN/OMD/CHST6/HS3ST6/GPC4/PRELP/CHIT1/EGF/SPOCK3/CHST9
BP	GO:0098657	import into cell	15/572	0.00083	15	WNK2/SLC29A2/SYNGR3/SLC27A2/SLC9A2/KCNJ11/TRPV6/SLC9A4/SLC7A2/CACNA2D1/KCNH2/KCNJ10/SLC6A4/ATP12A/LTF
BP	GO:0001763	morphogenesis of a branching structure	15/572	0.00107	15	EPHA7/MDK/BCL2/GPC3/LEF1/PBX1/FOXA1/SIX4/PTCH1/FGFR2/SLIT2/BMP7/SULF1/EYA1/EGF
BP	GO:0035637	multicellular organismal signaling	15/572	0.0016	15	NTRK2/SCN9A/KCNE3/DMRT3/FXYD6/MYH14/KCNJ11/CACNB4/CACNA2D1/CACNA1D/NRCAM/KCNH2/FGF12/SCN2A/ATP2A1
BP	GO:0071229	cellular response to acid chemical	15/572	0.00203	15	NTRK2/MYB/FZD7/RARB/GCLC/FGFR2/AKR1C1/SERPINF1/AKR1C3/RORB/AKR1C2/PPARG/PRKAA2/ALDH1A2/SLC6A4
BP	GO:0050807	regulation of synapse organization	15/572	0.00304	15	NTRK2/EPHA7/SIX4/BDNF/CTTNBP2/PTN/NTN1/SYNDIG1/APOE/LRRN1/NRCAM/GPC4/ROBO2/ADGRB1/PPP1R9A
BP	GO:0009952	anterior/posterior pattern specification	15/572	0.00318	15	HEY1/GPC3/LEF1/PBX1/HHEX/OTX1/CRB2/HOXB3/HOXA9/ALDH1A2/ALX1/TCF15/FOXH1/DMRT2/PAX1
BP	GO:0048762	mesenchymal cell differentiation	15/572	0.00331	15	HEY1/MDK/BCL2/GCNT2/LEF1/FOXA1/FGFR2/BMP7/HPN/CRB2/NRTN/OLFM1/ALDH1A2/FGF19/ALX1
BP	GO:0050803	regulation of synapse structure or activity	15/572	0.00444	15	NTRK2/EPHA7/SIX4/BDNF/CTTNBP2/PTN/NTN1/SYNDIG1/APOE/LRRN1/NRCAM/GPC4/ROBO2/ADGRB1/PPP1R9A

BP	GO:0051402	neuron apoptotic process	15/572	0.00706	15	NTRK2/EPHA7/MDK/BCL2/MYB/TRIM2/SIX4/GCLC/NUPR1/BDNF/APOE/CX3CL1/SCN2A/GABRB3/POU4F1
BP	GO:0030217	T cell differentiation	15/572	0.00733	15	MDK/BCL2/MYB/FZD7/LEF1/PLA2G2D/CD74/NKX2-3/FOXJ1/ZAP70/CR1/LILRB4/THEMIS/CCL19/PAX1
BP	GO:0022409	positive regulation of cell-cell adhesion	15/572	0.01236	15	SOX2/MDK/MYB/GCNT2/FOXA1/ALOX15/VCAM1/VTCN1/BMP7/CD74/SKAP1/ZAP70/LILRB4/CX3CL1/CCL19
BP	GO:0007611	learning or memory	15/572	0.01277	15	NTRK2/MDK/BDNF/AFF2/NRXN3/SERPINF1/PTN/GATM/PPP1R1B/APOE/KCNK2/FGF13/SLC6A4/GRIN2A/SCN2A
BP	GO:0003007	heart morphogenesis	15/572	0.01407	15	HEY1/RARB/PTCH1/FGFR2/SLIT2/BMP7/RBP4/ELN/OLFM1/EYA1/ALDH1A2/ROBO2/COL11A1/FOXH1/POU4F1
BP	GO:0046883	regulation of hormone secretion	15/572	0.01547	15	MYB/ADCY5/KCNS3/POMC/ICA1/ILDR1/TFR2/KCNJ11/NOS2/C1QTNF3/CACNA1D/RBP4/GPLD1/BLK/SPP1
BP	GO:0022898	regulation of transmembrane transporter activity	15/572	0.0186	15	BCL2/KCNE3/WNK2/FGF14/FXYD6/CTSS/KCNJ11/CACNB4/CACNA2D1/CACNA1D/GSTM2/HAP1/FGF12/GRIN2A/ATP2A1
BP	GO:0005996	monosaccharide metabolic process	15/572	0.03173	15	ALDH1A1/PGD/GCLC/POMC/UGT1A7/UGT1A6/KCNJ11/UGT1A9/C1QTNF3/FBP1/RBP4/GPLD1/UGT2A1/UGT1A8/TFF3
BP	GO:0007162	negative regulation of cell adhesion	15/572	0.03343	15	MDK/GCNT2/EPCAM/FZD7/PDE3B/NEXMIF/VTCN1/PLA2G2D/CD74/ADAM22/FOXJ1/ADAMDEC1/CX3CL1/CYP1B1/SCGB1A1
BP	GO:0090287	regulation of cellular response to growth factor stimulus	15/572	0.0361	15	GPC3/HHEX/SMOC2/SLIT2/RNF165/ASPN/SULF1/CRB2/SHISA2/TMEM108/PEG10/CHRDL1/SFRP4/SOSTDC1/SOST
BP	GO:0072073	kidney epithelium development	14/572	0.0001	14	EPHA7/BCL2/GPC3/EPCAM/PBX1/RARB/SIX4/PTCH1/FGFR2/SLIT2/BMP7/FOXJ1/EYA1/ROBO2
BP	GO:0030509	BMP signaling pathway	14/572	0.00034	14	GPC3/LEF1/GDF15/RGMA/RNF165/BMP7/SULF1/CRB2/CHRDL1/DSG4/SFRP4/SOSTDC1/SOST/COMP
BP	GO:0030203	glycosaminoglycan metabolic process	14/572	0.00042	14	GPC3/GCNT2/PXYLP1/CHST7/ABCC5/OGN/OMD/CHST6/HS3ST6/GPC4/PRELP/EGF/SPOCK3/CHST9
BP	GO:0031214	biomineral tissue development	14/572	0.0005	14	HEY1/GPC3/ALOX15/FGFR2/PKDCC/PTN/BMP7/OMD/TMEM119/ASPN/SPP1/COMP/LTF/ODAM
BP	GO:0110148	biomineralization	14/572	0.0005	14	HEY1/GPC3/ALOX15/FGFR2/PKDCC/PTN/BMP7/OMD/TMEM119/ASPN/SPP1/COMP/LTF/ODAM
BP	GO:0071772	response to BMP	14/572	0.00077	14	GPC3/LEF1/GDF15/RGMA/RNF165/BMP7/SULF1/CRB2/CHRDL1/DSG4/SFRP4/SOSTDC1/SOST/COMP
BP	GO:0071773	cellular response to BMP stimulus	14/572	0.00077	14	GPC3/LEF1/GDF15/RGMA/RNF165/BMP7/SULF1/CRB2/CHRDL1/DSG4/SFRP4/SOSTDC1/SOST/COMP
BP	GO:0008361	regulation of cell size	14/572	0.00126	14	EPHA7/ARHGAP4/BDNF/KEL/NTN1/APOE/MAP1B/RND2/FGF13/DEPTOR/NRCAM/OLFM1/SPP1/FSTL4
BP	GO:0061138	morphogenesis of a branching epithelium	14/572	0.00148	14	MDK/BCL2/GPC3/LEF1/PBX1/FOXA1/SIX4/PTCH1/FGFR2/SLIT2/BMP7/SULF1/EYA1/EGF

BP	GO:0044272	sulfur compound biosynthetic process	14/572	0.00244	14	CBS/CHST7/GCLC/GSTM4/OGN/GSTA1/OMD/CHST6/GSTM3/GSTM2/PRELP/GSTM5/MGST1/CHST9
BP	GO:0034764	positive regulation of transmembrane transport	14/572	0.00422	14	GPC3/KCNE3/WNK2/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/CX3CL1/HAP1/KCNH2/CD19/FGF19/ATP2A1
BP	GO:0030100	regulation of endocytosis	14/572	0.0044	14	GPC3/ALOX15/PRKD1/TFR2/APOE/APOC1/CLU/PPARG/SLC2A4/STAP1/CD22/EGF/SFRP4/CCL19
BP	GO:0009612	response to mechanical stimulus	14/572	0.00543	14	MDK/KIAA0319/PTCH1/GCLC/ETV1/TMEM150C/PTN/MAP1B/KCNK2/HPN/PPARG/CHI3L1/COL11A1/SOST
BP	GO:0043523	regulation of neuron apoptotic process	14/572	0.00543	14	NTRK2/EPHA7/MDK/BCL2/MYB/TRIM2/SIX4/GCLC/NUPR1/BDNF/APOE/CX3CL1/GABRB3/POU4F1
BP	GO:0071805	potassium ion transmembrane transport	14/572	0.0072	14	KCNE3/WNK2/KCNS3/KCNH1/SLC9A2/KEL/KCNJ11/SLC9A4/KCNK2/HPN/CACNA1D/KCNH2/KCNJ10/ATP12A
BP	GO:0007584	response to nutrient	14/572	0.00778	14	CYP26A1/ALDH3A1/GCLC/VCAM1/PTN/AKR1C3/BMP7/KCNJ11/MAP1B/PPARG/ALDH1A2/SPP1/PENK/SLC6A4
BP	GO:0051651	maintenance of location in cell	14/572	0.00778	14	FTL/PLCE1/TMSB15A/PLCH1/SCIN/APOE/GSTM2/CX3CL1/HAP1/CD19/PDIA2/CCL19/NR5A1/ATP2A1
BP	GO:0001649	osteoblast differentiation	14/572	0.00974	14	SOX2/LEF1/PTCH1/FGFR2/PRKD1/IGFBP5/BMP7/RORB/TMEM119/ITGA11/SPP1/PENK/GLI1/LTF
BP	GO:0001894	tissue homeostasis	14/572	0.01125	14	BCL2/GCNT2/TMEM119/MUC2/RBP4/LYZ/JCHAIN/MUC6/SPP1/ZG16B/MUC4/MUC13/LTF/TFF3
BP	GO:0048738	cardiac muscle tissue development	14/572	0.01294	14	DIPK2A/FZD7/RARB/FGFR2/BMP7/PI16/KCNK2/RBP4/MYH11/ALDH1A2/GLI1/COL11A1/FOXH1/POU4F1
BP	GO:0006813	potassium ion transport	14/572	0.01636	14	KCNE3/WNK2/KCNS3/KCNH1/SLC9A2/KEL/KCNJ11/SLC9A4/KCNK2/HPN/CACNA1D/KCNH2/KCNJ10/ATP12A
BP	GO:0032412	regulation of ion transmembrane transporter activity	14/572	0.02996	14	KCNE3/WNK2/FGF14/FXYD6/CTSS/KCNJ11/CACNB4/CACNA2D1/CACNA1D/GSTM2/HAP1/FGF12/GRIN2A/ATP2A1
BP	GO:1901617	organic hydroxy compound biosynthetic process	14/572	0.03531	14	ISYNA1/SLC27A2/ALOX15/PLCE1/CES1/CYP27A1/PLCH1/AKR1C3/APOE/INSM1/OCA2/PLCB4/PRKAA2/FGF19
CC	GO:0070382	exocytic vesicle	14/590	0.00391	14	SYNGR3/TMEM163/BDNF/CTTNBP2/LGI3/ICA1/SV2B/SV2A/HAP1/SYT2/PENK/GRIN2A/SYTL5/KIF1A
MF	GO:0004497	monooxygenase activity	14/559	2.70E-06	14	CYP26A1/FMO3/CYP4F3/AKR1C1/CYP27A1/AKR1C3/NOS2/AKR1C2/CYP2E1/PTGIS/CYP4X1/CYP1B1/CYP4F11/CYP11A1
MF	GO:0005506	iron ion binding	14/559	0.00033	14	P4HTM/FTL/CYP26A1/ALOX15/CYP4F3/CYP27A1/FA2H/CYP2E1/PTGIS/CYP4X1/CYP1B1/CYP4F11/LTF/CYP11A1
MF	GO:0008083	growth factor activity	14/559	0.00068	14	MDK/IL34/GDF15/FGF14/BDNF/PTN/BMP7/OGN/FGF13/FGF12/NRTN/EGF/FGF19/THBS4
BP	GO:0001657	ureteric bud development	13/572	8.08E-06	13	BCL2/GPC3/EPCAM/PBX1/RARB/SIX4/PTCH1/FGFR2/SLIT2/BMP7/FOXJ1/EYA1/ROBO2
BP	GO:0072163	mesonephric epithelium development	13/572	9.06E-06	13	BCL2/GPC3/EPCAM/PBX1/RARB/SIX4/PTCH1/FGFR2/SLIT2/BMP7/FOXJ1/EYA1/ROBO2

BP	GO:0072164	mesonephric tubule development	13/572	9.06E-06	13	BCL2/GPC3/EPCAM/PBX1/RARB/SIX4/PTCH1/FGFR2/SLIT2/BMP7/FOXJ1/EYA1/ROBO2
BP	GO:0001708	cell fate specification	13/572	1.01E-05	13	SOX2/LMO4/FZD7/MIAT/FOXA1/PTCH1/DMRT3/EYA2/TBX4/PTCH2/DMRTA2/EYA1/POU4F1
BP	GO:0001823	mesonephros development	13/572	1.41E-05	13	BCL2/GPC3/EPCAM/PBX1/RARB/SIX4/PTCH1/FGFR2/SLIT2/BMP7/FOXJ1/EYA1/ROBO2
BP	GO:0006024	glycosaminoglycan biosynthetic process	13/572	3.20E-05	13	GPC3/GCNT2/PXYLP1/CHST7/ABCC5/OGN/OMD/CHST6/HS3ST6/GPC4/PRELP/EGF/CHST9
BP	GO:0048640	negative regulation of developmental growth	13/572	4.26E-05	13	EPHA7/ARHGAP4/PTCH1/GDF15/PLAC8/NTN1/PI16/KCNK2/FGF13/RBP4/SPP1/FSTL4/SLC6A4
BP	GO:0006023	aminoglycan biosynthetic process	13/572	5.13E-05	13	GPC3/GCNT2/PXYLP1/CHST7/ABCC5/OGN/OMD/CHST6/HS3ST6/GPC4/PRELP/EGF/CHST9
BP	GO:0042471	ear morphogenesis	13/572	6.72E-05	13	LRIG1/MYO3A/SIX4/FGFR2/OTX1/STOX1/NTN1/DLX6/HPN/EYA1/NKX3-2/SLC44A4/COL11A1
BP	GO:0048706	embryonic skeletal system development	13/572	0.00013	13	PBX1/SIX4/FGFR2/BMP7/SULF1/RBP4/HOXB3/HOXA9/EYA1/NKX3-2/ALX1/COL11A1/DMRT2
BP	GO:0042552	myelination	13/572	0.00021	13	NTRK2/RARB/UGT8/KEL/PTN/ADAM22/PLLP/TG/FA2H/CLU/MYRF/KCNJ10/SCN2A
BP	GO:0007272	ensheathment of neurons	13/572	0.00024	13	NTRK2/RARB/UGT8/KEL/PTN/ADAM22/PLLP/TG/FA2H/CLU/MYRF/KCNJ10/SCN2A
BP	GO:0008366	axon ensheathment	13/572	0.00024	13	NTRK2/RARB/UGT8/KEL/PTN/ADAM22/PLLP/TG/FA2H/CLU/MYRF/KCNJ10/SCN2A
BP	GO:0048754	branching morphogenesis of an epithelial tube	13/572	0.00073	13	MDK/BCL2/GPC3/LEF1/PBX1/FOXA1/SIX4/PTCH1/FGFR2/SLIT2/BMP7/EYA1/EGF
BP	GO:0061351	neural precursor cell proliferation	13/572	0.00073	13	MDK/LEF1/FGFR2/SOX5/PTN/FGF13/INSM1/DMRTA2/CX3CL1/EGF/SLC6A4/GLI1/KIF1A
BP	GO:0030902	hindbrain development	13/572	0.00082	13	MDK/BCL2/LEF1/OTX1/PTN/BMP7/HAP1/HOXB3/ALDH1A2/EGF/SLC6A4/GLI1/POU4F1
BP	GO:0042133	neurotransmitter metabolic process	13/572	0.00087	13	GCHFR/CHDH/PHGDH/NOS2/SLC7A2/PTGIS/CLU/CYP1B1/ENPP6/MAOB/SLC44A4/SLC6A4/GRIN2A
BP	GO:0030324	lung development	13/572	0.00252	13	GPC3/FOXA1/FGFR2/PKDCC/PTN/IGFBP5/FOXJ1/TBX4/RBP4/ALDH1A2/CHI3L1/GLI1/AGR2
BP	GO:0030323	respiratory tube development	13/572	0.00307	13	GPC3/FOXA1/FGFR2/PKDCC/PTN/IGFBP5/FOXJ1/TBX4/RBP4/ALDH1A2/CHI3L1/GLI1/AGR2
BP	GO:0060401	cytosolic calcium ion transport	13/572	0.00307	13	BCL2/PLCE1/PLCH1/SLC35G1/TRPV6/CACNA2D1/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CCL19
BP	GO:0031345	negative regulation of cell projection organization	13/572	0.00537	13	EPHA7/ARHGAP4/KIAA0319/MYLIP/RGMA/SLIT2/NTN1/CRMP1/APOE/FGF13/STAP1/SPP1/FSTL4
BP	GO:0044242	cellular lipid catabolic process	13/572	0.01661	13	CEL/CYP26A1/SLC27A2/CYP4F3/AOAH/AKR1C3/APOE/APOC1/GLYATL2/GPLD1/CYP1B1/AADAC/ENPP6
BP	GO:0010001	glial cell differentiation	13/572	0.01719	13	SOX2/NTRK2/MDK/LEF1/IL34/PHGDH/PTN/ADAM22/FA2H/CLU/PPARG/MYRF/KCNJ10
BP	GO:0070663	regulation of leukocyte proliferation	13/572	0.01966	13	BCL2/HHEX/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP70/IKZF3/TNFSF18/CD22/CCL19/SCGB1A1

BP	GO:0051048	negative regulation of secretion	13/572	0.03226	13	ADRA2B/CD200/KCNJ11/CD74/APOE/STXBP6/C1QTNF3/BANK1/CX3CL1/MAOB/CD22/EGF/PPP1R9A
BP	GO:0090092	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	13/572	0.03516	13	GPC3/GDF15/RNF165/BMP7/ASPN/SULF1/CRB2/CILP/PEG10/CHRDL1/SFRP4/SOSTDC1/SOST
CC	GO:0005796	Golgi lumen	13/590	1.10E-05	13	GPC3/OGN/OMD/MUC2/PODXL2/GPC4/PRELP/MUC6/MUC20/MMP11/MUC4/MUC13/MUC5B
CC	GO:0008021	synaptic vesicle	13/590	0.00506	13	SYNGR3/TMEM163/BDNF/CTTNBP2/LGI3/ICA1/SV2B/SV2A/HAP1/SYT2/PENK/GRIN2A/KIF1A
MF	GO:0022843	voltage-gated cation channel activity	13/559	0.00057	13	KCNE3/KCNS3/KCNH1/TSPOAP1/KCNJ11/CACNB4/KCNK2/CACNA2D1/CACNA1D/KCNH2/KCNJ10/CACNA1B/GRIN2A
BP	GO:0007422	peripheral nervous system development	12/572	2.74E-06	12	NTRK2/GFRA3/ETV1/UGT8/BDNF/SERPINI1/ADAM22/NEFH/FA2H/GSTM3/ADGRB1/POU4F1
BP	GO:0042472	inner ear morphogenesis	12/572	4.50E-05	12	LRIG1/MYO3A/SIX4/FGFR2/OTX1/STOX1/NTN1/DLX6/HPN/EYA1/SLC44A4/COL11A1
BP	GO:0032526	response to retinoic acid	12/572	0.00012	12	MYB/FZD7/CYP26A1/RARB/PTCH1/FGFR2/SERPINF1/RORB/PPARG/RBP4/ALDH1A2/SLC6A4
BP	GO:0001676	long-chain fatty acid metabolic process	12/572	0.00013	12	FADS2/SLC27A2/ALOX15/CYP4F3/GSTM4/AKR1C3/GSTA1/CYP2E1/PTGIS/GSTM2/GLYATL2/CYP1B1
BP	GO:0033559	unsaturated fatty acid metabolic process	12/572	0.00014	12	FADS2/ALOX15/CYP4F3/AKR1C3/GSTA1/CD74/AKR1C2/CYP2E1/PTGIS/GSTM2/GLYATL2/CYP1B1
BP	GO:0061387	regulation of extent of cell growth	12/572	0.00014	12	EPHA7/ARHGAP4/BDNF/NTN1/APOE/MAP1B/RND2/FGF13/NRCAM/OLFM1/SPP1/FSTL4
BP	GO:0002062	chondrocyte differentiation	12/572	0.0004	12	MDK/COCH/RARB/SOX5/PKDCC/SCIN/SULF1/GPLD1/NKX3-2/COL21A1/COL11A1/COMP
BP	GO:0030326	embryonic limb morphogenesis	12/572	0.00046	12	GPC3/LEF1/PBX1/RARB/PTCH1/FREM2/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1
BP	GO:0035113	embryonic appendage morphogenesis	12/572	0.00046	12	GPC3/LEF1/PBX1/RARB/PTCH1/FREM2/BMP7/DLX6/TBX4/HOXA9/ALDH1A2/ALX1
BP	GO:0007586	digestion	12/572	0.00119	12	CEL/ADM2/AKR1C1/AKR1C2/SLC9A4/MUC2/RBP4/MUC6/CHIT1/MUC4/MUC13/TFF3
BP	GO:1904064	positive regulation of cation transmembrane transport	12/572	0.00161	12	KCNE3/WNK2/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/CX3CL1/HAP1/KCNH2/CD19/ATP2A1
BP	GO:0010977	negative regulation of neuron projection development	12/572	0.00298	12	EPHA7/ARHGAP4/KIAA0319/MYLIP/RGMA/SLIT2/NTN1/CRMP1/APOE/FGF13/SPP1/FSTL4
BP	GO:0034767	positive regulation of ion transmembrane transport	12/572	0.00314	12	KCNE3/WNK2/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/CX3CL1/HAP1/KCNH2/CD19/ATP2A1
BP	GO:0060402	calcium ion transport into cytosol	12/572	0.00349	12	BCL2/PLCE1/PLCH1/TRPV6/CACNA2D1/GSTM2/CX3CL1/HAP1/CD19/MS4A1/GRIN2A/CCL19
BP	GO:0003205	cardiac chamber development	12/572	0.00653	12	HEY1/LMO4/RARB/FGFR2/SLIT2/BMP7/KCNK2/RBP4/ROBO2/COL11A1/FOXH1/POU4F1

BP	GO:00 48167	regulation of synaptic plasticity	12/572	0.01279	12	NTRK2/FGF14/PTN/APOE/MAP1B/CX3CL1/IGSF11 /KCNJ10/GRIN2A/ADGRB1/PPP1R9A/CPLX2
BP	GO:19 01654	response to ketone	12/572	0.01607	12	ADCY5/SLIT2/SERPINF1/PTN/AKR1C3/KCNJ11/A KR1C2/PPARG/PRKAA2/MAOB/SPP1/CCL19
BP	GO:00 06694	steroid biosynthetic process	12/572	0.01792	12	PBX1/SLC27A2/TSPOAP1/CES1/CYP27A1/AKR1C 3/APOE/PRKAA2/FGF19/NR5A1/CYP11A1/NR0B1
BP	GO:00 50866	negative regulation of cell activation	12/572	0.01994	12	MERTK/MDK/GCLC/CD200/VTCN1/PLA2G2D/CD7 4/FOXJ1/APOE/BANK1/CX3CL1/SCGB1A1
BP	GO:00 02573	myeloid leukocyte differentiation	12/572	0.02366	12	GPC3/LEF1/IL34/HCLS1/UBD/CD74/NKX2- 3/LILRB4/PPARG/CCL19/LTF/POU4F1
BP	GO:00 35265	organ growth	12/572	0.02366	12	BCL2/DIPK2A/COCH/RARB/FGFR2/PI16/KCNK2/R BP4/COL21A1/SLC6A4/GLI1/COMP
BP	GO:00 50679	positive regulation of epithelial cell proliferation	12/572	0.02528	12	MDK/FZD7/FGFR2/STOX1/PRKD1/PTN/DLX6/CCL 26/HPN/EYA1/THBS4/ODAM
BP	GO:00 02064	epithelial cell development	12/572	0.02612	12	ARHGEF26/FOXA1/RARB/CLDN3/FOXJ1/SLC9A4/ HYDIN/INSM1/GSTM3/COL4A4/DNASE1L2/NKX3-2
BP	GO:00 50670	regulation of lymphocyte proliferation	12/572	0.02698	12	BCL2/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP 70/IKZF3/TNFSF18/CD22/CCL19/SCGB1A1
BP	GO:19 01215	negative regulation of neuron death	12/572	0.02698	12	NTRK2/MDK/BCL2/SIX4/GCLC/BDNF/CD200/SERP INF1/APOE/CX3CL1/GABRB3/POU4F1
BP	GO:00 32944	regulation of mononuclear cell proliferation	12/572	0.02787	12	BCL2/VCAM1/VTCN1/PLA2G2D/CD74/FOXJ1/ZAP 70/IKZF3/TNFSF18/CD22/CCL19/SCGB1A1
BP	GO:00 10810	regulation of cell-substrate adhesion	12/572	0.0336	12	MDK/BCL2/GCNT2/FZD7/SMOC2/ALOX15/NEXMIF /PTN/EMID1/SKAP1/CX3CL1/AGR2
BP	GO:00 50920	regulation of chemotaxis	12/572	0.03569	12	MDK/SMOC2/PRKD1/SLIT2/PTN/CD74/CCL26/CX CL17/STAP1/ROBO2/THBS4/CCL19
MF	GO:00 16298	lipase activity	12/559	0.0007	12	CEL/PLCE1/CES1/CES3/PLAAT3/PLCH1/PLA2G2D /PLA1A/LIPH/PLCB4/GPLD1/AADAC
MF	GO:00 20037	heme binding	12/559	0.00119	12	CBS/CYP26A1/CYP4F3/CYP27A1/NOS2/FA2H/CY P2E1/PTGIS/CYP4X1/CYP1B1/CYP4F11/CYP11A1
MF	GO:00 46906	tetrapyrrole binding	12/559	0.0022	12	CBS/CYP26A1/CYP4F3/CYP27A1/NOS2/FA2H/CY P2E1/PTGIS/CYP4X1/CYP1B1/CYP4F11/CYP11A1
BP	GO:00 51963	regulation of synapse assembly	11/572	0.00041	11	NTRK2/EPHA7/SIX4/BDNF/NTN1/SYNDIG1/LRRN1 /GPC4/ROBO2/ADGRB1/PPP1R9A
BP	GO:00 30282	bone mineralization	11/572	0.00075	11	GPC3/ALOX15/FGFR2/PKDCC/PTN/BMP7/OMD/T MEM119/ASPN/COMP/LTF
BP	GO:00 07613	memory	11/572	0.00094	11	MDK/BDNF/SERPINF1/PTN/PPP1R1B/APOE/KCN K2/FGF13/SLC6A4/GRIN2A/SCN2A
BP	GO:00 45471	response to ethanol	11/572	0.00161	11	EPS8/CLDN3/FGFR2/VCAM1/ADH7/CYP2E1/RBP4 /SLC2A4/MAOB/PENK/GRIN2A
BP	GO:00 35270	endocrine system development	11/572	0.00183	11	SOX2/MDK/PBX1/TG/INSM1/HOXB3/ALDH1A2/GLI 1/NR5A1/NR0B1/PAX1
BP	GO:00 01508	action potential	11/572	0.00263	11	NTRK2/SCN9A/KCNE3/MYH14/FGF13/CACNA2D1/ CACNA1D/NRCAM/KCNH2/FGF12/SCN2A
BP	GO:00 32355	response to estradiol	11/572	0.00279	11	ARNT2/FOXA1/PTCH1/PTN/BMP7/KCNJ11/MAP1B /ALDH1A2/PENK/SLC6A4/POU4F1

BP	GO:0007498	mesoderm development	11/572	0.00296	11	LEF1/FGFR2/TXNRD1/EYA2/BMP7/IKZF3/CRB2/EYA1/TCF15/FOXH1/POU4F1
BP	GO:0001837	epithelial to mesenchymal transition	11/572	0.00413	11	HEY1/MDK/GCNT2/LEF1/FOXA1/FGFR2/BMP7/HPN/CRB2/OLFM1/ALX1
BP	GO:0072006	nephron development	11/572	0.00436	11	BCL2/GPC3/PBX1/SIX4/PTCH1/PLCE1/BMP7/FOXJ1/SULF1/COL4A4/EYA1
BP	GO:0007605	sensory perception of sound	11/572	0.0051	11	LRIG1/MYO3A/COCH/MYH14/EPYC/HPN/CACNA1D/ESPNL/EYA1/COL11A1/GABRB3
BP	GO:1901861	regulation of muscle tissue development	11/572	0.00831	11	BCL2/FZD7/LEF1/SIX4/FGFR2/IGFBP5/PI16/KCNK2/RBP4/MEGF10/GLI1
BP	GO:0001764	neuron migration	11/572	0.0091	11	NTRK2/MDK/KIAA0319/GFRA3/NEXMIF/NTN1/MAP1B/IGSF10/FGF13/NRCAM/CX3CL1
BP	GO:0007519	skeletal muscle tissue development	11/572	0.01041	11	ZBTB18/BCL2/SIX4/HLF/NUPR1/KEL/MYH14/DMRTA2/ELN/MEGF10/COL19A1
BP	GO:0030833	regulation of actin filament polymerization	11/572	0.01136	11	EPS8/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/ELN/ADD2/PPP1R9A
BP	GO:0006633	fatty acid biosynthetic process	11/572	0.01237	11	FADS2/ALOX15/GSTM4/AKR1C3/CD74/APOC1/FA2H/CYP2E1/PTGIS/PRKAA2/MLXIPL
BP	GO:0050680	negative regulation of epithelial cell proliferation	11/572	0.0129	11	SOX2/GPC3/PTCH1/NUPR1/FGFR2/SERPINF1/PTN/APOE/HPN/SULF1/PPARG
BP	GO:0050954	sensory perception of mechanical stimulus	11/572	0.0129	11	LRIG1/MYO3A/COCH/MYH14/EPYC/HPN/CACNA1D/ESPNL/EYA1/COL11A1/GABRB3
BP	GO:0060538	skeletal muscle organ development	11/572	0.0152	11	ZBTB18/BCL2/SIX4/HLF/NUPR1/KEL/MYH14/DMRTA2/ELN/MEGF10/COL19A1
BP	GO:0043433	negative regulation of DNA-binding transcription factor activity	11/572	0.01582	11	PTCH1/NUPR1/CD200/BMP7/FOXJ1/PTGIS/CYP1B1/NWD1/SFRP4/FOXH1/NR0B1
BP	GO:0008064	regulation of actin polymerization or depolymerization	11/572	0.02228	11	EPS8/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/ELN/ADD2/PPP1R9A
BP	GO:0030832	regulation of actin filament length	11/572	0.0231	11	EPS8/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/ELN/ADD2/PPP1R9A
BP	GO:0030041	actin filament polymerization	11/572	0.02481	11	EPS8/ALOX15/HCLS1/SLIT2/TMSB15A/SCIN/CCL26/SPIRE2/ELN/ADD2/PPP1R9A
BP	GO:0043401	steroid hormone mediated signaling pathway	11/572	0.02481	11	LEF1/FOXA1/RARB/BMP7/RORB/NR3C2/PPARG/FOXH1/SCGB2A1/NR5A1/NR0B1
BP	GO:0007369	gastrulation	11/572	0.02754	11	SOX2/GPC3/FZD7/LEF1/FGFR2/TXNRD1/EYA2/BMP7/CRB2/EYA1/COL11A1
BP	GO:1903708	positive regulation of hemopoiesis	11/572	0.02754	11	MDK/MYB/LEF1/IL34/HCLS1/SCIN/CD74/ZAP70/LILRB4/CCL19/POU4F1
BP	GO:0030308	negative regulation of cell growth	11/572	0.0285	11	EPHA7/BCL2/ARHGAP4/SLIT2/NTN1/PI16/FGF13/PPARG/FBP1/SPP1/FSTL4
BP	GO:0099111	microtubule-based transport	11/572	0.02948	11	ICK/NEFH/MAP1B/UCHL1/AP3B2/HAP1/CABYR/TMEM108/DYNC1I1/KIF1A/ACTL8

BP	GO:1901888	regulation of cell junction assembly	11/572	0.03476	11	NTRK2/EPHA7/SIX4/BDNF/NTN1/SYNDIG1/LRRN1/GPC4/ROBO2/ADGRB1/PPP1R9A
MF	GO:0005178	integrin binding	11/559	0.00313	11	ICAM4/ITGBL1/VCAM1/PTN/ADAM22/CCN5/CX3CL1/ADAM23/SPP1/THBS4/COMP
MF	GO:0015079	potassium ion transmembrane transporter activity	11/559	0.01229	11	KCNE3/KCNS3/KCNH1/SLC9A2/KCNJ11/SLC9A4/KCNK2/HPN/KCNH2/KCNJ10/ATP12A
BP	GO:0021675	nerve development	10/572	0.00015	10	LRIG1/SIX4/BDNF/VCAM1/RNF165/SULF1/NRTN/HOXB3/GABRB3/POU4F1
BP	GO:0034308	primary alcohol metabolic process	10/572	0.00027	10	ALDH1A1/AKR1C1/AKR1C3/AKR1C2/ADH7/ADH1C/RBP4/CYP1B1/ALDH1A2/CYP11A1
BP	GO:0051899	membrane depolarization	10/572	0.00047	10	BCL2/SCN9A/GCLC/CACNB4/CACNA2D1/CACNA1D/KCNH2/FGF12/CACNA1B/SCN2A
BP	GO:0050905	neuromuscular process	10/572	0.00165	10	ADCY5/TMEM150C/UCHL1/FGF12/CSMD1/PENK/GRIN2A/TCF15/COMP/POU4F1
BP	GO:0014902	myotube differentiation	10/572	0.00232	10	BCL2/SIX4/KCNH1/GDF15/MYEF2/BDNF/KEL/TMEM119/CEACAM5/ADGRB1
BP	GO:0015918	sterol transport	10/572	0.00232	10	CEL/PTCH1/ABCA2/AKR1C1/CES1/APOE/APOC1/CLU/PPARG/EGF
BP	GO:0032411	positive regulation of transporter activity	10/572	0.00232	10	KCNE3/WNK2/SYNGR3/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/HAP1/ATP2A1
BP	GO:0042303	molting cycle	10/572	0.00232	10	LRIG1/BCL2/SOX21/FGFR2/IGFBP5/PTCH2/FA2H/DNASE1L2/DSG4/SOSTDC1
BP	GO:0042633	hair cycle	10/572	0.00232	10	LRIG1/BCL2/SOX21/FGFR2/IGFBP5/PTCH2/FA2H/DNASE1L2/DSG4/SOSTDC1
BP	GO:0070268	cornification	10/572	0.00232	10	KRT15/KRT19/KRT8/KRT20/DSG4/SPRR3/KRT7/KRT36/KRT13/TCHH
BP	GO:0098739	import across plasma membrane	10/572	0.00384	10	WNK2/SLC9A2/KCNJ11/TRPV6/SLC9A4/SLC7A2/CACNA2D1/KCNH2/KCNJ10/ATP12A
BP	GO:0001704	formation of primary germ layer	10/572	0.00407	10	SOX2/FZD7/LEF1/FGFR2/TXNRD1/EYA2/BMP7/CRB2/EYA1/COL11A1
BP	GO:0003206	cardiac chamber morphogenesis	10/572	0.00638	10	HEY1/RARB/FGFR2/SLIT2/BMP7/RBP4/ROBO2/COL11A1/FOXH1/POU4F1
BP	GO:0030183	B cell differentiation	10/572	0.00709	10	BCL2/HHEX/VCAM1/NKX2-3/CR2/IKZF3/CD79B/CD19/MS4A1/CD79A
BP	GO:0050921	positive regulation of chemotaxis	10/572	0.0087	10	MDK/SMOC2/PRKD1/SLIT2/PTN/CD74/CCL26/CXCL17/THBS4/CCL19
BP	GO:0035725	sodium ion transmembrane transport	10/572	0.01108	10	SCN9A/WNK2/SLC9A2/FXYD6/SLC4A11/SLC9A4/SCNN1A/FGF12/SCN2A/ATP12A
BP	GO:0097553	calcium ion transmembrane import into cytosol	10/572	0.01108	10	PLCE1/PLCH1/TRPV6/CACNA2D1/GSTM2/CX3CL1/HAP1/CD19/GRIN2A/CCL19
BP	GO:1902904	negative regulation of supramolecular fiber organization	10/572	0.01216	10	EPS8/SLIT2/TMSB15A/SCIN/APOE/MAP1B/FGF13/CLU/ADD2/PPP1R9A
BP	GO:1902107	positive regulation of leukocyte differentiation	10/572	0.01332	10	MDK/MYB/LEF1/IL34/HCLS1/CD74/ZAP70/LILRB4/CCL19/POU4F1

BP	GO:0045834	positive regulation of lipid metabolic process	10/572	0.01455	10	PRKD1/CD74/APOE/APOC1/PPARG/GPLD1/AADAC/CD19/CCL19/MLXIPL
BP	GO:0043524	negative regulation of neuron apoptotic process	10/572	0.0152	10	NTRK2/MDK/BCL2/SIX4/GCLC/BDNF/APOE/CX3CL1/GABRB3/POU4F1
BP	GO:0001890	placenta development	10/572	0.01878	10	HEY1/LEF1/KRT19/KRT8/FGFR2/PTN/BMP7/PTGIS/PPARG/SPP1
BP	GO:0016202	regulation of striated muscle tissue development	10/572	0.01878	10	BCL2/FZD7/LEF1/SIX4/FGFR2/PI16/KCNK2/RBP4/MEGF10/GLI1
BP	GO:0051017	actin filament bundle assembly	10/572	0.01957	10	EPS8/FAM171A1/SPIRE2/RND2/CX3CL1/ELN/ESPNL/ADD2/SYNPO2/PPP1R9A
BP	GO:0055067	monovalent inorganic cation homeostasis	10/572	0.02038	10	BCL2/ATP6V0E2/SLC9A2/SLC4A11/SLC9A4/SCNN1A/KCNH2/C7/KCNJ10/ATP12A
BP	GO:0048634	regulation of muscle organ development	10/572	0.02207	10	BCL2/FZD7/LEF1/SIX4/FGFR2/PI16/KCNK2/RBP4/MEGF10/GLI1
BP	GO:0061572	actin filament bundle organization	10/572	0.02295	10	EPS8/FAM171A1/SPIRE2/RND2/CX3CL1/ELN/ESPNL/ADD2/SYNPO2/PPP1R9A
BP	GO:0046661	male sex differentiation	10/572	0.02575	10	SYCP2/BCL2/SIX4/DMRT3/NUPR1/AKR1C3/HOXA9/NR5A1/MGST1/NR0B1
BP	GO:0010970	transport along microtubule	10/572	0.02673	10	ICK/NEFH/MAP1B/UCHL1/AP3B2/HAP1/TMEM108/DYNC1I1/KIF1A/ACTL8
BP	GO:0031960	response to corticosteroid	10/572	0.02774	10	MDK/BCL2/ABCA3/ALDH3A1/SLIT2/SERPINF1/AKR1C3/SOX30/MAOB/SCGB1A1
BP	GO:0099173	postsynapse organization	10/572	0.02878	10	CEL/EPHA7/LRRC4/PTN/NEFH/APOE/NRCAM/TMEM108/INA/PPP1R9A
MF	GO:0016709	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen	10/559	2.54E-07	10	CYP26A1/FMO3/CYP4F3/AKR1C1/CYP27A1/AKR1C3/NOS2/AKR1C2/CYP2E1/CYP4F11
MF	GO:0033293	monocarboxylic acid binding	10/559	2.98E-05	10	CYP26A1/AKR1C1/OXER1/UGT1A7/AKR1C2/APOC1/UGT1A9/PPARG/CYP4F11/UGT1A8
MF	GO:0008194	UDP-glycosyltransferase activity	10/559	0.02173	10	GCNT2/COLGALT2/MGAT3/UGT8/B4GALNT4/UGT1A7/UGT1A6/UGT1A9/UGT2A1/UGT1A8
BP	GO:0019748	secondary metabolic process	9/572	0.00017	9	BCL2/CBS/AKR1C1/UGT1A7/AKR1C3/AKR1C2/OCA2/CYP1B1/UGT1A8
BP	GO:0071300	cellular response to retinoic acid	9/572	0.00025	9	MYB/FZD7/RARB/FGFR2/SERPINF1/RORB/PPARG/ALDH1A2/SLC6A4
BP	GO:0098659	inorganic cation import across plasma membrane	9/572	0.00149	9	WNK2/SLC9A2/KCNJ11/TRPV6/SLC9A4/CACNA2D1/KCNH2/KCNJ10/ATP12A
BP	GO:0099587	inorganic ion import across plasma membrane	9/572	0.00149	9	WNK2/SLC9A2/KCNJ11/TRPV6/SLC9A4/CACNA2D1/KCNH2/KCNJ10/ATP12A

BP	GO:0010717	regulation of epithelial to mesenchymal transition	9/572	0.00174	9	MDK/GCNT2/LEF1/FOXA1/BMP7/HPN/CRB2/OLFM1/ALX1
BP	GO:0060993	kidney morphogenesis	9/572	0.00235	9	PRKX/BCL2/GPC3/PBX1/SIX4/PTCH1/BMP7/FOXJ1/EYA1
BP	GO:0070167	regulation of biomineral tissue development	9/572	0.00235	9	HEY1/PKDCC/PTN/BMP7/OMD/TMEM119/ASPN/COMP/LTF
BP	GO:0110149	regulation of biomineralization	9/572	0.00235	9	HEY1/PKDCC/PTN/BMP7/OMD/TMEM119/ASPN/COMP/LTF
BP	GO:0042100	B cell proliferation	9/572	0.00253	9	BCL2/LEF1/CD74/CR2/IKZF3/CD19/CD22/MS4A1/CD79A
BP	GO:0048709	oligodendrocyte differentiation	9/572	0.00292	9	NTRK2/MDK/IL34/PTN/FA2H/CLU/PPARG/MYRF/KCNJ10
BP	GO:0045807	positive regulation of endocytosis	9/572	0.00313	9	GPC3/TFR2/APOE/CLU/PPARG/STAP1/EGF/SFRP4/CCL19
BP	GO:0030301	cholesterol transport	9/572	0.00335	9	CEL/PTCH1/ABCA2/AKR1C1/CES1/APOE/APOC1/CLU/EGF
BP	GO:0022600	digestive system process	9/572	0.00359	9	CEL/AKR1C1/SLC9A4/MUC2/RBP4/MUC6/MUC4/MUC13/TFF3
BP	GO:0032414	positive regulation of ion transmembrane transporter activity	9/572	0.00465	9	KCNE3/WNK2/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/HAP1/ATP2A1
BP	GO:1903510	mucopolysaccharide metabolic process	9/572	0.00752	9	CHST7/ABCC5/OGN/OMD/CHST6/PRELP/EGF/SPOCK3/CHST9
BP	GO:0006690	icosanoid metabolic process	9/572	0.00841	9	ALOX15/CYP4F3/AKR1C3/GSTA1/CD74/AKR1C2/CYP2E1/PTGIS/CYP1B1
BP	GO:0060349	bone morphogenesis	9/572	0.00841	9	COCH/RARB/FGFR2/TMEM119/SFRP4/COL21A1/COMP/LTF/PAX1
BP	GO:0072089	stem cell proliferation	9/572	0.01156	9	EPCAM/LEF1/FGFR2/SOX5/PTN/MECOM/FGF13/DMRTA2/CX3CL1
BP	GO:0051928	positive regulation of calcium ion transport	9/572	0.01344	9	KCNE3/FGF14/CACNA2D1/CACNA1D/GSTM2/CX3CL1/HAP1/CD19/ATP2A1
BP	GO:0032368	regulation of lipid transport	9/572	0.01481	9	MYB/PTCH1/ABCA2/POMC/APOE/APOC1/PPARG/EGF/SPP1
BP	GO:0045667	regulation of osteoblast differentiation	9/572	0.01553	9	PTCH1/FGFR2/PRKD1/IGFBP5/BMP7/RORB/TMEM119/GLI1/LTF
BP	GO:0006639	acylglycerol metabolic process	9/572	0.01785	9	PLCE1/PLAAT3/NKX2-3/APOE/GPAT2/APOC1/CYP2E1/GPLD1/AADAC
BP	GO:0003231	cardiac ventricle development	9/572	0.01868	9	HEY1/LMO4/FGFR2/SLIT2/KCNK2/ROBO2/COL11A1/FOXH1/POU4F1
BP	GO:0006638	neutral lipid metabolic process	9/572	0.01868	9	PLCE1/PLAAT3/NKX2-3/APOE/GPAT2/APOC1/CYP2E1/GPLD1/AADAC
BP	GO:0031333	negative regulation of protein-containing complex assembly	9/572	0.02041	9	EPS8/LMO4/SVIP/SLIT2/TMSB15A/SCIN/CLU/ADD2/SOST
BP	GO:0048565	digestive tract development	9/572	0.02227	9	BCL2/RARB/FGFR2/PKDCC/NKX2-3/NKX3-2/ALDH1A2/GLI1/AGR2

BP	GO:0007292	female gamete generation	9/572	0.02423	9	SYCP2/MDK/BCL2/PTN/SPIRE2/YBX2/PIWIL2/M1AP/MEIOB
BP	GO:0098754	detoxification	9/572	0.02526	9	MARC1/TXNRD1/BMP7/GSTA1/GPX2/APOE/GSTM3/GSTM2/MGST1
BP	GO:0030879	mammary gland development	9/572	0.03209	9	LEF1/PTCH1/FGFR2/IGFBP5/NTN1/ELF3/HOXA9/EGF/SOSTDC1
BP	GO:0055123	digestive system development	9/572	0.03595	9	BCL2/RARB/FGFR2/PKDCC/NKX2-3/NKX3-2/ALDH1A2/GLI1/AGR2
MF	GO:0072341	modified amino acid binding	9/559	0.00198	9	CBS/GSTM4/SCIN/GSTM3/GSTM2/SYT2/GPR143/ADGRB1/MGST1
MF	GO:0016614	oxidoreductase activity, acting on CH-OH group of donors	9/559	0.02033	9	ALDH3A1/CHDH/PGD/PHGDH/AKR1C1/AKR1C3/AKR1C2/ADH7/ADH1C
BP	GO:0042573	retinoic acid metabolic process	8/572	4.06E-06	8	CYP26A1/UGT1A7/AKR1C3/ADH7/UGT1A9/ADH1C/ALDH1A2/UGT1A8
BP	GO:1904427	positive regulation of calcium ion transmembrane transport	8/572	0.00144	8	KCNE3/FGF14/CACNA2D1/GSTM2/CX3CL1/HAP1/CD19/ATP2A1
BP	GO:0021536	diencephalon development	8/572	0.00206	8	SOX2/OTX1/PTN/HAP1/ALDH1A2/GLI1/POU4F1/NR0B1
BP	GO:0110110	positive regulation of animal organ morphogenesis	8/572	0.00334	8	MDK/SIX4/FGFR2/STOX1/PTN/BMP7/HPN/ROBO2
BP	GO:0072384	organelle transport along microtubule	8/572	0.0045	8	NEFH/MAP1B/UCHL1/AP3B2/HAP1/DYNC1I1/KIF1A/ACTL8
BP	GO:0022404	molting cycle process	8/572	0.00555	8	LRIG1/BCL2/SOX21/FGFR2/IGFBP5/DNASE1L2/DSG4/SOSTDC1
BP	GO:0022405	hair cycle process	8/572	0.00555	8	LRIG1/BCL2/SOX21/FGFR2/IGFBP5/DNASE1L2/DSG4/SOSTDC1
BP	GO:2000177	regulation of neural precursor cell proliferation	8/572	0.00555	8	MDK/PTN/INSM1/DMRTA2/CX3CL1/EGF/SLC6A4/GLI1
BP	GO:0061053	somite development	8/572	0.00594	8	LEF1/SIX4/PTCH1/CRB2/ALDH1A2/TCF15/DMRT2/PAX1
BP	GO:0001656	metanephros development	8/572	0.00635	8	BCL2/GPC3/SIX4/PTCH1/BMP7/FOXJ1/EYA1/ROBO2
BP	GO:0030510	regulation of BMP signaling pathway	8/572	0.00678	8	GPC3/RNF165/SULF1/CRB2/CHRDL1/SFRP4/SOSTDC1/SOST
BP	GO:0033273	response to vitamin	8/572	0.00771	8	CYP26A1/PTN/BMP7/MAP1B/PPARG/ALDH1A2/SPP1/PENK
BP	GO:0006029	proteoglycan metabolic process	8/572	0.0082	8	PXYLP1/CHST7/HS3ST6/SULF1/HS3ST4/COL11A1/SPOCK3/CHST9
BP	GO:0062014	negative regulation of small molecule metabolic process	8/572	0.01106	8	NUPR1/AKR1C3/APOE/APOC1/C1QTNF3/FBP1/FGF19/UGT1A8
BP	GO:0007631	feeding behavior	8/572	0.01239	8	NTRK2/MRAP2/GDF15/ADM2/DACH1/UCHL1/TCF15/POU4F1
BP	GO:0046632	alpha-beta T cell differentiation	8/572	0.01239	8	BCL2/MYB/LEF1/PLA2G2D/NKX2-3/ZAP70/CCL19/PAX1

BP	GO:0018958	phenol-containing compound metabolic process	8/572	0.01383	8	BCL2/TG/CYP2E1/HPN/INSM1/OCA2/MAOB/GRIN2A
BP	GO:0006641	triglyceride metabolic process	8/572	0.01539	8	PLAAT3/NKX2-3/APOE/GPAT2/APOC1/CYP2E1/GPLD1/AADAC
BP	GO:0042136	neurotransmitter biosynthetic process	8/572	0.01622	8	GCHFR/NOS2/SLC7A2/PTGIS/CLU/CYP1B1/SLC44A4/SLC6A4
BP	GO:1990748	cellular detoxification	8/572	0.02185	8	TXNRD1/BMP7/GSTA1/GPX2/APOE/GSTM3/GSTM2/MGST1
BP	GO:0002688	regulation of leukocyte chemotaxis	8/572	0.02401	8	MDK/SLIT2/PTN/CD74/CXCL17/STAP1/THBS4/CCL19
BP	GO:0007127	meiosis I	8/572	0.02401	8	STAG3/SYCP2/MEI1/PIWIL2/M1AP/RNF212/TEX15/MEIOB
BP	GO:0046660	female sex differentiation	8/572	0.02514	8	MERTK/BCL2/NUPR1/SLIT2/DACH1/RBP4/ROBO2/NR5A1
BP	GO:0021782	glial cell development	8/572	0.02631	8	NTRK2/MDK/PHGDH/ADAM22/FA2H/CLU/MYRF/KCNJ10
BP	GO:0051153	regulation of striated muscle cell differentiation	8/572	0.02751	8	BCL2/FZD7/GDF15/BDNF/PI16/TMEM119/CEACAM5/ADGRB1
BP	GO:0061982	meiosis I cell cycle process	8/572	0.03004	8	STAG3/SYCP2/MEI1/PIWIL2/M1AP/RNF212/TEX15/MEIOB
BP	GO:0010811	positive regulation of cell-substrate adhesion	8/572	0.03271	8	MDK/SMOC2/ALOX15/PTN/EMID1/SKAP1/CX3CL1/AGR2
BP	GO:1903409	reactive oxygen species biosynthetic process	8/572	0.03411	8	GCHFR/NOS2/SLC7A2/PTGIS/CLU/CYP1B1/MAOB/ADGRB1
BP	GO:0071621	granulocyte chemotaxis	8/572	0.03555	8	MDK/SLIT2/CD74/CCL26/CX3CL1/CXCL17/THBS4/CCL19
MF	GO:0005501	retinoid binding	8/559	1.04E-05	8	CYP26A1/UGT1A7/ADH7/UGT1A9/C8G/RBP4/ALDH1A2/UGT1A8
MF	GO:0019840	isoprenoid binding	8/559	1.31E-05	8	CYP26A1/UGT1A7/ADH7/UGT1A9/C8G/RBP4/ALDH1A2/UGT1A8
MF	GO:0005518	collagen binding	8/559	0.00119	8	COCH/CTSS/PODN/ASPN/ITGA11/PCOLCE2/COMP/SPOCK3
MF	GO:0004620	phospholipase activity	8/559	0.01547	8	PLCE1/PLAAT3/PLCH1/PLA2G2D/PLA1A/LIPH/PLCB4/GPLD1
BP	GO:0042572	retinol metabolic process	7/572	0.00022	7	ALDH1A1/AKR1C3/ADH7/ADH1C/RBP4/CYP1B1/ALDH1A2
BP	GO:0030850	prostate gland development	7/572	0.0006	7	FOXA1/PTCH1/FGFR2/SERPINF1/BMP7/SULF1/GLI1
BP	GO:0010718	positive regulation of epithelial to mesenchymal transition	7/572	0.00078	7	MDK/GCNT2/LEF1/BMP7/CRB2/OLFM1/ALX1
BP	GO:0006749	glutathione metabolic process	7/572	0.00154	7	GCLC/GSTM4/GSTA1/GSTM3/GSTM2/GSTM5/MGST1
BP	GO:0007405	neuroblast proliferation	7/572	0.00254	7	LEF1/FGFR2/SOX5/PTN/FGF13/DMRTA2/CX3CL1

BP	GO:0034113	heterotypic cell-cell adhesion	7/572	0.00254	7	GCNT2/ALOX15/CD200/VCAM1/BMP7/SKAP1/NRCAM
BP	GO:1901862	negative regulation of muscle tissue development	7/572	0.00279	7	FZD7/LEF1/SIX4/IGFBP5/PI16/KCNK2/RBP4
BP	GO:0048645	animal organ formation	7/572	0.00335	7	FGFR2/BMP7/SULF1/EYA1/NKX3-2/ROBO2/FOXH1
BP	GO:0050771	negative regulation of axonogenesis	7/572	0.0051	7	EPHA7/ARHGAP4/SLIT2/NTN1/FGF13/SPP1/FSTL4
BP	GO:0019226	transmission of nerve impulse	7/572	0.00645	7	NTRK2/SCN9A/DMRT3/MYH14/NRCAM/FGF12/SCN2A
BP	GO:2001259	positive regulation of cation channel activity	7/572	0.00645	7	KCNE3/FGF14/CTSS/KCNJ11/CACNA2D1/GSTM2/HAP1
BP	GO:0033555	multicellular organismal response to stress	7/572	0.00695	7	MDK/BCL2/SCN9A/APOE/PENK/CACNA1B/THBS4
BP	GO:0086003	cardiac muscle cell contraction	7/572	0.00747	7	KCNE3/FGF13/CACNA2D1/CACNA1D/KCNH2/FGF12/ATP2A1
BP	GO:1901616	organic hydroxy compound catabolic process	7/572	0.00747	7	CEL/CYP4F3/CYP27A1/AKR1C3/APOE/ADH7/MAOB
BP	GO:0001707	mesoderm formation	7/572	0.00803	7	LEF1/FGFR2/TXNRD1/EYA2/BMP7/CRB2/EYA1
BP	GO:0008589	regulation of smoothened signaling pathway	7/572	0.00862	7	GPC3/FOXA1/SCUBE3/PTCH1/FGFR2/PTCH2/GLI1
BP	GO:0030500	regulation of bone mineralization	7/572	0.00862	7	PKDCC/PTN/BMP7/OMD/TMEM119/COMP/LTF
BP	GO:0048332	mesoderm morphogenesis	7/572	0.00924	7	LEF1/FGFR2/TXNRD1/EYA2/BMP7/CRB2/EYA1
BP	GO:0072028	nephron morphogenesis	7/572	0.00989	7	BCL2/GPC3/PBX1/SIX4/PTCH1/BMP7/EYA1
BP	GO:0003151	outflow tract morphogenesis	7/572	0.01057	7	RARB/FGFR2/BMP7/ELN/EYA1/ROBO2/FOXH1
BP	GO:0070509	calcium ion import	7/572	0.01129	7	TRPV6/CACNA2D1/CACNA1D/EGF/CACNA1B/MS4A1/ATP2A1
BP	GO:0050772	positive regulation of axonogenesis	7/572	0.01541	7	NTRK2/BDNF/SLIT2/NTN1/MAP1B/RND2/ROBO2
BP	GO:2001057	reactive nitrogen species metabolic process	7/572	0.01541	7	GCHFR/MARC1/NOS2/SLC7A2/PTGIS/CLU/CYP1B1
BP	GO:0001942	hair follicle development	7/572	0.01635	7	BCL2/SOX21/FGFR2/IGFBP5/DNASE1L2/DSG4/SOSTDC1
BP	GO:0042446	hormone biosynthetic process	7/572	0.01635	7	TSPOAP1/CYP27A1/AKR1C3/TG/SLC44A4/CYP11A1/CHST9
BP	GO:0098773	skin epidermis development	7/572	0.01835	7	BCL2/SOX21/FGFR2/IGFBP5/DNASE1L2/DSG4/SOSTDC1
BP	GO:0097306	cellular response to alcohol	7/572	0.01941	7	ADCY5/PTCH1/AKR1C3/AKR1C2/PPARG/GPLD1/PRKAA2

BP	GO:1901019	regulation of calcium ion transmembrane transporter activity	7/572	0.01941	7	KCNE3/FGF14/CACNB4/CACNA2D1/GSTM2/HAP1/ATP2A1
BP	GO:0045132	meiotic chromosome segregation	7/572	0.02051	7	STAG3/SYCP2/MEI1/M1AP/RNF212/TEX15/MEIOB
BP	GO:0045833	negative regulation of lipid metabolic process	7/572	0.02284	7	PDE3B/AKR1C3/APOE/APOC1/GPLD1/FGF19/UGT1A8
BP	GO:0048704	embryonic skeletal system morphogenesis	7/572	0.02407	7	SIX4/FGFR2/BMP7/HOXB3/EYA1/ALX1/COL11A1
BP	GO:1901655	cellular response to ketone	7/572	0.02407	7	ADCY5/SERPINF1/AKR1C3/AKR1C2/PPARG/PRKAA2/SPP1
BP	GO:0010771	negative regulation of cell morphogenesis involved in differentiation	7/572	0.02945	7	EPHA7/ARHGAP4/SLIT2/NTN1/FGF13/SPP1/FSTL4
BP	GO:0060840	artery development	7/572	0.03399	7	HEY1/MDK/APOE/EYA1/ROBO2/FOXH1/COMP
CC	GO:0016529	sarcoplasmic reticulum	7/590	0.00527	7	CCDC78/CACNA2D1/GSTM2/SLC2A4/THBS4/CMYA5/ATP2A1
MF	GO:0003707	steroid hormone receptor activity	7/559	0.00183	7	LEF1/RARB/RORB/NR3C2/PPARG/NR5A1/NR0B1
MF	GO:0016765	transferase activity, transferring alkyl or aryl (other than methyl) groups	7/559	0.00225	7	CBS/GSTM4/GSTA1/GSTM3/GSTM2/GSTM5/MGST1
MF	GO:0038024	cargo receptor activity	7/559	0.01009	7	LOXL4/ILDR1/TFR2/SBSPON/MEGF10/TMPRSS2/PRG4
MF	GO:0005249	voltage-gated potassium channel activity	7/559	0.02011	7	KCNE3/KCNS3/KCNH1/KCNJ11/KCNK2/KCNH2/KCNJ10
BP	GO:0048670	regulation of collateral sprouting	6/572	2.16E-05	6	EPHA7/BDNF/RND2/FGF13/SPP1/FSTL4
BP	GO:0030277	maintenance of gastrointestinal epithelium	6/572	2.95E-05	6	MUC2/RBP4/MUC6/MUC4/MUC13/TFF3
BP	GO:1901685	glutathione derivative metabolic process	6/572	3.95E-05	6	GSTM4/GSTA1/GSTM3/GSTM2/GSTM5/MGST1
BP	GO:1901687	glutathione derivative biosynthetic process	6/572	3.95E-05	6	GSTM4/GSTA1/GSTM3/GSTM2/GSTM5/MGST1
BP	GO:0048668	collateral sprouting	6/572	0.00014	6	EPHA7/BDNF/RND2/FGF13/SPP1/FSTL4
BP	GO:0060384	innervation	6/572	0.00014	6	LRIG1/VCAM1/RNF165/SULF1/GABRB3/POU4F1
BP	GO:0010669	epithelial structure maintenance	6/572	0.00021	6	MUC2/RBP4/MUC6/MUC4/MUC13/TFF3
BP	GO:1901021	positive regulation of calcium ion	6/572	0.00097	6	KCNE3/FGF14/CACNA2D1/GSTM2/HAP1/ATP2A1

		transmembrane transporter activity				
BP	GO:0071622	regulation of granulocyte chemotaxis	6/572	0.00211	6	MDK/SLIT2/CD74/CXCL17/THBS4/CCL19
BP	GO:0060443	mammary gland morphogenesis	6/572	0.00266	6	PTCH1/FGFR2/IGFBP5/NTN1/ELF3/SOSTDC1
BP	GO:0014009	glial cell proliferation	6/572	0.00408	6	MYB/IL34/PTN/CX3CL1/CLU/PENK
BP	GO:0032330	regulation of chondrocyte differentiation	6/572	0.00496	6	MDK/RARB/SOX5/PKDCC/SCIN/NKX3-2
BP	GO:2000179	positive regulation of neural precursor cell proliferation	6/572	0.00496	6	MDK/INSM1/DMRTA2/CX3CL1/EGF/GLI1
BP	GO:0030199	collagen fibril organization	6/572	0.00598	6	LOXL4/DPT/CYP1B1/MMP11/COL11A1/COMP
BP	GO:0045143	homologous chromosome segregation	6/572	0.00778	6	STAG3/SYCP2/MEI1/RNF212/TEX15/MEIOB
BP	GO:0001658	branching involved in ureteric bud morphogenesis	6/572	0.00918	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
BP	GO:0045843	negative regulation of striated muscle tissue development	6/572	0.00918	6	FZD7/LEF1/SIX4/PI16/KCNK2/RBP4
BP	GO:0048635	negative regulation of muscle organ development	6/572	0.00995	6	FZD7/LEF1/SIX4/PI16/KCNK2/RBP4
BP	GO:0006081	cellular aldehyde metabolic process	6/572	0.01075	6	ALDH1A1/ALDH3A1/AKR1C1/AKR1C3/CYP1B1/ALDH1A2
BP	GO:0016266	O-glycan processing	6/572	0.01075	6	MUC2/MUC6/MUC20/MUC4/MUC13/MUC5B
BP	GO:0010830	regulation of myotube differentiation	6/572	0.01161	6	BCL2/GDF15/BDNF/TMEM119/CEACAM5/ADGRB1
BP	GO:0032835	glomerulus development	6/572	0.01161	6	BCL2/PLCE1/BMP7/FOXJ1/SULF1/COL4A4
BP	GO:0032371	regulation of sterol transport	6/572	0.0125	6	PTCH1/ABCA2/APOE/APOC1/PPARG/EGF
BP	GO:0006026	aminoglycan catabolic process	6/572	0.01445	6	GPC3/OGN/OMD/GPC4/PRELP/CHIT1
BP	GO:0060675	ureteric bud morphogenesis	6/572	0.01445	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
BP	GO:0070192	chromosome organization involved in meiotic cell cycle	6/572	0.01445	6	STAG3/SYCP2/MEI1/RNF212/TEX15/MEIOB
BP	GO:0072171	mesonephric tubule morphogenesis	6/572	0.01549	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
BP	GO:0033627	cell adhesion mediated by integrin	6/572	0.01774	6	PDE3B/NEXMIF/ITGBL1/SKAP1/ITGA11/CYP1B1

BP	GO:00 42698	ovulation cycle	6/572	0.01895	6	MDK/SLIT2/SERPINF1/PTN/ROBO2/NR5A1
BP	GO:00 01756	somitogenesis	6/572	0.0202	6	LEF1/CRB2/ALDH1A2/TCF15/DMRT2/PAX1
BP	GO:00 42440	pigment metabolic process	6/572	0.02152	6	BCL2/UGT1A7/UGT1A9/OCA2/GPR143/UGT1A8
BP	GO:00 61035	regulation of cartilage development	6/572	0.02289	6	MDK/RARB/SOX5/PKDCC/SCIN/NKX3-2
BP	GO:00 43367	CD4-positive, alpha-beta T cell differentiation	6/572	0.0258	6	MYB/LEF1/PLA2G2D/NKX2-3/CCL19/PAX1
BP	GO:00 72078	nephron tubule morphogenesis	6/572	0.0258	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
BP	GO:00 86001	cardiac muscle cell action potential	6/572	0.0258	6	KCNE3/FGF13/CACNA2D1/CACNA1D/KCNH2/FGF 12
BP	GO:00 48844	artery morphogenesis	6/572	0.02895	6	HEY1/MDK/APOE/EYA1/FOXH1/COMP
BP	GO:00 60411	cardiac septum morphogenesis	6/572	0.02895	6	HEY1/RARB/FGFR2/SLIT2/BMP7/ROBO2
BP	GO:00 72088	nephron epithelium morphogenesis	6/572	0.02895	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
BP	GO:00 06809	nitric oxide biosynthetic process	6/572	0.03062	6	GCHFR/NOS2/SLC7A2/PTGIS/CLU/CYP1B1
BP	GO:00 08344	adult locomotory behavior	6/572	0.03062	6	EPS8/DMRT3/ADAM22/UCHL1/FGF12/KCNJ10
BP	GO:00 48678	response to axon injury	6/572	0.03062	6	BCL2/RGMA/PTN/MAP1B/KCNK2/SPP1
BP	GO:00 61333	renal tubule morphogenesis	6/572	0.03234	6	BCL2/GPC3/PBX1/SIX4/PTCH1/EYA1
MF	GO:00 04364	glutathione transferase activity	6/559	0.00016	6	GSTM4/GSTA1/GSTM3/GSTM2/GSTM5/MGST1
MF	GO:00 43394	proteoglycan binding	6/559	0.00084	6	SLIT2/CTSS/PTN/PLA2G2D/APOE/COMP
MF	GO:00 16903	oxidoreductase activity, acting on the aldehyde or oxo group of donors	6/559	0.00218	6	ALDH1A1/ALDH3A1/AKR1C3/ADH7/ALDH1L1/ALD H1A2
MF	GO:00 50840	extracellular matrix binding	6/559	0.00897	6	SLIT2/CTSS/ELN/SPP1/COL11A1/SPOCK3
BP	GO:00 52695	cellular glucuronidation	5/572	0.00022	5	UGT1A7/UGT1A6/UGT1A9/UGT2A1/UGT1A8
BP	GO:00 06063	uronic acid metabolic process	5/572	0.0007	5	UGT1A7/UGT1A6/UGT1A9/UGT2A1/UGT1A8
BP	GO:00 19585	glucuronate metabolic process	5/572	0.0007	5	UGT1A7/UGT1A6/UGT1A9/UGT2A1/UGT1A8
BP	GO:00 30325	adrenal gland development	5/572	0.00085	5	MDK/PBX1/INSM1/NR5A1/NR0B1
BP	GO:00 60037	pharyngeal system development	5/572	0.00102	5	SIX4/PTCH1/BMP7/EYA1/RIPPLY3

BP	GO:00 90022	regulation of neutrophil chemotaxis	5/572	0.002	5	MDK/SLIT2/CD74/THBS4/CCL19
BP	GO:00 34694	response to prostaglandin	5/572	0.00233	5	AKR1C3/AKR1C2/PPARG/PRKAA2/CCL19
BP	GO:00 48665	neuron fate specification	5/572	0.00354	5	FOXA1/DMRT3/DMRTA2/EYA1/POU4F1
BP	GO:19 02622	regulation of neutrophil migration	5/572	0.00456	5	MDK/SLIT2/CD74/THBS4/CCL19
BP	GO:00 86010	membrane depolarization during action potential	5/572	0.00514	5	SCN9A/CACNA2D1/CACNA1D/KCNH2/SCN2A
BP	GO:19 02742	apoptotic process involved in development	5/572	0.00577	5	LEF1/SLIT2/BMP7/MEGF10/ROBO2
BP	GO:00 08207	C21-steroid hormone metabolic process	5/572	0.00646	5	TSPOAP1/AKR1C1/AKR1C3/AKR1C2/CYP11A1
BP	GO:00 30501	positive regulation of bone mineralization	5/572	0.00646	5	PKDCC/PTN/BMP7/TMEM119/LTF
BP	GO:00 17145	stem cell division	5/572	0.00886	5	FZD7/LEF1/FGFR2/SOX5/FGF13
BP	GO:00 51154	negative regulation of striated muscle cell differentiation	5/572	0.00886	5	FZD7/BDNF/PI16/TMEM119/CEACAM5
BP	GO:00 06692	prostanoid metabolic process	5/572	0.00977	5	AKR1C3/GSTA1/CD74/AKR1C2/PTGIS
BP	GO:00 06693	prostaglandin metabolic process	5/572	0.00977	5	AKR1C3/GSTA1/CD74/AKR1C2/PTGIS
BP	GO:00 06775	fat-soluble vitamin metabolic process	5/572	0.00977	5	CYP26A1/CYP27A1/ALDH1A2/CYP4F11/CYP11A1
BP	GO:00 03416	endochondral bone growth	5/572	0.01076	5	COCH/RARB/FGFR2/COL21A1/COMP
BP	GO:00 48538	thymus development	5/572	0.0118	5	BCL2/LMO4/PBX1/SIX4/PAX1
BP	GO:00 02067	glandular epithelial cell differentiation	5/572	0.01292	5	FOXA1/RARB/FGFR2/INSM1/AGR2
BP	GO:00 07129	synapsis	5/572	0.01292	5	STAG3/SYCP2/RNF212/TEX15/MEIOB
BP	GO:00 70169	positive regulation of biomineral tissue development	5/572	0.0141	5	PKDCC/PTN/BMP7/TMEM119/LTF
BP	GO:00 98868	bone growth	5/572	0.0141	5	COCH/RARB/FGFR2/COL21A1/COMP
BP	GO:01 10151	positive regulation of biomineralization	5/572	0.0141	5	PKDCC/PTN/BMP7/TMEM119/LTF
BP	GO:00 02063	chondrocyte development	5/572	0.01536	5	COCH/SULF1/COL21A1/COL11A1/COMP
BP	GO:00 07140	male meiotic nuclear division	5/572	0.01536	5	SYCP2/MEI1/M1AP/TEX15/MEIOB

BP	GO:1990573	potassium ion import across plasma membrane	5/572	0.01536	5	WNK2/KCNJ11/KCNH2/KCNJ10/ATP12A
BP	GO:0035094	response to nicotine	5/572	0.01668	5	BCL2/VCAM1/KCNJ11/PPP1R1B/PENK
BP	GO:0048546	digestive tract morphogenesis	5/572	0.01668	5	BCL2/FGFR2/NKX2-3/GLI1/AGR2
BP	GO:0002931	response to ischemia	5/572	0.01808	5	BCL2/KCNJ11/UCHL1/CX3CL1/PANX2
BP	GO:0019369	arachidonic acid metabolic process	5/572	0.01956	5	ALOX15/AKR1C3/CYP2E1/PTGIS/CYP1B1
BP	GO:0031103	axon regeneration	5/572	0.01956	5	BCL2/RGMA/PTN/MAP1B/SPP1
BP	GO:0090102	cochlea development	5/572	0.01956	5	MYO3A/KCNK2/HPN/EYA1/GABRB3
BP	GO:0003179	heart valve morphogenesis	5/572	0.02111	5	HEY1/SLIT2/ELN/OLFM1/ROBO2
BP	GO:0032715	negative regulation of interleukin-6 production	5/572	0.02274	5	CD200/FOXJ1/C1QTNF3/BANK1/CX3CL1
BP	GO:1905517	macrophage migration	5/572	0.02274	5	MDK/CD200/CX3CL1/CXCL17/STAP1
BP	GO:0002763	positive regulation of myeloid leukocyte differentiation	5/572	0.02446	5	LEF1/IL34/HCLS1/CD74/POU4F1
BP	GO:0006636	unsaturated fatty acid biosynthetic process	5/572	0.02446	5	FADS2/ALOX15/AKR1C3/CD74/PTGIS
BP	GO:0046164	alcohol catabolic process	5/572	0.02446	5	CEL/CYP27A1/AKR1C3/APOE/ADH7
BP	GO:0043030	regulation of macrophage activation	5/572	0.02625	5	CD200/CD74/SLC7A2/CX3CL1/STAP1
BP	GO:0061098	positive regulation of protein tyrosine kinase activity	5/572	0.02625	5	NTRK2/GPRC5B/BDNF/STAP1/EGF
BP	GO:0050879	multicellular organismal movement	5/572	0.02812	5	CCDC78/MYH14/GSTM2/COMP/ATP2A1
BP	GO:0050881	musculoskeletal movement	5/572	0.02812	5	CCDC78/MYH14/GSTM2/COMP/ATP2A1
BP	GO:0060688	regulation of morphogenesis of a branching structure	5/572	0.02812	5	MDK/SIX4/FGFR2/BMP7/SULF1
BP	GO:0086002	cardiac muscle cell action potential involved in contraction	5/572	0.02812	5	KCNE3/CACNA2D1/CACNA1D/KCNH2/FGF12
BP	GO:0030837	negative regulation of actin filament polymerization	5/572	0.03211	5	EPS8/SLIT2/TMSB15A/SCIN/ADD2

BP	GO:0098930	axonal transport	5/572	0.03211	5	UCHL1/AP3B2/HAP1/TMEM108/KIF1A
BP	GO:0010656	negative regulation of muscle cell apoptotic process	5/572	0.03424	5	MDK/DIPK2A/NUPR1/BMP7/HSPB6
BP	GO:0031102	neuron projection regeneration	5/572	0.03424	5	BCL2/RGMA/PTN/MAP1B/SPP1
MF	GO:0030021	extracellular matrix structural constituent conferring compression resistance	5/559	0.00052	5	OGN/PODN/ASPN/PRELP/PRG4
MF	GO:0015020	glucuronosyltransferase activity	5/559	0.00353	5	UGT1A7/UGT1A6/UGT1A9/UGT2A1/UGT1A8
MF	GO:0005504	fatty acid binding	5/559	0.00403	5	OXER1/APOC1/PPARG/CYP4F11/UGT1A8
MF	GO:0016620	oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor	5/559	0.00458	5	ALDH1A1/ALDH3A1/AKR1C3/ALDH1L1/ALDH1A2
MF	GO:0017147	Wnt-protein binding	5/559	0.00584	5	MERTK/FZD7/WIF1/EGF/SFRP4
MF	GO:0004879	nuclear receptor activity	5/559	0.0159	5	RARB/RORB/PPARG/NR5A1/NR0B1
MF	GO:0098531	ligand-activated transcription factor activity	5/559	0.0159	5	RARB/RORB/PPARG/NR5A1/NR0B1
MF	GO:0005245	voltage-gated calcium channel activity	5/559	0.0173	5	TSPOAP1/CACNB4/CACNA2D1/CACNA1D/CACNA1B
MF	GO:0005044	scavenger receptor activity	5/559	0.02199	5	LOXL4/SBSPON/MEGF10/TMPRSS2/PRG4
MF	GO:0008146	sulfotransferase activity	5/559	0.02372	5	CHST7/CHST6/HS3ST6/HS3ST4/CHST9

Supplementary file 4. Complete list of FDA-approved, anti-neoplastic and immunotherapeutic drugs that are potential options for the treatment of HNSCC according to the activation status of the beta-adrenergic pathway.

Gene	Drug	Sources	PMIDS
ABCC5	Fluorouracil	PharmGKB	
ADH1C	Tretinoin	NCI	11959987
ALDH1A1	Carboplatin	PharmGKB	
ALDH1A1	Cyclophosphamide	PharmGKB	
ALDH1A1	Thiotepa	PharmGKB	
ALDH1A1	Tretinoin	DrugBank	15245423|16166285|15366004|16207763|16837774
ALDH1A2	Tretinoin	NCI|DrugBank	15299009|15069081|11306068|15652703|15366004|15950969|15950488|14623241
ALDH3A1	Carboplatin	PharmGKB	
ALDH3A1	Cyclophosphamide	PharmGKB	
ALDH3A1	Thiotepa	PharmGKB	
APOE	Prednisone	NCI	3185288
APOE	Tretinoin	NCI	3468509
BCL2	Carboplatin	ClearityFoundationBiomarkers	
BCL2	Docetaxel	TdgClinicalTrial|DrugBank	17674353|15277270|15161985|15643508|15714982|15685445
BCL2	Epirubicin	NCI	14503796
BCL2	Floxuridine	NCI	8324744
BCL2	Mitoxantrone	NCI	11751483
BCL2	Oxaliplatin	ClearityFoundationBiomarkers|NCI	14977850
BCL2	Paclitaxel	TdgClinicalTrial|ClearityFoundationClinicalTrial|NCI|TEND|DrugBank	16741658|16895478|17230521|10620631|17119350|17062688
BCL2	Streptozotocin	NCI	16741044
BCL2	Teniposide	NCI	9842975
BCL2	Tretinoin	NCI	9402847
BDNF	Anakinra	NCI	14580934
BDNF	Dactinomycin	NCI	10899924
BDNF	Fluorouracil	NCI	18702703
BDNF	Paclitaxel	NCI	16778834
BDNF	Topotecan	NCI	15569250
BDNF	Vincristine	NCI	15569250
BLK	Dasatinib	ChemblInteractions	
BLK	Ibrutinib	GuideToPharmacologyInteractions	
CD19	Blinatumomab	TdgClinicalTrial|GuideToPharmacologyInteractions|ChemblInteractions|DrugBank	25883042
CDA	Cytarabine	NCI	14744791|8791999|12008078
CDA	Gemcitabine	NCI	12477049
CEL	Dactinomycin	NCI	2016288
CES1	Capecitabine	PharmGKB	
CGB5	Mitomycin	NCI	6418555
CP	Anakinra	NCI	7682588
CP	Hydroxyurea	NCI	9473738
CP	Vincristine	NCI	9392881
CSF2	Cytarabine	NCI	8819077|8450676
CSF2	Interferon alfa-2b	NCI	10522033
CSF2	Mechlorethamine	NCI	10640980
CSF2	Mycophenolic acid	NCI	9822358
CSF2	Procarbazine	NCI	10640980
CSF2	Streptozotocin	NCI	16342200
CSF2	Temozolomide	NCI	12610499|16100942

CSF2	Vinblastine	NCI	10640980
CYP1B1	Paclitaxel	PharmGKB	
CYP2E1	Cytarabine	PharmGKB	
CYP2E1	Fluorouracil	NCI	12904931
DSCAM	Carboplatin	PharmGKB	
DSCAM	Paclitaxel	PharmGKB	
EPHX1	Docetaxel	PharmGKB	
FGFR2	Interferon alfa-2a	TTD	
FGFR2	Pazopanib	CIViC|DoCM	23786770|24550739
FGFR2	Sunitinib	CKB	27149458
FGFR2	Thalidomide	TdgClinicalTrial|TEND|DrugBank	20616958
GCLC	Carboplatin	NCI	11911273
GFAP	Procarbazine	NCI	8806841
GLI1	Tretinoin	NCI	11034076
IL11	Azacitidine	NCI	12543079
IL11	Fluorouracil	NCI	7691257|1832057
IL1A	Mitomycin	NCI	8195120
ISG15	Irinotecan	MyCancerGenomeClinicalTrial	
KCNH2	Amsacrine	DrugBank	15148258
KCNJ11	Streptozotocin	NCI	11798815
MDK	Tretinoin	NCI	1819274
MMP1	Leflunomide	NCI	16762150
MMP1	Sirolimus	NCI	16914544
MS4A1	Ibritumomab tiuxetan	MyCancerGenome, TdgClinicalTrial, GuideToPharmacologyInteractions, DrugBank	11418316|15045033|11879282|20113680|11752352|12011122|10541376
MS4A1	Obinutuzumab	TdgClinicalTrial, GuideToPharmacologyInteractions, ChemblInteractions, DrugBank, TTD, FDA	19513948
MS4A1	Rituximab	MyCancerGenome|TdgClinicalTrial|GuideToPharmacologyInteractions|ChemblInteractions|TEND|DrugBank|TTD|FDA	20350667|11752352|20350663
MS4A1	Tositumomab	TdgClinicalTrial|GuideToPharmacologyInteractions|ChemblInteractions|TEND|DrugBank|TTD	11418316|14748653|11879282|12899647|11752352|15023434|13129395
MUC2	Fluorouracil	NCI	14576935
MYB	Fluorouracil	NCI	15001837
MYB	Paclitaxel	NCI	15001837
MYCN	Cyclophosphamide	NCI	12439032
MYCN	Dinutuximab	FDA	
MYCN	Tretinoin	NCI	11107126
MYCN	Vincristine	NCI	12439032
NFE2	Paclitaxel	NCI	14761679
NOS2	Nilotinib	GuideToPharmacologyInteractions	
NR0B1	Tretinoin	DrugBank	17139284|17016423
NRG1	Carboplatin	CIViC	23390248
NRG1	Cytarabine	NCI	2676043
NRG1	Dactinomycin	NCI	10383144
NRG1	Gemcitabine	CIViC	23390248
NRG1	Mycophenolic acid	NCI	10597237
NRG1	Paclitaxel	CIViC	23390248
NRG1	Vincristine	NCI	17999741
PGD	Dacarbazine	DrugBank	10592235|20235752
PTCH1	Tretinoin	NCI	12455633
PTGS2	Capecitabine	PharmGKB	
PTGS2	Lenalidomide	DrugBank	15598423|12720152
PTGS2	Oxaliplatin	PharmGKB	
PTGS2	Pomalidomide	DrugBank	17308870
PTGS2	Thalidomide	TdgClinicalTrial|DrugBank	12710892|15446566|15982930|21507989|15598423|15892618
PTHLH	Vinblastine	NCI	9784008
RARB	Tretinoin	ChemblInteractions|NCI	17001699

RARRES1	Tretinoin	TEND|DrugBank	15897880|15059893
RET	Everolimus	CKB	26294908|27683183
RET	Sorafenib	MyCancerGenome|CKB|GuideToPharmacologyInteractions|NCI|CIViC|DrugBank|TTD	20368568|17664273|17016424|15466206|16507829
RET	Sunitinib	TALC|MyCancerGenome|TdgClinicalTrial|CKB|GuideToPharmacologyInteractions|NCI|CGI|CIViC|TEND|DoCM	11351254|27149458|20696054|20368568|19255327|18541894|21455200|16849418|9681850|23056499|22025146|20065189|21422803|25157968|20847059|20943719|28447912|9839497|18073307|21470995
RET	Tretinoin	NCI	7867726
RORB	Tretinoin	GuideToPharmacologyInteractions	
SLC29A2	Mercaptopurine	NCI	17088032
SLC2A4	Streptozotocin	NCI	10098523|9421368|2354749
SPP1	Tacrolimus	NCI	16103732
SPP1	Tretinoin	NCI	9224725
TG	Azacitidine	NCI	2476239
TG	Interferon alfa-2a	NCI	2149997
TG	Prednisone	NCI	2745931
TG	Tretinoin	NCI	10946899|11563543
TH	Streptozotocin	NCI	2568957
TUBB2A	Brentuximab vedotin	ChemblInteractions	
TUBB2A	Cabazitaxel	ChemblInteractions	
TUBB2A	Paclitaxel	ChemblInteractions	
TUBB2A	Trastuzumab emtansine	ChemblInteractions	
TUBB2A	Vinblastine	TdgClinicalTrial|TEND	
TUBB2A	Vincristine	TdgClinicalTrial|TEND	
VCAM1	Mercaptopurine	NCI	7694584
VEGFC	Lenalidomide	ClearityFoundationClinicalTrial	

ANEXO B – Comitê de Ética em Pesquisa: The Cancer Genome Atlas Program

The Cancer Genome Atlas Program

NATIONAL CANCER INSTITUTE & NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Human Subjects Protection and Data Access Policies

Summary
The Cancer Genome Atlas (TCGA) Program is designed to catalog, at an unprecedented scale, genomic variations associated with cancer. TCGA is generating large volumes of detailed genomic data derived from human tumor specimens. The genomic information is combined with newly collected and/or existing clinical information gathered from many different patient populations. The genomic and clinical information is organized into two categories: one that is openly accessible to the public and one that has controlled access, available only to qualified researchers obligated to secure the data. The open access data set contains information that does not pose a risk of patient re-identification. The controlled access data set, in which data have been stripped of names, addresses, birth dates and other traditional identifiers, nevertheless contains information that could carry a small risk for re-identification by comparing TCGA data with information in other databases. Ensuring, to the extent possible, the privacy of specimen donors and confidentiality of their data, while promoting and encouraging impactful scientific discovery, has been a paramount concern to TCGA.

This document describes a set of policies that the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) have adopted to address the protection of privacy of participants donating specimens and associated data to TCGA. Three key human subjects protection and data access policies have been developed and implemented by TCGA. The first policy describes participant protection considerations and conclusions in the context of the "Common Rule" (45-CFR-46, governing human subjects protections in federally funded research) and TCGA policies on informed consent. TCGA values a thorough and understandable informed consent process, which includes a comprehensive discussion about the protocol, benefits, risks, etc., with each participant. TCGA management staff (Project Team) has developed documents that can serve as guides to assist investigators in developing their own protocols, and consent forms and processes. This policy leaves the responsibility for the ultimate decision about whether the research conducted under TCGA involves "human subjects" or not to local Institutional Review Boards. The second policy summarizes what information is included in TCGA datasets, how those data are deposited into the program's online databases and TCGA data access mechanisms that are in place. The third policy describes what is being done to ensure compliance with the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA).

These policies have been reviewed throughout the course of the TCGA Program and have been modified as experience is gained and lessons are learned, when the Project Team receives suggestions for clarification or improvements from the many involved researcher or participant communities and as underlying regulations or policies are modified.

Introduction
In 2005, the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI) initiated a collaboration to pursue a Pilot Project to determine the feasibility of comprehensively cataloging the genomic alterations associated with human cancer. Three cancers, involving the brain (glioblastoma multiforme), the lung (squamous cell carcinoma of the lung), and the ovaries (serous cystadenocarcinoma of the ovary), were selected for study. The Pilot Project assessed the technical feasibility and potential value of conducting a comprehensive genomic analysis of selected tumors, including the characterization of DNA copy number changes, rearrangements, transcriptional profiling, epigenetic modifications, and sequence variation. A number of genomic analysis platforms were applied to a common set of molecular analytes obtained from clinically annotated, high quality, tumor tissues case-matched with a source of germline DNA for comparison. The genomic characterization data, along with recommendations from an expert panel, were used to identify targets for DNA sequencing in tumor and normal tissues for detection of variations. Because a common set of donor samples was used in all platforms, the Pilot Project was able to verify that cancer-associated genes and/or genomic regions can be identified by combining research results from large-scale genomic analyses with tumor biology and clinical data; and that the genomic characterization and DNA sequencing of tissue samples isolated from heterogeneous tumor specimens can be achieved in an efficient and cost-effective manner (TCGA Research Network, 2008). Furthermore, combining genomic analyses with tumor biology and clinical data provided new insights into the biology of tumors and resulted in the identification of potential diagnostic markers and therapeutic targets for selected cancers.

The Pilot Project was judged to be successful and, as such, TCGA was expanded in 2009 to study over 20 additional cancers. The goal for the expansion of TCGA is to rapidly and efficiently generate analogous genomic and clinical data for many major cancer types. As in the TCGA Pilot, genomic and clinical data generated by all the components of TCGA Program are deposited into web-based databases (with both open and controlled

access). More information on TCGA data sets can be found at the TCGA Data Coordinating Center (DCC) (https://tcga-data.nci.nih.gov/tcga/tcgaHome2.jsp) and the Cancer Genomics Hub (CGHub) (https://cghub.ucsc.edu/).

TCGA data are generated by a wide network of researchers from many institutions that provide comprehensive integrated data and analysis. There are five core functions performed by members of the TCGA Network: 1) clinical site patient enrollment, data collection, and tissue collection; 2) centralized data standardization and sample processing; 3) genomic characterization and DNA sequencing; 4) data collection, management and distribution and 5) data analysis. The specific names of these components for TCGA are described in the table below. Note that the table describes generic institutional roles in TCGA; many institutions participate in more than one role.

Entity	Function	Name in Program
Clinical sites	Patient consent and enrollment. Sample collection and QC.	Tissue Source Sites (TSS)
	Clinical data entry	
Centralized biospecimen and clinical data processing center	Sample pathology and QC. RNA and DNA isolation. Clinical data standardization. Analyte distribution.	Biospecimen Core Resource (BCR)
Molecular characterization centers	Genomic characterization of single nucleotide variants, DNA copy number changes and rearrangements. mRNA and miRNA transcription profiling. Epigenetic modifications. DNA sequencing.	Genome Characterization Centers (GCC) Genome Sequencing Centers (GSC)
Centralized data storage and redistribution centers	Primary sequence data repository. Genomic characterization data and analysis results repository.	Cancer Genomics Hub (CGHub) Data Coordinating Center (DCC)
Bioinformatic analysis centers	Cross-platform and crosscancer integrated dataset analyses	Genome Data Analysis Centers (GDAC)

*For further information about TCGA components, please visit the TCGA Program website (http://cancergenome.nih.gov).

The nature of TCGA data, including linked cohorts of cancer patients, their clinical annotation and extensive genomic data published on networked databases, raised novel human subjects protection issues when the program was initiated in 2005. These issues are now more broadly discussed throughout the genomics community, but many of TCGA's policies serve as potential precedent and models. TCGA management has continually sought broad input in understanding these emerging issues and establishing policies for managing TCGA data in light of complex scientific, ethical, legal and societal concerns. As a first step, the NCI and NHGRI convened a workshop in 2006 to examine both general and TCGA-specific issues of broadly releasing large quantities of coded, but linked clinical and genomic data.
A summary of this initial workshop can be found on the TCGA website:
(http://cancergenome.nih.gov/PublishedContent/Files/pdfs/6.5.1.2_TCGA_DataRelease.Workshop_101_706.pdf).
Since this workshop, NIH Institutes have held numerous forums on participant protection in genomic studies and the knowledge gained from these forums have continued to inform TCGA policy.

Background
A difficult aspect to establishing sound TCGA policies has been balancing the requirement to protect participants donating tissues and data with the importance to biomedical research of making TCGA clinical and molecular data available to a broad research community. The information below summarizes the issues discussed and key conclusions in three areas related to the protection of the research participants who contributed tissues and data to TCGA: informed consent, data access policies, and HIPAA regulations. This information is specifically intended to communicate TCGA policies to the research investigators, their institutional officials, and the public; and describe the rationale behind decisions of NCI and NHGRI staff regarding these important policy issues. The NCI and

NHGRI are providing this background information to convey that the conclusions were the result of an extensive deliberative process that revealed a range of well-considered opinions; and that the conclusions and policies are open to modification due to the exploratory nature of the program and the transforming state of the science.

The NCI and NHGRI received input from many sources. As may be expected, there was not unanimity of views with regard to many of the specific issues involved. TCGA policies on participant protection take into account all the input accrued by the NCI and NHGRI, including:

- A large number of national and international subject matter experts.
- Policies established for related programs at those Institutes, such as for the Cancer Genetic Markers of Susceptibility project (CGEMS; http://ocg.cancer.gov/resources/genome-wideassociation-studies-cancer-genetic-markers-susceptibility-cgems-initiative) and the NHGRI Medical Sequencing Program (http://www.genome.gov/15014882), and across NIH such as for the Genetic Association Information Network (GAIN; http://www.fnih.org/work/pastprograms/genetic-association-information-network-gain).
- Ongoing development of policy regarding Genome-Wide Association Studies (http://grants.nih.gov/grants/gwas/).
- Principal Investigators and managers of large, networked clinical trial groups that include a molecular and translational research component, including several cooperative groups and Specialized Programs of Research Excellence (SPORE) and their successors (http://trp.cancer.gov/).

(The above links are active as of January 16, 2014, but may change.)

TCGA has attempted to harmonize this information to present a consolidated set of policies to the research community. Nevertheless, these policies should not be considered static; the policies are expected to evolve over the course of the program. TCGA is designed to learn from all aspects of the program, including not only the complex workflow to generate biological data from clinically annotated tissues, but also from the ethical and legal environment in which it operates. It is expected that because of this thorough process the TCGA policies can serve as models for other genome-scale biomedical research efforts in all disease areas.

Part 1: Donor Protections: "Human Subjects" Considerations and the Policy on Informed Consent
Almost all of the institutions involved in TCGA, whether they are clinical sites that are enrolling donors; collecting and contributing their tissue and data; processing and distributing these materials; or involved in generating genomic data, are recipients of federal funds. (There are several collaborators at foreign sites, including tissues source sites who abide by HIPAA requirement even if not legally obligated to do so.) Consequently, these sites are subject to 45-CFR-46 (the "Common Rule") governing protection of human research subjects. TCGA Project Team review of applicability of these regulations to the program, and its decision on the implementation of an informed consent policy are described below.

"Human subjects" or not

Most interpretations of guidance from the NIH Office for Human Research Protections (OHRP) conclude that research using de-identified coded datasets by an investigator accessing TCGA data does not involve human subjects when certain strictures on the flow of "identifiable private information" are put in place. This conclusion is based on OHRP "Guidance on Research Involving Coded Private Information or Biological Specimens" published on October 16, 2008 which can be found at http://www.hhs.gov/ohrp/policy/cdebiol.html and attached in the Appendix. This guidance states:

Under the definition of human subject at 45 CFR 46.102(f), obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. *using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and*

2. *using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.*

In general, OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For

*example, OHRP does not consider research involving **only** coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:*

1. *the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and*

2. *the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:*

    1. *the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);*

    2. *there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or*

    3. *there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.*

The flow of data in TCGA and contractual obligations with sites contributing specimens and data meet the tests specified above to prevent "identifiable private information" from being passed to researchers. There are both protocols in place to prevent the transmission of such information from clinical sites, and contractual obligations upon entities and affiliated investigators to not attempt to contact or identify subjects or their relatives (see the section on HIPAA-compliant Data Use Agreements, below). Consequently, a strict interpretation of the regulations and OHRP guidance would indicate that TCGA does not constitute human subjects research for investigators generating data as part of TCGA research network nor for those investigators accessing and analyzing TCGA datasets, with the exception of the contributing investigators from the clinical sites where the donors are enrolled.

Nevertheless, a number of subject matter experts thought that TCGA should adhere to a more stringent policy for protection of participants and their relatives than called for in the OHRP guidance. Several reasons were commonly cited, including:

- A belief that participants should be specifically consented for this type of project with largely unspecified future use of the generated data.
- The long-standing precedent that human subjects are involved even when there is de-identified, but linked, clinical information being made broadly available to the research community.

A hypothetical, but technically possible, risk that de-identified high density genotyping, sequence or clinical data can be matched against a third party database to effectively re-identify an individual. In such an event, de-identified clinical data could be linked back to a participant risking their privacy and the confidentiality of their information. These expert conclusions were also based on interpretation of other OHRP guidance, including: "Issues to Consider in the Research Use of Stored Data or Tissues" published November 7, 1997 which can be found at http://www.hhs.gov/ohrp/policy/reposit.html and OHRP Decision Charts of September 24, 2004, which can be found at http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html.

The lack of consensus led the NCI and NHGRI not to adopt a program-level policy but to work with all participating institutions and their IRBs after providing them information on TCGA processes and guidance derived from consultations with numerous experts and stakeholders. TCGA expects investigators and their institutions to consider, based on their own standards of research practice, whether or not research involving coded and potentially re-identifiable information in TCGA datasets meets the definition of "human subjects" or not. The NCI and NHGRI presume that this determination will be made consistent with the institutional policies and in consultation with the local IRB.

Even if the local conclusion is that TCGA involves "human subjects," institutions and their review boards should consider whether the proposed research qualifies for exemption #4, quoted below:

> *45 CFR 46.101(b)(4)Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.*

Informed Consent

During the process of establishing TCGA human subjects protection policies, the NCI and NHGRI Project Team and subject matter experts sought input from diverse constituencies and reviewed dozens of protocols and informed consent documents used by investigators and other groups implementing tissue and clinical data collections for genomic studies. This review led to the critical observation that many existing protocols and consent processes in 2005 did not adequately describe modern, high-throughput genetic and genomic studies. Specifically, the reviewed consents did not convey the unprecedented scale of data generated from such genomic studies, nor the risks to privacy and confidentiality when such data can be quickly and widely shared on the internet. It is important to note, however, that over the course of TCGA, protocols and consents cognizant of these issues have become more globally adopted.

Initial Informed Consent Policy

These findings led the Project Team to initially decide that living donors of tissue specimens and data to TCGA would be consented specifically for TCGA and be provided with specific information about the program, the types of data being generated, and the potential risks to them. It was understood that this policy would necessitate that still-living donors who had in the past contributed samples to existing collections (i.e. retrospective collections) would need to be re-contacted and re-consented. Over the course of the Pilot Project, the Project Team received considerable feedback on this policy and began to review relevant informed consent permissions that, while not TCGA specific, did address many of the concerns about a project with this scope of data generation and distribution. The Project Team revisited this consent policy and modified the policy as described below.

Revised Informed Consent Policy

Under the revised TCGA consent policy, re-consent of still-living participants is no longer a programimposed requirement. The Project Team has developed a memo describing best practices for informed consent for participating in TCGA. This document is on the TCGA web site at http://cancergenome.nih.gov/abouttcga/policies/informedconsent. Upon request, TCGA staff will review informed consents from interested investigators, and issue a non-binding opinion memo to the contributing Principal Investigator (PI) that describes the degree to which the existing consent document is consistent with the goals and activities of TCGA. Specifically, the memo will review if the informed consent document includes key concepts related to TCGA such as genetic research, broad sharing of biospecimens and clinical data via the internet, the possibility of future research use, the use of electronic database with partial public access and the risk of loss of privacy. The memo will also note if a component of the reviewed consent is specifically incompatible with TCGA. A PI may choose to use this memo as supporting documentation in an application to the local IRB. Ultimately, the local IRB will determine if the existing consent document is sufficient for submission of specimens and data to TCGA.

Samples from deceased individuals

A significant number of the samples and data entering TCGA are from individuals now deceased. TCGA policies are in accordance with the “Common Rule” that use of these samples does not constitute human subjects research and that they may be used without IRB approval. Participating institutions in TCGA are, of course, subject to their own policies, and TCGA will make available any requested documentation to provide investigators and their IRBs with sufficient information to make their own determination.

Documentation of IRB approval

TCGA policies require that all PIs contributing annotated biospecimens provide documentation to the Biospecimen Core Resource and the Project Team that their IRBs have either a) approved the use of data and specimens for TCGA studies, or b) do not consider participation to constitute “human subjects research,” and therefore do not have purview. Specifically, NCI policy requires contributing site PIs funded by NCI to provide a copy of the protocol, or letter from their IRB, that specifically mentions TCGA in the approval for use of the samples and data. NHGRI policy differs slightly in that a PI’s TCGA tissue provision protocol, or approval letter from the IRB, need not specifically mention TCGA and will be reviewed and approved by an NHGRI program staff member. NGHRI approval is contingent upon sample and data use in genetic/genomic studies with wide data sharing and without data use limitations.

Part 2: TCGA Data Access Policies

The participant protection and data access policies developed for TCGA are designed to balance two important goals: to facilitate investigations of genomic changes related to cancer and, at the same time, to respect and protect the participants whose data and materials have been contributed to TCGA.

The Program’s ultimate goal is to create a database of genomic and phenotypic (i.e. clinical) data that can be used in correlative analyses to support research to alleviate suffering and death from cancer. Thus, TCGA policy is to

promote wide dissemination of these data for use by the biomedical research community and to assure their maximum utility. TCGA data are considered a community resource. To achieve this, the NCI and the NHGRI are committed to the rapid and complete release of TCGA datasets for use by all investigators throughout the global scientific community who, along with their institutions, certify their agreement with TCGA policies. All investigators in TCGA's research network are required to adopt the program's policies on data access, publication, and intellectual property, many of which are specifically designed to address participant protection. TCGA data release goals include full recognition that participants donating to this program expect to have their privacy protected and their data safeguarded according to the law and to best ethical practice.

Background

Because the data collected and generated by TCGA derive from a complex research network, the following background section lays the groundwork for understanding TCGA data policies by explaining how the data are collected, generated, and stored. Key characteristics of the data that can potentially affect the privacy of participants will be highlighted. After the background explanation, TCGA's data access policies are described.

TCGA data sets are comprised of information imported and generated along a multi-step workflow, culminating in clinical and molecular datasets housed in two central databases developed and maintained by TCGA: the TCGA Data Coordination Center (DCC) and the primary sequence data repository at the Cancer Genomics Hub (CGHub). (TCGA data may also be housed at other databases developed by collaborators). Those data which could be analyzed to theoretically identify a participant will be managed with additional levels of restriction, including both technical security and a requirement that investigators and institutions accede to the terms of data use and participant protection obligations stated in this policy document.

This section describes the steps by which participants are enrolled, and their clinical data and tissue samples, and the molecular data from those samples are collected, generated, and deposited into TCGA databases. The steps are outlined because the involvement of multiple institutions and data exchanges between those institutions impact the policies and legal requirements attached to the data. The following figure and workflow summary describe TCGA data generation process.

1. Retrospective collections and potential prospective collections that can provide tissue samples and associated clinical data that meet the requirements of TCGA are identified by NCI. In addition to the biological quality of the materials, a key requirement of the biospecimens is that the ethical and legal stringency of the human subjects protocols under which the collections were established enable clear access to the resource by TCGA. TCGA staff makes final decisions about which cancers are chosen for the program and which institutions are engaged to participate in the program and transfer samples and data into the TCGA research network. See the DCC website (https://tcgadata.nci.nih.gov/tcga/tcgaHome2.jsp) for an up-to-date list of cancers and contributing sites.

   The following are important characteristics of the material transfer from contributing sites (Tissue Source Sites) to TCGA network that are imparted to the data access policies:

   - Clinical data associated with specimens are stripped of direct patient identifiers before distribution by the contributing site. Specifically, the data received by the TCGA research network are compliant with HIPAA defined "Limited Data Set" and do not include the designated identifiers (see HIPAA compliance section for details).

   - The tissue source site will maintain a link between donor IDs and materials transferred to TCGA, so that longitudinal and outcomes data can be associated with the genomic

     data. This link will not be made available to the TCGA program, but will be used to enable the flow of additional participant data, accumulated over time, into TCGA.

2. A Biospecimen Core Resource (BCR) was established by the Program. A BCR is a central site using uniform protocols to receive and process all tissues and clinical data. The BCR is the TCGA interface to all Tissue Source Sites (TSS), from which it collects tissue samples and clinical data. Details about the BCR can be viewed at: http://cancergenome.nih.gov/abouttcga/overview/howitworks/bcr.

   The BCR operations include the following biospecimen processing and data generating, formatting and distribution functions:

   - Pathology review of each received tissue specimen, during which typical surgical pathology data (e.g. tumor stage and grade) are collected and compared to the participant's diagnostic surgical pathology report submitted by the contributing institution. Additionally, information on cellular

composition and digital images are captured. These data are captured in a structured electronic format to support inclusion in the program database.

- Isolation of nucleic acid analytes from the samples with concomitant quality control (QC) to ensure suitability for use by the Centers. Nucleic acids are isolated from the samples using strict quality controls, and then distributed to the Centers.
- Distribution of analyte aliquots to the Centers.
- Formatting and standardization of incoming clinical data and locally generated pathology and molecular QC data into data structures compliant with standards from the NCI's data. All data associated with TCGA will use terminologies and Common Data Element structures as maintained by the NCI Center for Bioinformatics in their centralized Enterprise Vocabulary Service (EVS) and cancer Data Standards Registry (caDSR) servers.

The following are important characteristics of the sample and data transfer to and from the BCR that are imparted to the participant protection and data access policies:

- BCR establishes contractual relationships, including Material Transfer Agreements, Data Use Agreements, and warrants of compliance with relevant Common Rule and HIPAA regulations to protect the ethical, legal and technical requirements established by TCGA policies relating to access and transfer of participant information. These requirements apply to relationships with contributing sites transferring samples and data to the program, and all entities receiving samples and/or data from the BCR.
- BCR generates a secondary donor/sample identifier (TCGA ID), and maintains a link between this TCGA ID and the ID received from each contributing site. It is important to note that TCGA is a second link in the ID reference, thus the TCGA ID is effectively twiceremoved from the patient's primary ID. The TCGA ID will be the one distributed to the Centers along with the analytes.

- The BCR will transmit only minimal clinical data (for example, diagnosis, tissue, gender, and approximate age), sample histopathology and molecular QC results, and sample logistical information to TCGA molecular characterization Centers as necessary to support their molecular characterization operations. Such clinical information transmitted to Centers will meet the definition of De-Identified per HIPAA.
- The BCR will transmit clinical data to TCGA Data Coordinating Center (DCC) (See below). These data are compliant with HIPAA Limited Data Set specification. The BCR has executed Data Use Agreements with the DCC. (See the section on HIPAA compliance, below.)

3. Genome Characterization Centers (GCC) and Genome Sequencing Centers (GSC) conduct the DNA, RNA, and protein-based molecular characterizations. The Centers will receive samples and log them into locally managed material management / LIMS databases. The Centers also will have access to sample logistics and QC data from the BCR, as necessary, and may store local copies of such data for operational support. Center databases will maintain the link between the TCGA IDs provided by the BCR and the derived data.

   The Centers will conduct a variety of high-throughput comprehensive genome-wide analyses using established technologies. The following are key aspects of Center operations that relate to data access policies developed by TCGA:

   - Centers will <u>not</u> receive directly from the BCR any clinical data covered by the program's HIPAA compliant Data Use Agreements as part of operations for TCGA data generation. Center investigators who wish to retrieve the clinical data must do so directly from the DCC.
   - As data are generated by the Centers, they will be deposited in the DCC and/or CGHub according to the rapid data release policies of TCGA. Centers will only distribute data to the DCC and CGHub.

4. TCGA has established a Data Coordinating Center (DCC) which links together all data generated by the program into a single integrated resource, with links made to the primary sequence data managed by the University of California, Santa Cruz (UCSC) Cancer Genomics Hub (CGHub). UCSC has obtained trusted partner status with the National Institutes of Health for providing storage, integration and dissemination of protected TCGA data and other cancer genomics data.

   To help ensure the protection of participants in a manner consistent with the policies of TCGA, the DCC and CGHub database staff has taken steps to ensure that the database cannot readily be used to identify donors. The DCC or CGHub database do not receive any direct identifiers such as name, medical record number, address, social security numbers, contact information, or any other HIPAA

identifiers excluded under the definition of a Limited Data Set – as noted above, such data are not collected by TCGA.

Furthermore, all access to TCGA data that are individually genetically unique and pose a theoretical risk of participant re-identification may only be accessed via the DCC or CGHub, in accordance with TCGA restricted-tier data access policies. These data resources will implement the database and software applications with security capabilities that apply the policies established by the TCGA Project Team and Data Access Committee, requiring user authentication against the NIH database of approved investigators.

Policies

As described in Part 1 above, it is technically possible that genomic information (DNA sequence, genotype, etc.) generated in TCGA could lead to identification of an individual if similar data from that person (or blood relative) were obtained from a third-party database and correlated (as could happen in a forensic analysis). There also is a risk of individual identification by computer-based analysis of the clinical data in conjunction with, for example, third-party demographic and healthcare management databases. This potential identification would then link the individual to their clinical information collected by TCGA, and could lead to loss of privacy.

Although the risk of this occurring is judged to be small at present, the NCI and NHGRI have decided to apply stricter requirements than are currently required by the NIH Office for Human Research Protections (OHRP). (See Part 1 on Human Subjects considerations for more discussion and policies related to recruitment of donors and the informed consent process). The data access policies described below encapsulates these requirements. The first set of policies describes limitations to data content and requirements to access that content resident at the DCC and CGHub. The second set of policies covers a key issue regarding data access across TCGA pipeline, i.e. reaching back from the DCC and CGHub to link tissue sample IDs at the BCR.

Policy on Access to TCGA Data Managed by DCC

To minimize the risk of participant identification, the TCGA Project Team established a policy that TCGA data be made available from a two-tiered data access system. The first tier will be publicly accessible and contain only data that cannot be analyzed to generate a dataset unique to an individual. A second tier will contain composite genomic and clinical data that are associated to a unique, but not directly identified, person. Access to this tier will require researchers and their institutions to ascribe to the Data User Certification described below.

Open-Access Data Tier: Open-access data will be available in public databases. These data types include:

- TCGA Case identifier, individual sample identifiers (barcodes of analyte aliquots sent to Characterization and Sequencing centers), and image identifiers (pointers to pathology images used to confirm histology).
- De-Identified clinical and demographic data.
- Tissue sample histopathology, including de-identified pathology reports.
- Gene expression profiles.
- Copy-number aberrations, as long as the experimental approach did not utilize single nucleotide polymorphisms (SNPs) analysis.
- Data summaries such as copy number alternations and loss of heterozygosity by SNP analysis, genotype frequencies for each locus.
- Summaries or aggregations of germ-line variants.
- Somatic mutations.
- Logistics and QC data.
- Microsatellite instability (MSI) locus summary calls.

Controlled-Access Data Tier: The controlled-access data tier will not be freely available to the public, but will be made available to any *qualified* researcher for the purpose of biomedical research, once the investigator, along with his/her institution, has certified agreement to the statements within TCGA Data Use Certification (DUC). The data types in the controlled access tier include:

- Individual-level germline variant data (e.g. SNP6 .cel files).
- Whole exome and whole genome sequence data (.bam files residing at CGHub). RNA and miRNA sequence data (.bam files residing at CGhub).
- Raw MSI data.

Process for DCC Data Access

Investigators seeking access to TCGA data in the controlled-access database will be asked to complete a Data Access Request (DAR) at the NCBI dbGaP Authorized Access webpage

(https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login). The submission of the DAR ensures that investigators, along with their institutions and collaborators, understand the broad goals and policies of TCGA participant protection and have specifically agreed to the requirements and terms of access. Such terms include assurance that the data will be used for "appropriate research" in accord with the definition on TCGA, including any limitations on such use. Specific terms and conditions for access to and use of TCGA datasets by Approved Users can be found in TCGA Data Use Certification (DUC) document.

DARs will be evaluated by a Data Access Committee established by the NCI and NHGRI. It is anticipated that most DARs will be evaluated within two weeks of receipt. Applicants that are approved will become Approved Users, subject to adherence to TCGA policies.

All Approved Users will certify through the DAR process that they will not distribute TCGA controlledaccess data in any form to any third parties, other than those of their own research staff who have agreed to the terms of the DAR. Approved User's execution of the DUC obliges them not to attempt to identify or contact individual participants or their relatives. For collaborative projects, any independent investigator from a separate institution involved in the use of TCGA data is required to submit a separate DAR. All Approved Users and their institutions will be required to acknowledge responsibility for ensuring that all uses of the data are consistent with federal, state, and local laws and regulations, and any relevant institutional policies.

Policy on Access to Sample IDs

TCGA is organized as a series of "linked" protocols, in that the samples and molecular data generated from them are not anonymized. (The term "anonymized" is used in the technical "human subjects research" sense to mean that all links between the sample and data back to the patient have been irretrievably broken.) Many participants who have contributed samples and data to TCGA are still living, and the medical centers at which they were enrolled for tissue banking continue to collect clinical, longitudinal and outcomes data that can be transmitted to TCGA under this linked protocol.

Tissue source sites may be able to leverage TCGA generated data to a great extent to further understand the cancer for which they enrolled donors and contributed tissues to the program. This is possible for two reasons. First, it is not currently possible to transmit the full breadth of donor clinical information that may exist at a contributing site or with a contributing investigator to TCGA. For example, many TCGA donors, after resection of tissues, are placed onto therapeutic trials at these institutions and extensive data are collected. Second, most contributing tissue source sites contain "sister" samples, from the same tumor as the one donated to TCGA. The potential scientific value of such additional data collection and focused tissue studies is very high.

- To enable this, however, contributing sites would need to access the link between their contributing site sample ID and TCGA ID generated at the BCR in order to link their research biorepository records to the genomic characterization data generated by the Centers. To ensure that the best possible cancer research is supported by TCGA, the program is not categorically opposed to such linkage, but has established a policy that sample ID links between contributing site IDs and TCGA IDs will only be revealed to a contributing site investigator documenting an IRB approved protocol to use this information.

TCGA Data Access Policy review

All TCGA policies are subject to change as deemed necessary to sustain program principles and priorities, to ensure the highest standards for responsible research conduct, and to be consistent with comparable policies established by the NIH, NCI and NHGRI for other programs. Accordingly, TCGA policies are reviewed periodically to ensure they are consistent with any changes in overarching regulations (e.g. HIPAA) and reflect lessons learned throughout the program. The NCI, NHGRI, their advisory boards, and their subject matter experts will continually evaluate the risks and benefits associated with collection, generation and deposition of all TCGA data and will consider modification of these policies accordingly, when appropriate.

Part 3: TCGA HIPAA Privacy Rule Compliance
Background

US-based clinical sites (TCGA Tissue Source Sites (TSS)) at which participants are enrolled and clinical data are collected to annotate biospecimens are "covered entities" under HIPAA. Therefore, those clinical data are Protected Health Information (PHI), as defined by the Health Insurance Portability and Accountability Act (HIPAA), and subject to the HIPAA "Privacy Rule" set in place to protect the confidentiality of patient information. (Note that some data collected from non-US sites is not technically subject to HIPAA, but the program does not treat such data differently.) The purpose of this rule is to minimize social risks to patients resulting from non-permitted distribution of their health information. This purpose is achieved by regulating the conditions under which clinical data may be disclosed, and includes various mechanisms ranging from obtaining patient authorization, waiver from an IRB, or limiting the data content so that the data do not specifically identify an individual.

Scientifically, however, TCGA goals are best supported if the program can maximize the breadth of clinical information associated with tumor samples, as TCGA is primarily creating datasets for the purpose of hypothesis generation. Consequently, it is not predictable what clinical data elements will correlate with molecular characteristics and therefore it is preferable to collect the greatest possible amount of clinical information per donor. Nevertheless, the transfer of patient data from contributing sites to TCGA must be compliant with HIPAA. Currently, HIPAA only applies to patient data being disclosed by covered contributing sites and not to molecular data generated from samples within TCGA.

Therefore the goal of TCGA HIPAA policy is to set up a fully HIPAA-compliant clinical data pipeline that enables the maximal amount of potentially relevant clinical data annotating biospecimens to be transmitted to the program. It is noted that the HIPAA Privacy Rule is a U.S. Federal regulation that can be superseded to greater levels of restriction by state and local laws. TCGA will address this eventuality in the context of sample and data procurement relationships with each contributing site, and necessary additional restrictions will be embedded in the material transfer agreements and data transmission operations with that site.

HIPAA Implementation under Limited Data Set Regulations and TCGA Policy

Of the mechanisms permitted for clinical data disclosure by covered entities under HIPAA, two were considered for contributing sites collaborating with TCGA. First, HIPAA-defined De-Identification, per 164.514(b)(2)(i), that defines a safe harbor for clinical data that have been stripped of 18 specified data types considered identifying. Clinical data, devoid of these identifiers, are no longer considered "individually identifying" and are therefore not subject to the regulation. Second, distribution of clinical data compliant with the Limited Data Set (LDS) definition at 165.514 (e)(2). The permissible content of LDS compliant clinical data is very similar to HIPAA-defined de-identified clinical data except that more precise date/time and geographic information may be included. The LDS option for permitted disclosures was added to the privacy rule in late 2002, resulting in the so-called "modified privacy rule," after a comment period indicated that the original rule would significantly hamper research. (Specific excerpts from the HIPAA regulations for the two types of data described above are in the Appendix.)

The LDS option was chosen after consultation with TCGA advisors because it was suggested that some investigators would benefit from the additional data (specifically, accurate dates of clinical events) allowed under the rule. TCGA implemented the necessary policies, contracts (i.e. the Data Use Agreement), information technology, and operations to be compliant with HIPAA disclosure and transmission of clinical data from covered entities to the program.

Key features of LDS Disclosures for Research

The Limited Data Set option for permissible disclosures of clinical data was put in place specifically to support research projects like TCGA. Under HIPAA, key features of the LDS option include:

- LDS-compliant data are still considered Protected Health Information (PHI), so disclosure can be regulated.
- The regulations specify data elements that must be stripped from clinical data to become compliant with the LDS definition. In comparison to the HIPAA definition of de-identification, the list is exactly the same except: (a) date / time information, such as birthdays or procedure dates, may be included; (b) geographical information, at the level of town or city, state, and zip code, may be included; and (c) the catch-all 18th identifier ("Any other unique identifying number, characteristic, or code") is not included.
- LDS disclosure must be for the purpose of research, public health, or health care. LDS may be
- disclosed without an authorization or an IRB or privacy board waiver of authorization or alteration of authorization. (For documentation, see the Appendix for (a) HHS Office of Civil Rights (OCR) guidance; and (b) Page 53231 of HHS Federal Register commentary and response on privacy rule.)
- LDS may be disclosed for research without requirement of HIPAA accounting regulations, under which covered entities must maintain a tracking database of all disclosures. (See the Appendix for HHS OCR guidance specific to this subject.)
- Disclosure of LDS requires that the discloser and recipients to enter into a Data Use Agreement (DUA) a contractual requirement under which recipient obliges to:
    - Use the data only for intended purposes;
    - Not attempt to identify or contact individuals;
    - Further disclose the information only as permitted in the DUA;
    - Ensure the data are safeguarded;
    - DUA restrictions upon any of its agents or contractors.

Impose the

HIPAA implementation within TCGA

Operationally, clinical data in TCGA flow unidirectionally from contributing sites (typically HIPAA "covered entities") to the BCR, then from the BCR to the DCC, and finally from the DCC to researchers.
This data flow is graphically described in Figure 1.

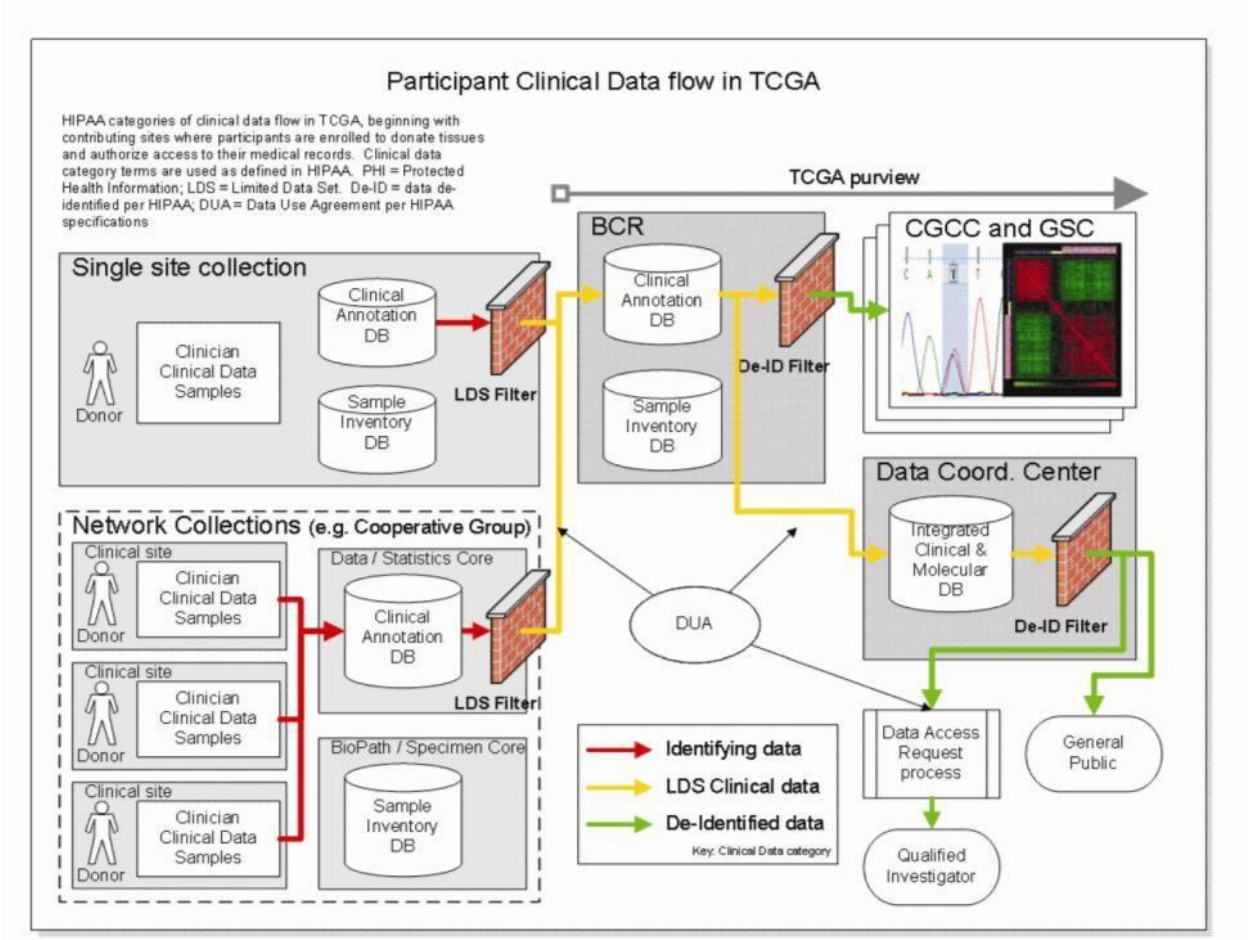


Figure 1. Data flow diagram illustrating what HIPAA category of data is permitted to be transmitted between TCGA collaborating entities.

HIPAA and PHI Data flow <u>into</u> the TCGA Program

The flow of data into TCGA is regulated by a set of Data Use Agreements (DUA) between several entities in the consortium, as illustrated in Figure 1. Those DUA include the following components:

- An originating DUA is in place between the HIPAA "Covered Entity" contributing site (TSS) and BCR contractor(s). (Note, that if the contributing site is itself a "hub" of a network (e.g. as in a cooperative group setting), the DUA in place between the contributing site and the BCR may not be the originating DUA.) The DUA with the BCR is in the form of an enhanced Material Transfer Agreement (MTA), since such a contract was already going to be required between any contributing site and the BCR to cover the transfer of tissue samples. NCI worked with several university technology transfer officers to develop an MTA that included a HIPAA compliant DUA, which thus addresses both the physical material and LDS data transfer from a contributing site to the BCR. The MTA includes a warrant by the discloser that all PHI associated with TCGA tissue donors will be compliant with the Limited Data Set specification. The DUA also pre-authorizes additional LDS-compliant data disclosure from the BCR to the DCC for purposes of the program. • A DUA is in place between BCR contractor(s) and DCC (which is, in fact, the NCI) to permit transfer of LDS compliant data to the government. (The BCR's functional role with clinical data is to reformat them to be comparable between clinical sites and compliant with NCI data standards.)
- No DUA is in place between the BCR and GCC or GSC as these Centers will only receive minimal data associated with the molecular analytes being received. Those data will be De-Identified per the HIPAA definition.

HIPAA and Data distribution <u>from</u> the TCGA Program to Investigators

The HIPAA policy covering data distribution from TCGA to investigators has evolved since the program's inception in 2006. In general, as information systems have become more sophisticated, the program has been able to

incrementally restrict the distribution of LDC by making more of the data pipeline contain data compliant with HIPAA's definition of De-Identified.

Originally, during the Pilot Project, data distributed from the TCGA DCC to the broader investigator community included specific dates of participant clinical events. Thus, these data were technically PHI, compliant with a HIPAA LDS. (No geographical information is included in TCGA data.) A DUA was included as part of the TCGA Data User Certification (DUC) (see the section above on Process for DCC Data Access) executed between the DCC (NCI) and any researcher's employer.

At the end of Pilot phase, a decision was made to modify the above policy and make the distributed clinical data fully compliant with the HIPAA De-Identified definition. To be clear, the TCGA research network still receives HIPAA LDS, but no longer distributes it. Specifically, clinical event dates are no longer part of the data sets distributed from the DCC to investigators. All dates have been converted to negative or positive intervals referenced from the day of diagnosis. Any dates remaining are rounded to full years, thus meeting the HIPAA De-Identified test. It should be noted that the DCC retains full dates in its internal archives, but access to these dates requires specific permission from the Project Team.

Beginning in 2014, the process of converting full dates to intervals will move to an even earlier step in the TCGA data pipeline, to further limit such data's exposure. Under the new process, the BCR is responsible for this conversion, and the BCR will only distribute HIPAA fully De-Identified data to the DCC for inclusion in the TCGA database. The BCR will separately, regularly transfer LDS data (i.e. with dates) to the NCI for archival purposes.

Important Notes

Regardless of the detailed point in the data pipeline where the data are converted from LDS to DeIdentified and that all investigators only receive De-Identified data, all investigators and their institutions are still required to enter into a DUA. This requirement is in place for two reasons: a) some legacy data sets still potentially contain LDS; and, b) the terms of a DUA also include restrictions on redistribution of molecular data that are individually genotypic. Such genotypic data did not derive from a covered entity and are not covered by HIPAA, but the same restrictions emplaced by the DUA on HIPAA data also provide important participant protections on the genetic data.

TCGA's HIPAA compliance policy is designed to enable the maximum amount of data to flow into TCGA databases, there may be other conflicting policies that may reduce o restrict the data submitted to the TCGA database. For example, IRBs from contributing sites may place greater restrictions on the amount of participant data submitted with tissue samples to TCGA. It is also possible that TCGA policies, as promulgated by the Project Team, may place greater restrictions on participant data accepted by the program or on what data residing in TCGA databases are made available to researchers. Such policies, often based on other sometimes conflicting bioethical considerations and future assessments of risks to participants, are described elsewhere in this document.

ANEXO C – Normas de publicação da Cancer Research

Cancer Research

Online ISSN: 1538-7445

Editor in-Chief:

Dr. Chi Van Dang

https://cancerres.aacrjournals.org/

Acesso em 07 de Outubro de 2020.