Universidade Estadual Paulista “Júlio de Mesquita Filho”
Faculdade de Medicina Veterinária e Zootecnia

PROTEOMA DO CARCINOMA MAMÁRIO FELINO FIXADO EM FORMALINA E CONSERVADO EM PARAFINA

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Botucatu, SP
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"Pessoalmente, sempre senti que o melhor médico do mundo é o Veterinário. Ele não pode perguntar aos seus pacientes qual é o problema...ele só precisa saber."

Will Rogers

RESUMO

AFOLABI, O.O. **PROTEOMA DO CARCINOMA MAMÁRIO FELINO FIXADO EM FORMALINA E CONSERVADO EM PARAFINA.** Botucatu – SP. 2025. 121p. Defesa (Doutorado) – Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

O proteoma do carcinoma mamário felino fixado em formalina e incluído em parafina (FFCP) é uma opção para estudo dos tumores, haja vista a quantidade e variedade de amostras disponíveis, possibilitando investigações complexas, descoberta de biomarcadores e compreensão dos mecanismos fisiopatológicos dos tumores. O carcinoma mamário felino é considerado modelo experimental para o câncer de mama humano devido ao seu comportamento biológico e características histopatológicas semelhantes, o que pode facilitar a identificação de potenciais alvos terapêuticos e indicadores prognósticos. Ademais, este tipo de tumor nas gatas é caracterizado por sua natureza agressiva e baixa taxa de sobrevivência, apresentando 2 vezes mais tendência e 5 vezes mais probabilidade de desenvolver formas malignas quando comparado aos cães. Com base nisso, este estudo pretende caracterizar o proteoma de carcinoma mamário felino de 2 tipos, cribiforme (mais agressivo) e tubulopapilar (menos agressivo), de amostras FFPE obtidas de um banco histológico, a fim de identificar potenciais biomarcadores associados à progressão tumoral e do prognóstico. Para tanto, 21 amostras de carcinoma mamário felino FFPE foram obtidas de um banco de dados histológico e distribuídas em 2 grupos (cribiforme, n = 12 e tubulopapilar, n = 9). Após desparafinação e reidratação, as amostras foram digeridas com tripsina e a proteômica foi analisada por nLC-MS/MS por abordagem *shotgun*. Os dados foram submetidos à análise multivariada (análise de componentes principais), teste t, *fold change* e volcano plot (FDR < 0,05). Foram identificadas 976 proteínas, sendo que 148 proteínas tiveram abundância diferencial entre os grupos. A PCA revelou uma sobreposição entre os dois grupos em ambos os tipos de amostra, conforme evidenciado pelo mapa de calor. Das quinze principais proteínas analisadas que estavam presentes em ambos os tumores, 14 delas apresentaram maior expressão no tumor cribriforme em comparação ao tumor tubulopapilar, enquanto apenas 1 apresentou maior expressão no tumor tubulopapilar. De todas as proteínas extraídas das amostras, 4 proteínas eram exclusivas de FMC cribriforme e tubulopapilar, a saber, uma proteína não caracterizada (A0A337S6M6), nucleoproteína AHNAK (A0A337S8X8), glicerol quinase (A0A337SAZ0), miosina-2 (A0A337SF79); e glicosilceramidase beta 3 (A0A2I2UCJ0), beta-2-glicoproteína 1 (M3WH75), proteína contendo domínio SEA (M3WNR4) e proteína contendo domínio EF-hand (A0A337SCP2), respectivamente. Duas proteínas, a subunidade alfa da proteína 1 do complexo T (M3VZ89) e o Reticulon-3 (A0A5F5XKU7), indicando prognóstico desfavorável semelhante ao do câncer de mama humano, foram identificadas em ambos os grupos. As proteínas identificadas estavam relacionadas à esteroidogênese ovariana, processamento e apresentação de antígenos, processamento de proteínas, glicólise/gliconeogênese, sinalização de cálcio, geração e metabolismo de energia, reorganização citoesquelética, regulação do ciclo celular, dobramento de proteínas e resposta imune, refletindo alterações específicas do tumor na homeostase proteica e na maquinaria celular. Esses achados demonstram as diferenças nos mecanismos moleculares que impulsionam o FMC cribiforme e tubulopapilar, as vias metabólicas envolvidas e as proteínas específicas aumentadas, talvez causando os efeitos específicos e possíveis diferenças entre essas duas formas de tumores. Além disso, a identificação de duas proteínas específicas indicativas de mau prognóstico

demonstra a similaridade, em nível molecular, entre esses dois tumores e o câncer de mama humano.

Palavras-chave: Câncer, biomarcador, LC-MS/MS, resposta-imune, prognóstico

ABSTRACT

AFOLABI, O.O. **PROTEOME OF FORMALIN-FIXED, PARRAFIN-EMBEDDED FELINE MAMMARY CARCINOMA.** Botucatu – SP. 2025. 121p. Defesa (Doutorado) – Faculty of Veterinary Medicine and Animal Science, Botucatu Campus, São Paolo State University.

The proteome of formalin-fixed, paraffin-embedded (FFCP) feline mammary carcinoma is an option for studying tumors, given the quantity and variety of samples available, enabling complex investigations, discovery of biomarkers, and understanding of the pathophysiological mechanisms of tumors. Feline mammary carcinoma is considered an experimental model for human breast cancer due to its similar biological behavior and histopathological characteristics, which can facilitate the identification of potential therapeutic targets and prognostic indicators. Furthermore, this type of tumor in cats is characterized by its aggressive nature and low survival rate, presenting a 2-fold greater tendency and 5-fold greater probability of developing malignant forms when compared to dogs. Based on this, this study aims to characterize the proteome of two types of feline mammary carcinoma, cribriform (more aggressive) and tubulopapillary (less aggressive), from FFPE samples obtained from a histological bank, in order to identify potential biomarkers associated with tumor progression and prognosis. For this purpose, 21 FFPE feline mammary carcinoma samples were obtained from a histological database and distributed into 2 groups (cribriform, n = 12 and tubulopapillary, n = 9). After deparaffinization and rehydration, the samples were digested with trypsin and proteomics were analyzed by nLC-MS/MS using a shotgun approach. The data were subjected to multivariate analysis (principal component analysis), t-test, fold change and volcano plot (FDR < 0.05). A total of 976 proteins were identified, with 148 proteins showing differential abundance between the groups. PCA revealed an overlap between the two groups in both sample types, as evidenced by the heat map. Of the fifteen main proteins analyzed that were present in both tumors, 14 of them showed higher expression in the cribriform tumor compared to the tubulopapillary tumor, while only 1 showed higher expression in the tubulopapillary tumor. Of all proteins extracted from the samples, 4 proteins each were unique to cribriform and tubulopapillary FMC, namely, an uncharacterized protein (A0A337S6M6), AHNAK nucleoprotein (A0A337S8X8), glycerol kinase (A0A337SAZ0), myosin-2 (A0A337SF79); and glucosylceramidase beta 3 (A0A2I2UCJ0), Beta-2-glycoprotein 1 (M3WH75), SEA domain-containing protein (M3WNR4), and EF-hand domain-containing protein (A0A337SCP2) respectively. 2 proteins, T-complex protein 1 subunit alpha (M3VZ89) and Reticulon-3 (A0A5F5XKU7)indicating poor prognosis similar to human breast cancer, being identified in both groups. The proteins identified were related to ovarian steroidogenesis, antigen processing and presentation, protein processing, glycolysis/gluconeogenesis, calcium signalling, energy generation and metabolism, cytoskeletal reorganization, cell cycle regulation, protein folding and immune response reflecting tumor-specific alterations in protein homeostasis and cellular machinery. These findings demonstrate the differences in the molecular mechanisms driving cribriform and tubulopapillary FMC, the metabolic pathways involved, and the specific proteins abundance, perhaps causing the specific effects and possible differences between these two forms of tumors. Furthermore, the identification of two specific

proteins indicative of poor prognosis demonstrates the similarity, at the molecular level, between these two tumors and human breast cancer.

Keywords: Cancer, biomarker, LC-MS/MS, immune-response, prognosis

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CAPÍTULO 1

1. INTRODUÇÃO E JUSTIFICATIVA

Os tumores mamários não são comuns em gatas, mas quando ocorrem, são normalmente malignos. O mais frequente é o carcinoma mamário felino, uma neoplasia maligna, caracterizada por sua natureza agressiva e baixa taxa de sobrevivência. Este tipo de tumor apresenta características similares ao câncer de mama em mulheres e cadelas, ressaltando a importância de pesquisas nestas espécies de animais domésticos, como modelos experimentais para humanos (Frénel & Nguyen, 2023). Na prática clínica veterinária, os carcinomas mamários em felinos representam uma preocupação significativa, uma vez que nas gatas a probabilidade de desenvolver a forma maligna é 5 vezes maior que em cadelas (Monteiro et al., 2025; Pinello et al., 2022).

Pelo lado reprodutivo, o carcinoma mamário felino tem impactos significativos na reprodução da espécie (Little, 2011), limitando a vida reprodutiva em vista da redução do potencial reprodutivo e aumento da mortalidade (Cunha et al., 2017; Goericke-Pesch & Packeiser, 2022). Também pode causar disfunção das glândulas mamárias e consequente produção inadequada de leite em fêmeas lactantes (Pérez-Alenza et al., 2004a). Além disso, compromete o bem-estar tanto animal quanto humano, pois os gatos, sendo animais de companhia, quando acometidos pelo carcinoma mamário sofrem dor que também repercute sobre seus tutores, podendo causar problemas de saúde, depressão e desequilíbrio emocional (Heath, 2018).

Os carcinomas mamários felinos são descritos morfologicamente como ductais ou lobulares, classificação baseada no componente epitelial da glândula mamária ou invasão do estroma circundante, aparecendo nos ductos ou lóbulos mamários (Baba & Câtoi, 2007; Goldschmidt et al., 2011; Zappulli et al., 2013). No entanto, além da localização do tipo celular, na prática histopatológica, o carcinoma mamário felino também é classificado como de acordo com o número de células, tipo e localização da secreção (Makki, 2015). Apesar disso, a classificação desse tipo de tumor apresenta dominância de certos padrões, como carcinoma tubulopapilar e cribiforme (Cserni, 2020; Nascimento & Otoni, 2020; Silva et al., 2017).

Além do histopatológico, a classificação molecular dos tumores mamários felinos pode identificar padrões comportamentais específicos e fornecer aplicações potenciais na prática clínica e oncológica comparativa (Soares et al., 2016). Neste contexto, 6 subtipos de neoplasia mamária são biologicamente distintos e classificados na imuno-histoquímica como luminal, HER2-positivo e triplo-negativo (tipo basal e tipo normal) (Soares et al., 2016). Os subtipos luminal B e triplo negativo basal são os mais

comuns em gatas (Soares, 2016; Saad et al., 2008). Em estudos translacionais entre carcinoma mamário felino e câncer de mama humano, uma associação entre fenótipos moleculares e histopatologia foi evidenciada, e revelou tanto diferenças críticas quanto semelhanças nos microambientes tumorais (Brunetti et al., 2013; Burrai et al., 2010).

A proteômica é uma ferramenta que pode elucidar complexidades do carcinoma mamário felino, utilizando amostras de tecido fixadas em formalina e conservadas em parafina (FFCP), particularmente para o estudo de biomarcadores. Esta abordagem permite estudar os mecanismos fisiopatológicos das doenças, dado o elevado número de amostras armazenadas nos setores de patologia (Kobayashi et al., 2024; Longuespée et al., 2014, 2018; Maes et al., 2013). Essa ferramenta analítica tornou-se especialmente aplicada a tumores, pois o tecido removido cirurgicamente é, na maioria dos casos, enviado para análise histopatológica. Nesse contexto, os tumores mamários felinos estão disponíveis em bancos de amostras histopatológicas e podem servir como uma valiosa fonte de estudos, fornecendo informações sobre a fisiopatologia da doença, identificando moléculas para o diagnóstico de tumores mais agressivos e permitindo o desenvolvimento de terapias direcionadas (Broeckx et al., 2014; Dagher et al., 2019; Paphussaro, 2024; Zhu et al., 2019).

Além da oportunidade de estudar amostras preservadas, os tumores mamários felinos também representam um modelo valioso para a pesquisa translacional em mulheres, já que cães e gatos desenvolvem espontaneamente a doença (Abadie et al., 2018). Além disso, o comportamento biológico e as características histopatológicas dos tumores mamários felinos se assemelham aos das mulheres, tornando-se útil para identificar potenciais alvos terapêuticos e indicadores prognósticos (MacEwen et al., 1984).

A variedade na biologia do tumor sugere que diferentes espécies animais podem apresentar perfis distintos na expressão de proteínas, o que refletem respostas fisiológicas distintas, mas relacionadas à doença neoplásica (Kim et al., 2019). Ao integrar metodologias proteômicas quantitativas com amostras de carcinoma mamário felino FFCP, esta pesquisa busca identificar proteínas específicas que são desreguladas durante a progressão do tumor, investigando seu potencial como biomarcadores para diagnóstico aprimorado ou alvo para terapias eficazes. Além disso, o uso de amostras FFCP podem facilitar o estudo dos tumores. Portanto, este estudo tem como objetivo descrever o proteoma de dois tipos de tumor mamário felino FFCP usando as mais

recentes plataformas analíticas proteômicas, para facilitar uma melhor compreensão da heterogeneidade tumoral.

2. REVISÃO DE LITERATURA

2.1. Epidemiologia e patogênese do carcinoma mamário felino

O carcinoma mamário felino é um tumor caracterizado por sua natureza agressiva, baixas taxas de sobrevivência e é o tumor maligno mais comum nas gatas, (Gameiro et al., 2021; Hassan et al., 2017). As gatas têm quatro pares de glândulas mamárias, a saber, torácica, abdominal superior, abdominal inferior e inguinal. É comum que gatas desenvolvam múltiplos tumores mamários, com escassa literatura indicando que as glândulas mamárias torácica e inguinal são as mais comumente afetadas (Weijer & Hart, 1983; Hayes & Mooney, 1985; Figura 1).

Os fatores causais do carcinoma mamário felino são, em sua maioria, desconhecidos, mas multifatoriais, com fatores predisponentes como idade, raça, sexo, exposição hormonal e estado reprodutivo (Hayes et al., 1981; Mills et al., 2014). É o câncer mais diagnosticado em gatas depois do tumor de pele e neoplasias hematopoiéticas, sendo responsável por mais de 80-90% de todos os casos de tumores mamários nesta espécie (Soares et al., 2016). Tem uma incidência anual estimada de 13 a 25 por 100.000 gatas, com 17% dos tumores mamários atribuíveis ao carcinoma mamário felino, e representa 12% de todos os tumores em gatos com uma idade média de detecção entre 10 e 12 anos, e um intervalo de 2,5 a 13 anos (Hassan et al., 2017; Misdorp, 2002).

Os tumores mamários estão situados no tecido subcutâneo associado ou ao redor das glândulas mamárias (Figura 1; Papadopoulou et al., 2009). Esses tumores geralmente parecem firmes e variam em tamanho, desde nódulos pequenos e móveis até massas ulceradas fixas maiores (Vieira et al., 2025). Aumento dos linfonodos regionais ou sentinelas, tipicamente os linfonodos axilares ou inguinais, dependendo da localização do tumor, também pode ser observado (Barraza et al., 2024). No entanto, os gânglios linfáticos ligeiramente aumentados ou que parecem normais e não palpáveis não descartam a possibilidade de metástase (Arz et al., 2023; Barrs & Beatty, 2012). As gatas podem parecer clinicamente saudáveis, apesar de terem doença avançada, com quase metade das fêmeas com metástases distantes não mostrando sinais externos de doença (Petrucci et al., 2021).

Os tumores mamários malignos superam em número os tumores benignos em

gatas, correspondendo a 80-90% (Lopes, 2024). Com base na idade de incidência, fatores de risco, histopatologia, aspectos prognósticos, padrão metastático e resposta à terapia, o carcinoma mamário felino foi proposto como um modelo útil para o câncer de mama humano (Cannon, 2015; Cassali et al., 2020; Cassali et al., 2018; Morris, 2013).

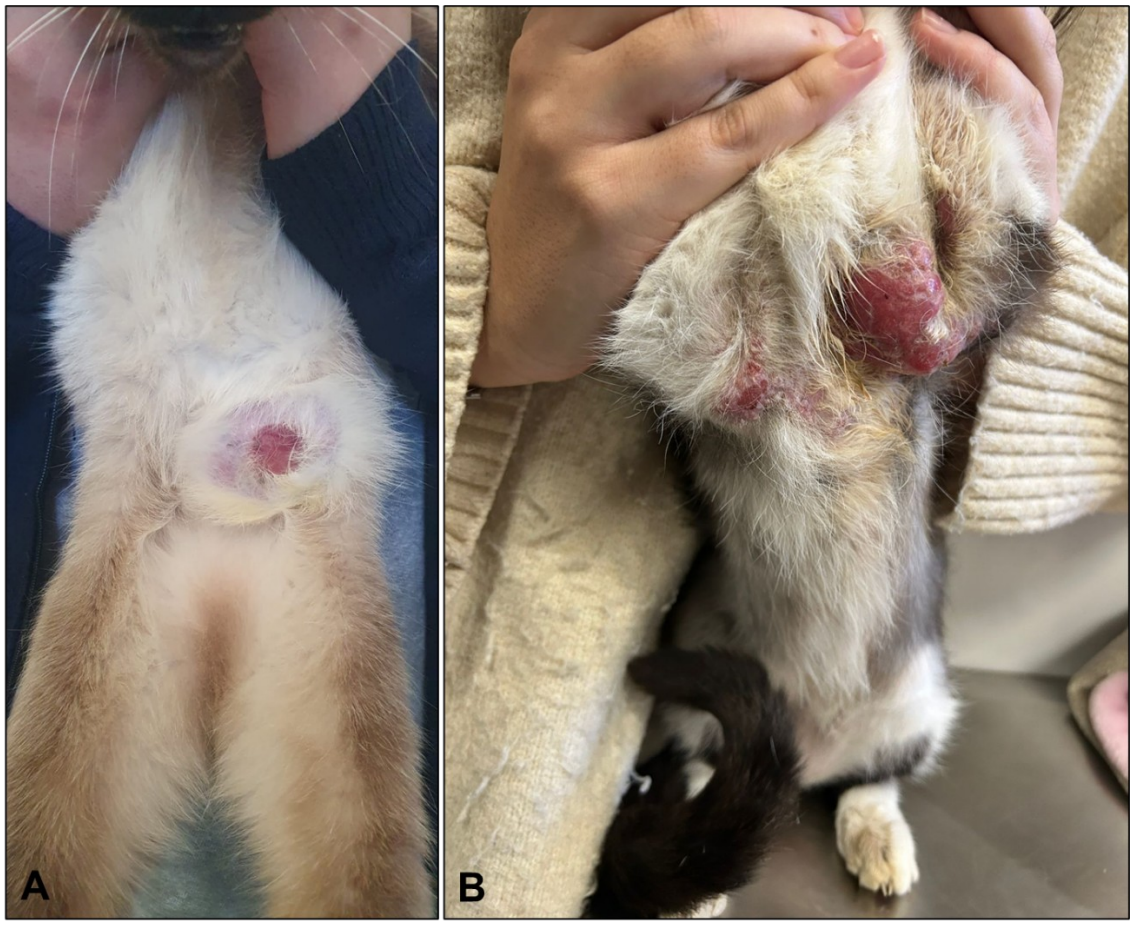

Figura 1. Carcinoma mamário felino em diferentes regiões. A. Região inguinais. B. Região torácica (Fonte: Área de Reprodução de Pequenos Animais, Departamento de Cirurgia Veterinária e Reprodução Animal, UNESP, Botucatu)

Embora existam relatos contraditórios, alguns estudos estabeleceram uma predisposição da raça para o desenvolvimento de carcinoma mamáario felino, com gatas siamesas e persas tendo um risco duas vezes maior do que aquelas de pelo curto (Berselli et al., 2021), com idade média de início aos 9 anos (Jacobs et al., 2010; Souza et al., 2024). A ocorrência de CMF, embora rara em gatos machos, ocasionalmente ocorre em animais em idade mais avançada, (média 12,8 anos) e com semelhanças às

das fêmeas, tais como uma progressão clínica agressiva como observada em fêmeas (Pérez-Alenza et al., 2004b; Skorupski et al., 2005).

2.2. Classificação geral, histológica e molecular do carcinoma mamário felino

Na oncologia, os tumores são classificados com base em três critérios principais: tamanho do tumor (T), envolvimento de linfonodos (N) e metástase para tecidos distantes (M) (Goldschmidt et al., 2011; Gonzalez-Ormerod, 2024; Tabela 1). Este sistema de classificação, denominado TNM, foi adaptado de humanos para classificar tumores na medicina veterinária, incluindo o carcinoma mamário felino.

Considerando este sistema de classificação, um dos fatores preditivos mais cruciais para o diagnóstico de carcinoma mamário felino é o tamanho do tumor. Estudos anteriores demonstraram que tumores maiores que 3 cm estão associados a desfechos desfavoráveis e uma taxa de sobrevivência inferior a 6 meses, enquanto tumores menores que 2 cm apresentam um prognóstico mais favorável, com taxa de sobrevivência pós-cirúrgica superior a 3 anos (Monteiro et al., 2025).

Outro fator que indica alta taxa de metástase é o envolvimento de linfonodos, com elevado número de casos de carcinoma mamário felino demonstrando invasão dos linfonodos regionais (Nirmalan et al., 2008). Ainda é comum neste tipo de tumor, a alta taxa de metástases, especialmente para linfonodos regionais e pulmões, já que a neoplasia é agressiva (MacEwen et al., 1984).

A invasão linfovascular e a tendência associada às metástases, com consequente mau prognóstico, são características comuns neste tipo tumoral (Soares et al., 2016). Quando a metástase está presente, o prognóstico do paciente é significativamente pior. Para enfatizar a importância da classificação TNM no manejo do carcinoma mamário felino foi estabelecido que gatas diagnosticadas com tumores T3 e envolvimento positivo dos linfonodos (N1), geralmente apresentam um tempo médio de sobrevivência menor do que gatos com tumores T1N0, com um período de sobrevivência inferior a 1 ano, mesmo com tratamento intensivo (Zappulli et al., 2015).

A avaliação histológica do carcinoma mamário felino é fundamental para estabelecer marcadores prognósticos e abordagens terapêuticas. O sistema de classificação histológica para esse tipo de tumor foi desenvolvido há alguns anos e a contagem de figuras mitóticas e o pleomorfismo nuclear foram incluídos, já que podem proporcionar maior estratificação da agressividade tumoral, levando a um prognóstico mais fidedigno (Dagher et al., 2019). Com base na aparência histológica, o carcinoma

mamário é classificado por sua origem no epitélio de revestimento interno dos ductos ou nos lóbulos que suprem os ductos mamários (Makki, 2015; Figura 2). Vários subtipos do carcinoma mamário felino foram identificados, sendo o carcinoma simples o mais comum, seguido pelos carcinomas papilar, tubular, sólido e anaplásico (Zappulli et al., 2013; Figura 3).

Tabela 1. TNM: sistema de estadiamento clínico do carcinoma mamário felino.

Estádio clínico	**Diâmetro do tumor (T)**	**Linfonodo regional (N)**	**Metástase à distância (M)**
I	< 2cm (T_1)	Negativo (N_0)	Negativo (M_0)
II	2 – 3cm (T_2)	Negativo (N_0)	Negativo (M_0)
III	> 3 cm (T_3)	Negativo ou positivo (N_0 ou N_1)	Negativo (M_0)
	≤ 3 cm (T_1 – T_2)	Positivo (N_1)	Negativo (M_0)
IV	Qualquer T	Qualquer N	Positivo (M_1)

(Adaptado de Morris, 2013)

A classificação dos tipos histológicos do carcinoma mamário felino revelou a dominância de certos padrões, notadamente o carcinoma tubulopapilar (Silva et al., 2017). Esses tumores apresentam comportamento biológico agressivo, evidenciado por características como alto índice mitótico, pleomorfismo nuclear e invasão vascular (Cassali et al., 2020).

A classificação histológica também pode ser baseada no sistema de Elston e Ellis, também conhecido como Sistema de Classificação de Nottingham e suas outras versões modificadas, como Elston e Ellis Mitótico Modificado e Sistemas de Classificação de Elston e Ellis Revisado para classificar o carcinoma mamário felino (Petterino et al., 2006; Rasotto et al., 2011; Tabela 2). O sistema de classificação Elston e Ellis representa o padrão ouro na avaliação do câncer de mama humano invasivo, usando características histopatológicas distintas, como a porcentagem de formação de túbulos, pleomorfismo nuclear e contagem mitótica, que são pontuadas e somadas para produzir um grau, que se correlaciona com o grau de malignidade e prognóstico (Rakha et al., 2010). O uso desse sistema de classificação é baseado em evidências que sugerem que o carcinoma mamário felino representa um modelo adequado para câncer de mama

humano, particularmente os carcinomas estrogênio-negativos mais agressivos (Hayes et al., 1981).

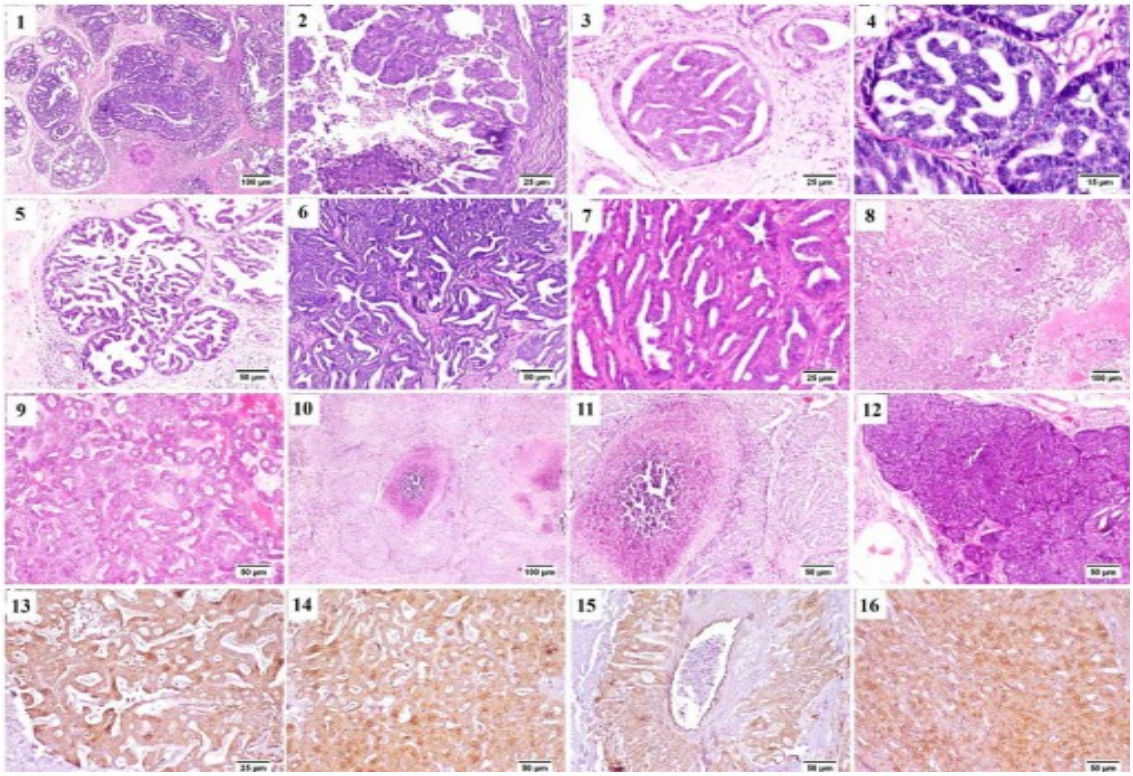

Figura 2. Fotomicrografia de lâminas histológicas de glândula mamária de gata corada com H&E (1) carcinoma papilífero (2) carcinoma micropapilar (3) carcinoma ductal *in situ* (4) maior ampliação, mitose frequente de células neoplásicas intraductais (5) carcinoma papilífero cístico (6) carcinoma tubular (7) maior ampliação, carcinoma tubular (8) carcinoma cribriforme (9) maior ampliação, carcinoma cribriforme (10) comedocarcinoma (11) maior ampliação, comedocarcinoma com área necrótica central (12) carcinoma sólido (13-16) (Ali et al., 2020).

Associada à avaliação histológica, a imuno-histoquímica revela a superexpressão de marcadores como HER2, Ki-67 e COX-2, estabelecendo a base para sua relevância em oncologia comparada, uma vez que estão presentes nos subtipos mais agressivos de câncer de mama humano (Masood et al., 2024). O Ki-67 é um marcador do complexo de adesão caderina-catenina e pode indicar as vias de adesão celular na progressão tumoral (Figueira et al., 2016). Essencialmente, o Ki-67 indica proliferação celular, e sua avaliação é considerada fundamental como critério histológico (Figueira et al., 2016; Silva et al., 2017).

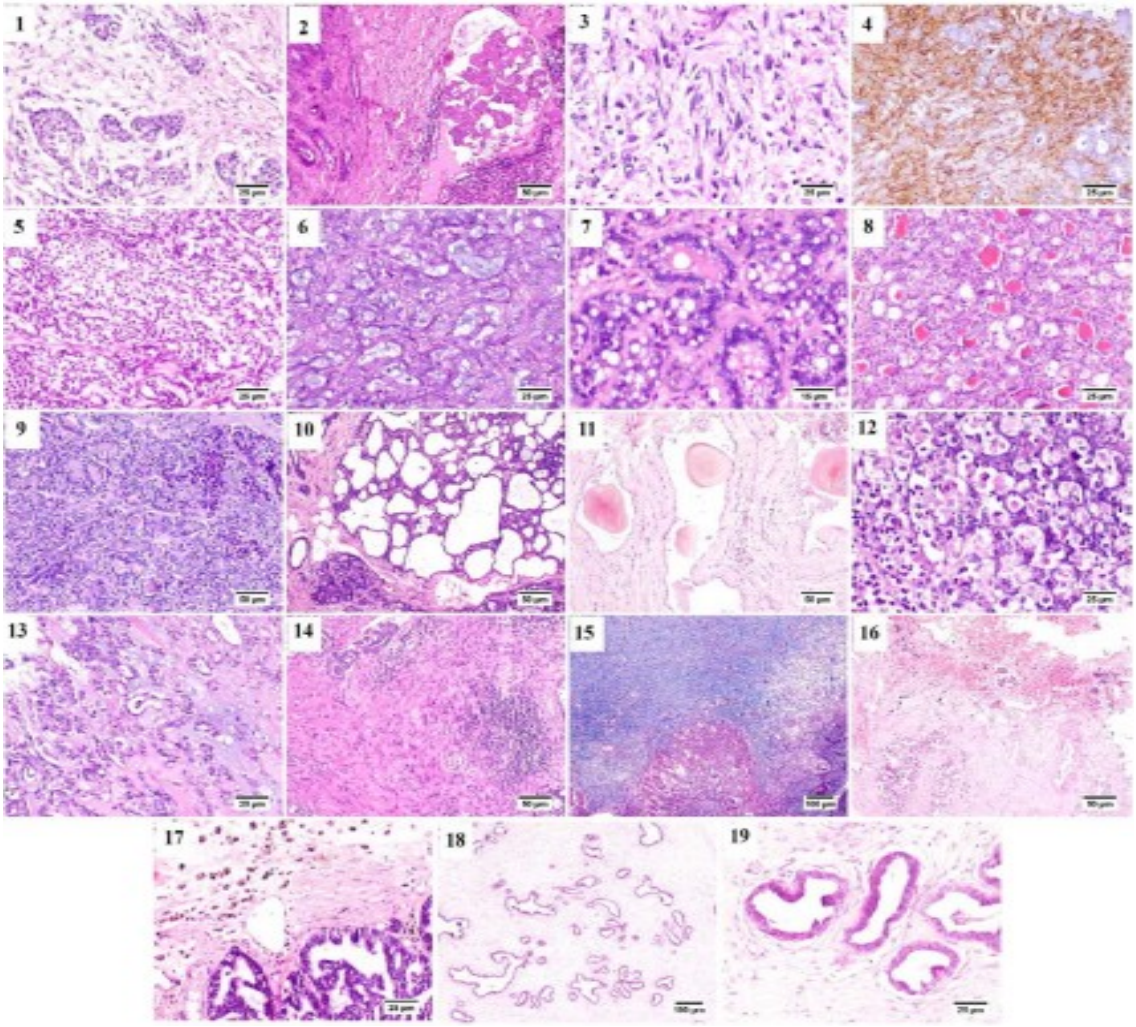

Figura 3. Fotomicrografia de lâminas histológicas de glândula mamária de gata (1) desmoplasia (2) invasão vascular por células anaplásicas (3) população pleomórfica de células mioepiteliais (4) células positivas para vimentina imunomarcadas (5) carcinoma rico em glicogênio (6) carcinoma mucinoso (7) carcinoma rico em lipídios (8) hiperplasia lobular (9) hiperplasia lobular com atipia (10) ductos dilatados cisticamente (11) ectasia do ducto com corpos amiláceos, (12) apoptose com cariorrexe (13) alteração mixomatosa (14) fibroplasia estromal com infiltração linfocítica (15) tecido fibroso proliferativo corado de azul com coloração de MTC (16) Hemorragia extensa, (17) macrófagos carregados de hemossiderina, (18) hiperplasia fibroepitelial (Ali et al., 2020).

O progresso em direção à integração de fenótipos moleculares com histopatologia é evidente em estudos que traçam paralelos entre o carcinoma mamário felino e o câncer de mama humano, ilustrando divergências e similaridades críticas em microambientes tumorais (Brunetti et al., 2013; Burrai et al., 2010). Por exemplo, a

perda da expressão do receptor hormonal (receptores de estrogênio e progesterona) encontrada em tumores malignos contrasta fortemente com os padrões de expressão observados em lesões benignas. Isso pode refletir diferenças inerentes na dependência hormonal, o que é essencial ao considerar estratégias terapêuticas (Brunetti et al., 2013).

Tabela 2. Sistemas de classificação de Elston e Ellis (EE), Elston e Ellis modificados mitóticos (EEMM) e Elston e Ellis revisados (EER) para avaliação de carcinoma mamário invasivo em gatas.

Sistema de classificação aplicável	**Característica histológica**		**Pontuação**
	Formação de túbulos		
EE, EEMM, REE	Compreende a maior parte do tumor (>75%)		1
	Presente em grau moderado (10%–75%)		2
	Pouca ou nenhuma presença (<10%)		3
	Pleomorfismo nuclear		
EE, EEMM	Núcleos pequenos, regulares e uniformes		1
	Tamanho, vesiculação e variabilidade moderadamente aumentados		2
	Cromatina vesicular com variação acentuada de tamanho e forma		3
	Contagem mitótica		
EE, EEMM, REE	EE	EEMM, REE	
	0–8	0–50	1
	9–16	51–70	2
	≥17	≥71	3
	Invasão linfovascular		
REE only	Ausente		0
	Presente		1
	Forma nuclear		
REE only	≤5% anormal		1
	6%–25% anormal		2
	>25% anormal		3

Continuação

Total de pontos	Nota	Comentário
3-5	I	Bem diferenciado
6-7	II	Moderadamente diferenciado
8-9 or 8-10 (REE)	III	Pouco diferenciado

Fonte: Ghodasara et al. (2017); Mills et al. (2014)

Entender os mecanismos moleculares que sustentam o carcinoma mamário felino é fundamental para o desenvolvimento de protocolos de tratamento eficazes. A participação das vias de sinalização STK/ROK e STAT5 na transformação fibrótica e progressão neoplásica em tecidos mamários felinos foi analisada, com achados que corroboram evidências prévias que associam a sinalização hiperativa à malignidade. A redução na expressão de *STAT5* fosforilado sugere um potencial mecanismo tumorigênico pelo controle regulatório alterado (Maniscalco et al., 2019; Owaki et al., 2024). A investigação da expressão gênica, como *TWIST1*, forneceu *insights* sobre o potencial metastático do carcinoma mamário felino, no qual níveis significativamente mais baixos de mRNA *TWIST1* em lesões malignas, em comparação com as benignas, o identificam como um fator-chave na determinação do fenótipo tumoral e da agressividade (Baptista et al., 2012).

2.2.1. Mecanismos celulares e moleculares envolvidos no carcinoma mamário felino

Foi previamente estabelecido que a paisagem do microambiente tumoral, que denota diferentes subpopulações de fenótipos de células imunes, contribui de maneiras diferentes para a biologia do tumor (Nascimento et al., 2022; Nascimento & Ferreira, 2021). Os glóbulos brancos circulantes oferecem um meio valioso e direto de avaliar o estado inflamatório de um paciente e são utilizados como marcadores prognósticos em vários cânceres humanos como estão observados quando, devido a sinais de microambiente, os neutrófilos associados ao tumor mudam seu fenótipo para o tipo antitumoral (N1) ou pró-tumorigênico (N2) (Mishalian et al., 2017). Estudo anterior estabeleceu a partir da avaliação de subpopulações de leucócitos do sangue periférico que as proporções neutrófilo-linfócito, neutrófilos e números de glóbulos brancos

mudam, e que esta proporção é um marcador prognóstico independente no carcinoma mamário felino (Petrucci et al., 2021).

A análise imuno-histoquímica demonstrou distribuição heterogênea da infiltração de células inflamatórias no carcinoma mamário felino, sendo os linfócitos T CD3+ os linfócitos mais abundantes das subpopulações de células imunes, seguidos pelos linfócitos B CD20+, embora a infiltração intratumoral de linfócitos infiltrantes tumorais (TILs) CD4+, CD8+, CD56+ e FoxP3+ também tenha sido observada em menor quantidade, sendo os subconjuntos de células T CD8+ mais abundantes os linfócitos T CD8+ (Nascimento et al., 2022; Rodrigues-Jesus et al., 2024). Todos os subtipos de células imunes foram encontrados no compartimento estromal do tumor, com exceção dos linfócitos T CD8+ e macrófagos CD68+, que estavam localizados no compartimento intratumoral (Nascimento et al., 2022).

A inflamação frequente observada no carcinoma mamário felino é sugestiva do papel desempenhado pela presença e localização de células imunes associadas ao tumor no desfecho clínico da doença, uma vez que foi estabelecida relevância estatística entre a presença de uma reação inflamatória intralesional e perilesional mais proeminente e várias características clínico-patológicas associadas ao pior prognóstico, incluindo estádio clínico, tamanho do tumor, contagem mitótica, invasão linfovascular e metástase em linfonodos (Hughes & Dobson, 2012). Além disso, a reação inflamatória presente em diferentes tipos de tumores mamários felinos também está associada ao desenvolvimento de tumores mais agressivos (Hughes & Dobson, 2012; Rodrigues-Jesus et al., 2024).

A incidência de carcinoma mamário de gatas tem sido associada à mutação de alguns genes e a superexpressão de algumas proteínas específicas (Lin et al., 2020). Em alguns genes como o supressor *TP53*, genes do fator de crescimento, o receptor de tirosina kinase 2 erbB-2, conhecido como *ERBB2*, *HER2* ou *EGFR2*, receptor estimulador de macrófagos 1 (*MST1R*) e *TWIST 1*, foram observadas mutações estabelecendo-os como genes críticos de câncer, pois são importantes no processo tumorigênico (Adega et al., 2016; Ludwig et al., 2022; Sara Isabel Rodrigues dos Santos, 2015; Walerych et al., 2012).

2.2.2 Fatores hormonais envolvidos no carcinoma mamário felino

Os carcinomas mamários felinos são tumores hormônio-dependentes, sendo que as gatas previamente expostas aos hormônios ovarianos apresentam maior risco de

desenvolver a doença (Lopes, 2024). A influência de hormônios como estrogênio e progesterona como importantes fatores de risco na patogênese da doença têm sido estudada, com evidências de que a ovariohisterectomia reduz significativamente o risco de desenvolvimento tumoral (Nosalova et al., 2024). À medida que as gatas envelhecem, os benefícios protetores da ovariohisterectomia contra tumores mamários diminuem rapidamente, com pouca ou nenhuma vantagem observada após os 2 anos de idade (Overley et al., 2005).

O risco de desenvolver tumores mamários ao longo da vida é reduzido para 91% em gatas esterilizadas antes do primeiro estro, enquanto a esterilização antes de um ano reduz o risco para 86%, em comparação com uma redução de apenas 10 a 20% em gatas esterilizados após vários ciclos estrais (Overley et al., 2005). Além disso, o uso de progestinas sintéticas pode promover a formação de tumores mamários em gatos machos e fêmeas (Misdorp et al., 1991; Skorupski et al., 2005). Isso indica que as chances de desenvolver carcinogênese mamária são aumentadas pela exposição prolongada aos hormônios ovarianos, de maneira semelhante ao câncer de mama positivo para receptores hormonais em humanos.

2.3. Biomarcadores e diagnóstico do carcinoma mamário felino

Os biomarcadores são essenciais para aumentar a precisão do diagnóstico, acompanhar a progressão da doença e informar as opções de tratamento do carcinoma mamário (Masood et al., 2024). Várias proteínas, como HER2, BCL-2, RON, Ki67 e COX-2, foram estabelecidas como biomarcadores válidos para o diagnóstico e tratamento deste tipo de tumor (Gameiro et al., 2021a; Gameiro et al., 2021b). Embora a heterogeneidade da doença não possa ser explicada com base apenas em marcadores moleculares, o exame combinado de múltiplas alterações moleculares e suas metástases são importantes para entender como o tumor progride (Gameiro, Nascimento, et al., 2021; Araújo et al., 2016).

A sobrevida global é reduzida e o prognóstico é pior quando há elevada marcação com anti-Ki67 associado ao tamanho tumoral, invasão angiolinfática, baixa diferenciação tumoral e áreas necróticas (Soares et al., 2016). Além disso, há uma alta expressão simultânea de HER-2, Cox-2 e Ki67 em carcinomas mamários primários e metástases em linfonodos pareados, embora não haja relevância prognóstica demonstrável desses marcadores moleculares expressos em linfonodos metástase (Maria João da Costa Soares, 2016).

Além dos marcadores anteriores, a expressão de Sox2, o fator de transcrição da caixa Y da região determinante do sexo (SRY)-2, que pertence a família de fatores Yamanaka, o qual é importante para a conversão de células somáticas em pluripotentes, e tem sido associado à resistência à terapia e mau prognóstico no carcinoma mamário felino (Poot, 2016). Assim como no câncer de mama em mulheres, em gatas, o Sox2 está associado à baixa sobrevida nos casos de carcinomas mamários invasivos (Truchot et al., 2021).

2.4. Diagnóstico e prognóstico do carcinoma mamário felino

O diagnóstico provisório e definitivo de carcinoma mamário felino é baseado na avaliação citológica e histológica do tecido mamário, respectivamente (Lopes, 2024). A confirmação de uma linhagem celular pode ser realizada por citologia, mas a histologia é a ferramenta adequada para determinar se uma massa neoplásica é benigna ou maligna (Petrucci et al., 2021a; Petrucci et al., 2021b).

A classificação TNM, juntamente com a expressão de receptores hormonais, é um mecanismo essencial para diagnóstico, prognóstico e planejamento terapêutico, pois permite melhor compreensão do desenvolvimento do tumor e das opções terapêuticas (Castagnaro et al., 1998; Seixas et al., 2011). A presença de metástases reduz o tempo de sobrevivência para apenas alguns meses (Cassali et al., 2025). Um melhor prognóstico pode ser alcançado pela detecção precoce dos tumores e intervenção cirúrgica rápida, incluindo a castração, visto que o carcinoma mamário felino apresenta rápida invasão dos tecidos locais e metástase para órgãos distantes (Mills et al., 2014).

2.5. Opções de manejo e tratamento para o carcinoma mamário felino

Para um prognóstico favorável, especialmente relacionado ao tempo de sobrevida no carcinoma mamário felino, é necessária a detecção precoce e terapia intensiva (Giménez et al., 2010). O tratamento de escolha mais amplamente utilizado no carcinoma mamário felino é a exérese cirúrgica; e a mastectomia total pode ser acompanhada pelo tratamento quimioterápico, imunoterapia e radioterapia (Giménez et al., 2010).

A mastectomia sem a remoção dos linfonodos sentinelas, é limitado em seu efeito curativo, dependendo da presença de ulceração e metástase (Hahn et al., 1994; Novosad, 2003). Apesar disso, a exérese cirúrgica não está associada a longa sobrevida (Cunha et al., 2016; Gonzalez-Ormerod, 2024).

A inclusão de quimioterapia adjuvante, além do tratamento cirúrgico do carcinoma mamário felino, tem se mostrado eficaz, melhorando o prognóstico da doença e está associada a um maior tempo de sobrevida (Borrego et al., 2009; Lo et al., 2019). Fármacos como carboplatina, paclitaxel, doxorrubicina isolada ou combinada com ciclofosfamida, epirrubicina, mitoxantron, toceranibe e clorambucil têm sido usados com relativo sucesso, com pesquisas comprovando que cães com carcinoma mamário tratados com a combinação de carboplatina e ciclofosfamida apresentam maior porcentagem de sobrevivência do que aqueles tratados apenas com carboplatina (Machado et al., 2022; Novosad et al., 2006; Skverchinskaya et al., 2023).

Os quimioterápicos têm mecanismos diferentes, mas têm um benefício comum devido à sua capacidade de induzir uma resposta imune antitumoral específica que retarda o crescimento do tumor. (Machiels et al., 2001). A quimioterapia oferece o tratamento mais eficaz para tumores metastáticos (Gottesman et al., 2002), no entanto, como é observado nas respostas à quimioterapia em outras doenças, as células cancerígenas podem resistir a vários fármacos simultaneamente, resultando em resistência a múltiplas drogas, observada como impacto terapêutico insignificante no tumor recidivante, o que é comum no carcinoma mamário felino (Bergman, 2003; Bergman & Harris, 1997). A resistência aos medicamentos tem dois mecanismos principais, adquiridos e intrínsecos com possibilidade de sobreposição dos mecanismos (Bergman, 2003). Resistência adquirida aos medicamentos envolve o acúmulo de medicamentos e o aumento do reparo do DNA, impedindo-os de atingir concentrações efetivas e permitindo que as células sobrevivam aos medicamentos que têm como alvo o DNA (Bergman & Harris, 1997; Drukman & Kavallaris, 2002). Já o mecanismo intrínseco da resistência aos medicamentos pode estar associado ao ciclo celular e mediado pela adesão celular (Cabral, 2001; Klopfleisch et al., 2016).

Embora resistência a múltiplos medicamentos tenham sido atribuída principalmente à superexpressão da glicoproteína de permeabilidade (P-gp), um membro da família de transportadores de ligação a ATP (ABC) e uma bomba de efluxo ligada à membrana que atua no transporte ativo transmembrana de uma variedade de substratos (O’Brien & Cordon-Cardo, 1991). Outras proteínas relacionadas ao transporte, como proteína relacionada à resistência pulmonar e proteína de resistência a múltiplos medicamentos, que é idêntica à transportador de ânions orgânicos multiespecífico que atua mediando o transporte de moléculas carregadas e parece ser dependente dos níveis celulares de glutationa (Bergman, 2003; Broxterman et al., 1995).

Reaproveitamento estratégico de medicamentos, que envolve a cooptação de medicamentos anteriormente usados para tratar outras doenças não cancerígenas, como ivermectina e aspirina (Giuliano et al., 2022; Sultana et al., 2022); e as combinações de medicamentos podem, no entanto, fornecer respostas alternativas engenhosas para combater o problema da resistência a múltiplos medicamentos na terapia do câncer (Correia et al., 2021).

2.6. Carcinoma mamário felino como modelo translacional para câncer de mama humano

Os modelos animais são úteis na compreensão da carcinogênese mamária, que tem amplas implicações para o diagnóstico, tratamento e prognóstico do câncer humano (Cassali et al., 2025). As gatas pertencem a uma espécie que apresenta espontaneamente tumores de mama (Hahn et al., 1994) e pode ser considerada um modelo experimental para estudo dessas alterações nas mulheres (Uzozie & Aebersold, 2018). Estudos sugerem que os resultados obtidos em felinos podem ser observados em humanos, estabelecendo uma base para *insights* entre espécies (Cassali et al., 2020; Coscia et al., 2018; Mantsiou et al., 2020), embora existam diferenças relacionadas a frequência e ocorrência dos tipos de tumores mamários entre as espécies (Adega et al., 2016; Kwon et al., 2023). Contudo, similaridades podem ser destacadas, tais como as lesões intraepiteliais pré-invasivas espontâneas observadas nas (hiperplasias e neoplasias mamárias felinas e que) apresentam características moleculares observadas no câncer de mama humano, como alterações cromossômicas (De Maria et al., 2005; Santos et al., 2012; Santos, 2015), mecanismos de progressão tumoral, resposta terapêutica e resistência ao tratamento (Cassali et al., 2025).

2.7. Proteômica de amostras fixadas em formalina e preservadas em parafina

A proteômica é uma ferramenta capaz de elucidar processos relacionadas ao desenvolvimento tumoral e as proteínas podem ser utilizadas para descoberta de biomarcadores, auxiliando na detecção e diagnóstico de doenças, compreensão dos mecanismos de desenvolvimento e progressão, e alvos terapêuticos e prognóstico. Contudo, para que estes estudos sejam conduzidos é necessário material disponível de diferentes tipos tumorais como o tecido neoplásico (Blonder & Veenstra, 2009; Ding et al., 2019).

Amostras de tecido fresco são consideradas preferenciais para proteômica, já que após a colheita, as proteínas são rapidamente congeladas e preservadas em seu estado natural. No entanto, esse processo é limitante devido à dificuldade em reunir um número adequado de amostras, o que pode acarretar morosidade na pesquisa, haja vista que os tumores mamários em gatas são pouco frequentes, muito agressivos e necessitam de estudos moleculares a fim de encontrar melhores opções de tratamento, diagnóstico e contribuir para o prognóstico. Neste sentido, as amostras FFCP oferecem uma alternativa, já que podem ser armazenadas por anos em quantidades à temperatura ambiente, preservando a morfologia do tecido, eliminando os problemas de armazenamento de amostras (Davalieva et al., 2021; Klockenbusch et al., 2012; Specht et al., 2001).

Uma limitação importante do uso de amostras FFCP para análise de proteínas é a ligação cruzada induzida pela formalina entre os aminoácidos, que prejudica a estrutura das proteínas e leva à formação de proteínas do tipo quimérica (Toews et al., 2008). Entretanto, muitas técnicas envolvendo o uso de detergentes e diferentes tampões foram um marco na superação do problema de reticulação de aminoácidos em amostras de FFCP (Shi et al., 1991; Broeckx et al., 2016; Fu et al., 2013).

A extração de proteínas das amostras FFCP inclui a retirada da parafina com banhos de xilol e hidratação com uma sequência decrescente de álcool, combinações de tampões, detergentes, leva à reversão das ligações cruzadas induzidas pela formalina nos aminoácidos (Addis et al., 2009; Carnielli et al., 2018). A principal hipótese sugere que o aquecimento dos tecidos FFCP com tampões, detergentes e/ou agentes redutores, como Tris HCl, SDS, DTT, desoxicolato de sódio, lauril-sarcosinato de sódio e ditiotreitol ou glicina desnatura as proteínas, permitindo que as moléculas de água penetrem e quebrem as ligações formalina-proteína (Broeckx et al., 2016; Fu et al., 2013).

Em vista desta disponibilidade dos bancos de dados de amostras que podem ser analisadas na oncologia, estudos tem focado em comparações entre os dados obtidos do tecido fresco e FFCP, identificando proteínas em níveis comparáveis aos tecidos frescos (Gustafsson et al., 2015). Técnicas de extração, digestão e a maior sensibilidade dos equipamentos de LC-MS/MS têm aprimorado os resultados (Figura 4; Pino et al., 2020; Wiśniewski et al., 2013). Apesar das diferenças já detectadas nos resultados comparados entre amostras frescas/congeladas e FFCP a análise de ontologia gênica não revelou diferenças entre os dois tipos de conservação de amostras (Obi et al., 2023).

A presença de modificações epigenéticas e modificações pós-traducionais pode afetar significativamente a função e a estabilidade das proteínas, influenciando seus papéis na biologia e no comportamento tumoral (Das et al., 2024; Di Gloria & Niccolai, 2022). Alterações na abundância das proteínas e modificações podem influenciar as vias celulares, incluindo aquelas relativas à proliferação, apoptose e comportamento metastático. Analisar o perfil proteico do carcinoma mamário felino pode ser revelador, dadas as características histológicas únicas e apresentações clínicas de tumores mamários nesta espécie em comparação à outras espécies (Das et al., 2023; Zakrzewski et al., 2019).

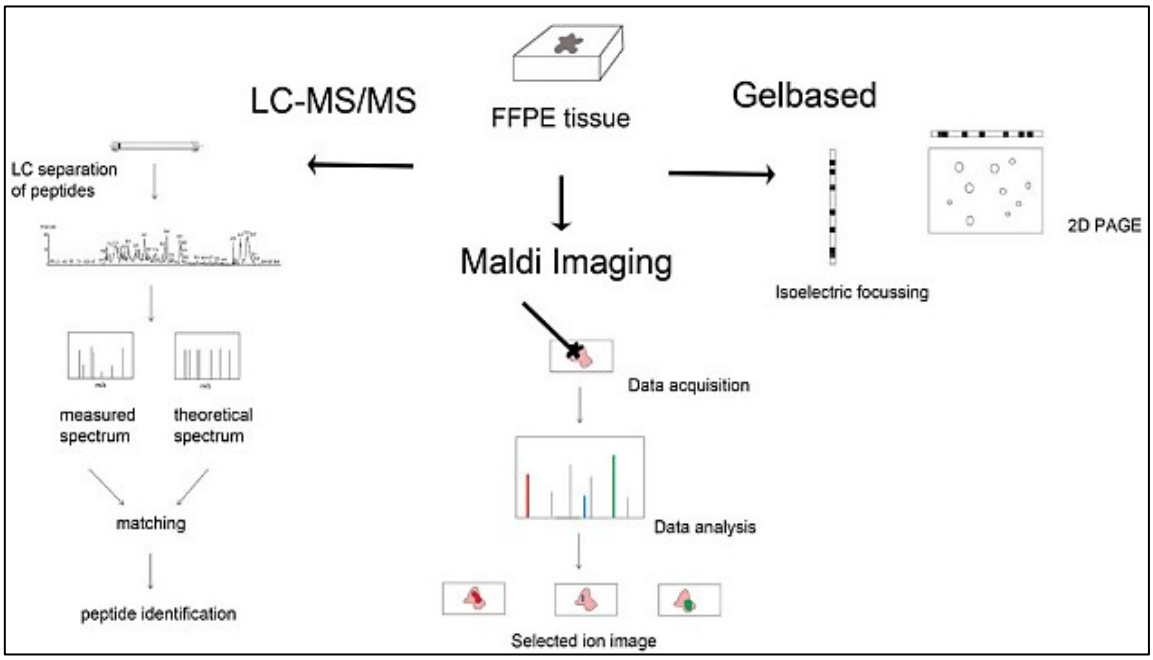

Figura 4. Diferentes plataformas analíticas utilizadas em proteômica FFPR (Fonte: Maes et al., 2013).

3. CONSIDERAÇÕES FINAIS

A proteômica permite conduzir análises de alto rendimento de amostras de FFCP, aumentando a compreensão do microambiente tumoral no carcinoma mamário felino. A proteômica pode contribuir para investigar as complexidades das neoplasias, permitindo a comparação de diferentes amostras de FFCP, destacando métodos que geram dados confiáveis, apesar da preservação histórica do tecido (Zhu et al., 2019). A capacidade de caracterizar proteomas complexos a partir de amostras de FFCP arquivadas é crucial para o desenvolvimento de biomarcadores que possam ser aplicados à prática clínica.

No futuro, é essencial uma visão geral contínua e abrangente das metodologias que combinam sequenciamento de última geração com análise de proteínas na pesquisa do câncer, sendo essas técnicas determinantes na identificação de mutações genéticas e alterações nos perfis de expressão proteica que se correlacionam com o prognóstico da doença. Com relação ao carcinoma mamário felino, tais abordagens integrativas, que combinam avaliações histopatológicas com dados do proteoma podem levar à identificação de novos alvos terapêuticos e melhorar a precisão diagnóstica.

4. HIPÓTESE E OBJETIVOS

4.1. Hipótese

Assinaturas proteômicas distintas podem ser identificadas em diferentes tipos de carcinoma mamário felino fixado em formalina e conservado em parafina (FFCP).

4.2. Objetivo geral

Descrever e comparar o proteoma de dois tipos de carcinoma mamário felino, cribiforme (mais agressivo) e tubulopapilar (menos agressivo), a fim de identificar biomarcadores associados à progressão tumoral, prognóstico e potenciais alvos terapêuticos.

4.3. Objetivos específicos

- ✓ Descrever o proteoma de amostras de tecido de carcinoma mamário felino dos subtipos cribiforme (mais agressivo) e tubulopapilar (menos agressivo) FFCP.
- ✓ Comparar o proteoma entre grupos de amostras cribiformes (mais agressivo) e tubulopapilar (menos agressivo) para identificar proteínas com diferentes abudâncias.
- ✓ Comparar os achados deste estudo com resultados descritos na literatura de tumores mamários em mulheres

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CAPÍTULO 2

ARTIGO CIENTÍFICO[2]

Tumores mamários felinos como modelo para estudo do câncer de mama humano: abordagem proteômica

Feline mammary tumor as a model to study human breast cancer: proteomics approach

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ABSTRACT

Feline mammary carcinoma is a common and aggressive cancer in cats, with a lower survival rate and a significantly higher risk of malignancy compared with dogs. Due to its spontaneous onset, aggressive behaviour, and histopthological resemblance to human breast cancer, it serves as a valuable comparative model. These similarities make it suitable for studying tumor progression, metastasis, and therapeutic responses. Proteomics enables large-scale identification of differentially expressed proteins, helping uncover molecular mechanisms, biomarkers and conserved therapeutic targets between species. This study focused on characterizing the proteome of formalin-fixed, paraffin-embedded (FFPE) feline mammary carcinoma samples from two tumor types: cribiform, (n = 12) and tubulopapillary (n = 9). After deparaffinization and in-gel trytic digestion, shotgun proteomics was used, followed by data were normalization and statistical analysis – including principal component analysis (PCA), fold change, t test and volcano plot - using MetaboAnalyst. PCA indicated a 39.3% overlap between both tumor groups. A Variable Importance in Projection (VIP) score highlighted 14 proteins upregulated in cribiform carcinoma, and one in tubulopapillary. Two proteins associated with poor prognosis were identified in both tumor types and are also found in human breast cancer. Four unique proteins were identified in each tumor subtype, and Venn diagram revealed shared proteins among human, cribiform and tubulopapillary carcinomas. Both tumor types showed protein enrichment in glycolysis, spliceosome, and antigen presentation pathways, with some variation in endoplasmic reticulum and lysosome processing, implying tumor-induced metabolic reprogramming, altered RNA processing and regulation and immune evasion. These findings reinforce the relevance of feline mammary carcinoma as a model for human breast cancer research.

Keywords: Biomarker, carcinoma, FFPE, immune-response, prognosis, proteome, LC-MS/MS

1. INTRODUCTION

Feline mammary carcinoma is the most common malignant tumor in cats, marked by its aggressive nature and poor prognosis with survival rates remaining low despite clinical intervention (1-3). Notably, multiple mammary tumors often develop simultaneously, necessitating a thorough examination of all mammary glands in any cat presenting with nodular lesions (4). The etiology of mammary carcinoma in queens remains multifactorial, with hormone exposure, breed, reproductive status, age, and sex identified as significant risk factors (5,6).

Mammary carcinoma ranks as the third most diagnosed tumor in cats after skin and hematopoietic malignancies, accounting for 80-90% of feline mammary neoplasms (7,8). The estimated annual incidence ranges from 13 to 25 per 100,000 female cats, with peak diagnosis typically between 10 to 12 years of age (2,9). Clinically, these tumors manifest within the subcutaneous tissue associated with the mammary glands, often presenting as firm nodules or ulcerated masses, with regional lymph node involvement – particularly axillary or inguinal – frequently observed (10,11). The presence of lymph node enlargement is not a definitive indicator of metastasis, as dissemination can occur even in the absence of palpable changes (12,13); however, can be associated with metastasis in the queens.

Given its metastatic potential, particularly to regional lymph nodes and lungs, the feline mammary carcinoma is widely recognized as a valuable comparative model for human breast cancer, sharing similarities in risk factor, metastatic behaviour, and histopathological characteristics (14,15). Prognostic evaluation often relies on tumor size and lymph node involvement, with larger tumors and positive nodal status correlating significantly reduced survival times (16,17). Histological classification, incorporating mitotic index and nuclear pleomorphism, offers essential prognostic information, while immunohistochemical markers such as HER2, Ki-67, and COX-2, which are overexpressed in aggressive in feline mammary carcinoma subtypes, highlight its relevance in comparative oncology (18).

The discovery of biomarkers is essential in biomedical research for improving disease detection, understanding progression, and guiding therapy (19,20). Proteomics is a tool that allows us to find biomarkers and to propose targeted therapies. While frozen tissues are ideal for proteomics, formalin-fixed, paraffin-embedded (FFPE) samples offer practical advantages for storage and retrospective analyses despite

formalin-induced cross-linking with amino acids and peptides (21). Advances in shotgun proteomics involving LC-MS/MS now enable protein identification from FFPE samples comparable to that from fresh tissues (23-25). Based on these studies, we aimed to investigate the molecular mechanisms involved in the feline mammary carcinoma pathogenesis, the protein expression involved, how they influence their sub-cellular metabolic pathways and to make a translational association with human breast cancer proteome.

2. MATERIALS AND METHODS

2.1. Reagent

All reagents used were of the highest degree of purity and are from the companies GE Healthcare (Uppsala, Sweden), Biorad (Hercules, CA, USA) and Sigma-Aldrich (São Paulo, Brazil), otherwise they will be mentioned.

2.2. Samples

Twenty-one FFPE samples of malignant feline mammary tumors, obtained from the Pathology Laboratory of the State University of Londrina – UEL (Londrina, Paraná) were used. The samples were selected according to the histological characteristics of the tumor, with 12 cribriform (aggressive) and 9 tubulopapillary (lightly aggressive) samples from adult female cats.

2.3. Ethical aspects

The ethical aspects recommended by the National Council for Animal Experiments (CONCEA) were considered at each stage of this study, which was approved by the Institutional Committee for Ethics in the Use of Animals (CEUA), under protocol number 000.331.

2.4. Sample preparation for proteomics

Ten fragments of 10 µm thickness were cut from the tissue blocks preserved in paraffin and placed in a tube for protein extraction. The tissue was dewaxed in a xylene bath (2 times) for 10 minutes at room temperature. Then, a series of 10-minute baths in ethanol with decreasing concentrations (100%, 95% and 70%) was used to rehydrate the tissue. After removal from the last ethanol bath, RIPA buffer (150 mmol NaCl, 1% Triton X-100, 1% sodium deoxycholate, 0.1% SDS in 50 mmol TRIS-HCl pH 7.5;

Peach et al., 2012) containing protease inhibitors (0.8 mmol ethylenediaminetetraaceticacid [EDTA], 1.0 µg/mL aprotinin, 1.0 µg/mL leupeptin and 35.0 µg/mL phenylmethyl sulfonylfluoride [PMSF] in 50 mmol Tris–HCl pH 7.2); (26) were added and the samples were stored at -80 ºC. The samples were thawed, sonicated in an ice bath (27, 28), and centrifuged for 30 minutes at 10,000xg, at 4 ºC. The total protein concentration was determined in a nanospectrophotometer (NanoDrop™ 2000, Thermo Fisher Scientific™, São Paulo, São Paulo, Brazil) using the A280 method and the samples were stored at -80 ºC until tryptic digestion.

For tryptic digestion, a SDS-PAGE was prepared with 50 µg of total protein. The run was allowed until the samples reached the 10% separating gel. The gels were stained with colloidal Coomassie G-250 and the single band formed was cut out of the gel for tryptic digestion. A sample containing 50 µg of bovine serum albumin was used in one of the gel wells for run control.

2.5. Proteomics

The gel fragments were digested according to Shevchenko et al. (29), with modifications (26). The bands were destained 3 times with 50% acetonitrile in 25 mmol ammonium bicarbonate. Then, the fragments were dehydrated with 100% acetonitrile. The reduction of the disulfide bridges was carried out with 20 mmol DTT in 50 mmol ammonium bicarbonate and the alkylation with 55 mmol iodoacetamide in 50 mmol ammonium bicarbonate. Thereafter, the digestion was carried out with trypsin (1: 25 substrate/trypsin) (Promega Trypsin, Part No V511, 20 ng/µL) for 14 hours. After this period, the trypsin was blocked with 5% formic acid and 50% acetonitrile. Peptides were eluted in 1% formic acid and 60% methanol, and then in 50% formic acid and 50% acetonitrile. Sample volume was reduced (SpeedVac™, SPD1010 Integrated SpeedVac™ Systems, Thermo Fisher Scientific Inc., Waltham, MA, USA) and samples stored at -20 ºC until mass spectrometry (~5 days).

A 1 µL aliquot was used for mass spectrometry (Orbitrap Velos with electron transfer dissociation [ETD], Thermo Fisher Scientific, Waltham, MA, USA) connected to the EASY-nLC II system (Proxeon Biosystem, West Palm Beach, FL, USA) via a nanoelectrospray ion source. Peptides were separated by a gradient of 2–90% acetonitrile in 0.1% formic acid using a 150 mm column at a flow rate of 300 nL/min over 45 min, with a gradient of 30% acetonitrile being reached in 30 min. The nanoelectrospray voltage was set to 2.2 kV and the source temperature will be 275 °C.

All instrument methods were set to data-dependent acquisition mode. Full-scan MS spectra (m/z 300–1600) was acquired on the Orbitrap analyser after accumulation to a target value of 1×106. The resolution in the Orbitrap was set to r = 60,000 and the 20 most intense peptide ions with charge states ≥2 sequentially isolated to a target value of 5,000 and fragmented in the linear iontrap using low-energy CID (normalized collision energy of 35%). The signal threshold to trigger an MS/MS event was set to 1,000 counts. Dynamic exclusion was enabled with an exclusion list size of 500, exclusion duration of 60 seconds and a repeat count of 1. An activation q = 0.25 and activation time of 10 ms was used (Carnielli et al., 2018).

2.6. LC–MS/MS raw data analysis

Protein identification was performed in MaxQuant v.1.5.8 against the Uniprot *Felis catus* taxonomy (UP000011712). Carbamidomethylation was set as a fixed modification, and N-terminal acetylation and methionine oxidation as variable modifications, a maximum missed trypsin cleavage of 2, and a tolerance of 10 ppm for precursor mass and 1 Da for-fragment ions was set for protein identification. Filtering was performed for 1% FDR at peptide and protein levels, using the reverse target-decoy database strategy with reverse peptide sequences as decoy entries. Bioinformatics analysis was performed using Perseus, version 1.6. Logarithmic transformation was also performed, and filters was applied to eliminate proteins with reverse sequences and proteins were identified only by a modified peptide.

2.7. Statistical analysis

The proteomics results were normalized to exclude proteins that do not represent the population studied. In this way, proteins present in at least 50% + 1 of the samples in each group was considered. Outliers were corrected by dividing the emPAI of each protein, in each sample, by the sum of the emPAIs of the same protein in all samples.

To analyze the proteomics results, non-hierarchical clustering of multivariate analysis in the MetaboAnalyst 6.0 software was used (www.metaboanalyst.ca/). Principal component analysis (PCA) was performed to describe the variation of the samples in the scoring matrix. A heatmap was also constructed for group comparison. T-test, fold change and volcano plot was performed to determine the difference between groups, considering values as significant when false discovery rate (FDR) was < 0.05. Kegg pathway and fold enrichment were used for pathway analysis and ShinyGO

(https://bioinformatics.sdstate.edu/go/) for gene ontology. A comparison of the proteins found will be conducted with data from The Human Protein Atlas. (https://www.proteinatlas.org/).

3. RESULT

The proteomics returned 973 proteins in two groups (Figure 1). For the PCA, there was an observed slight overlap of expressed proteins between the cribiform and tubulopapillary groups as demonstrated with the sum of the principal components (X and Y axes) 1 and 2 being less than 50% (Figure 2A). The division of the two groups can be confirmed in the dendrogram (Figure 2B).

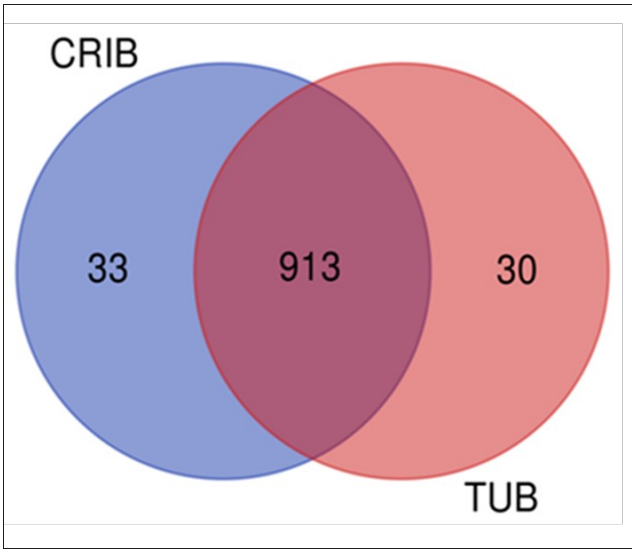


Figure 1. Venn diagram of proteins found in cribiform and tubulopapillary groups of feline mammary carcinoma. http://bioinformatics.psb.ugent.be/webtools/Venn/

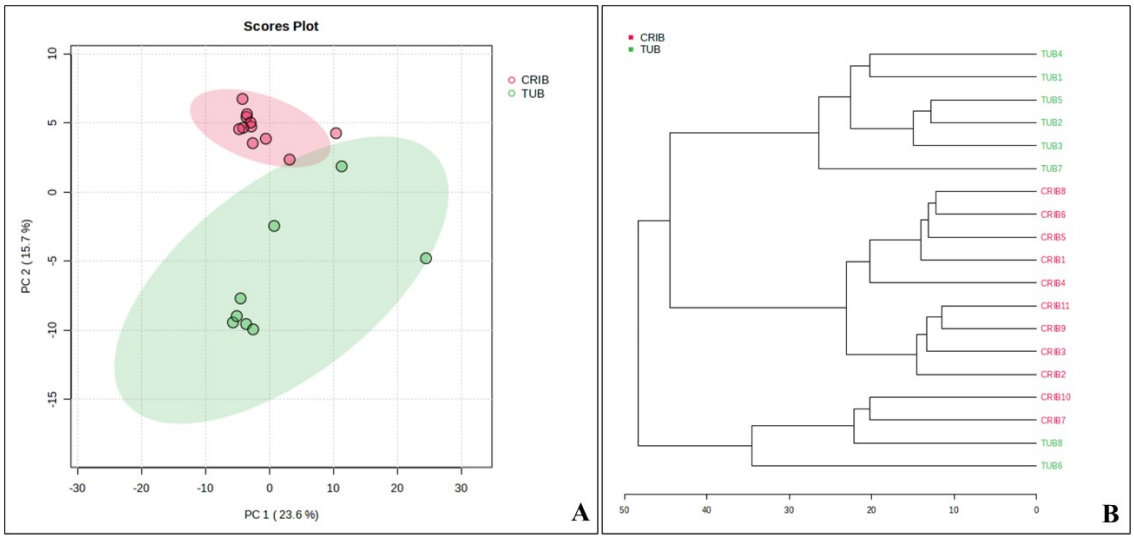


Figure 2. Feline mammary carcinoma proteins, (A) Dendrogram of emPAIs of proteins from the cribiform and tubulopapillary groups and (B) principal component analysis (PC1 + PC2 = 39,3%).

UniProtKB (http://www.uniprot.org/) describes the results obtained for each group, including the molecular function, biological process and cellular component of each protein. The identified proteins in both groups were then compared with the proteins expressed in human breast cancer (Figure 3; Supplementary Table 1) using The Human Protein Atlas (https://www.proteinatlas.org/).

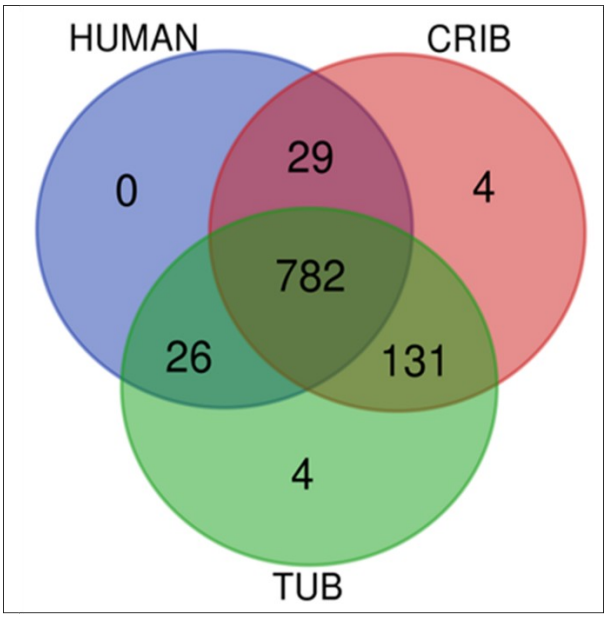


Figure 3. Venn diagram of proteins found in feline mammary carcinoma compared with human breast cancer proteins. http://bioinformatics.psb.ugent.be/webtools/Venn/.

One hundred and forty-eight proteins were differentially abundant between cribiform and tubulopapillary groups, and they were used to construct the heatmap, which clearly revealed the differences between the groups (Figure 4).

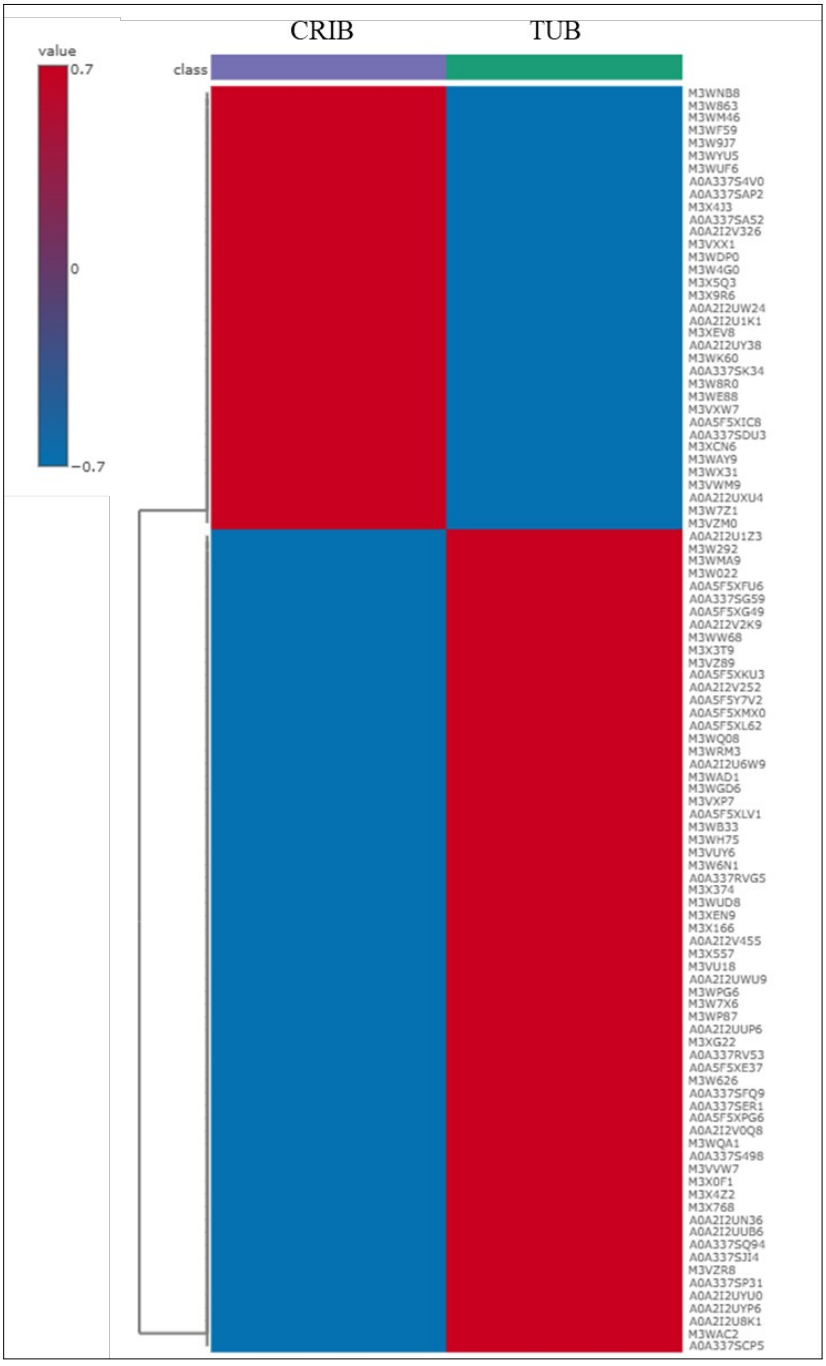
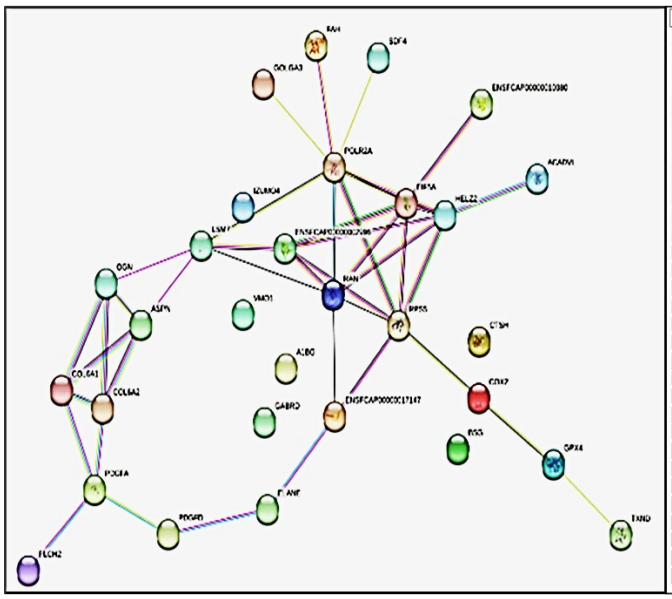


Figure 4. Heatmap of cribiform and tubulopapillary feline mammary carcinoma samples demonstrating the relative abundance of proteins in each group, with red and blue representing greater and lesser abundance, respectively.

Analysis of protein-protein interaction revealed that a proportion of the differentially abundant proteins found in cribiform and tubulopapillary groups were functionally connected (Figure 5).



Protein Symbol / ID	Full Protein Name
RAN	Ras-related nuclear protein
RPS5	40S ribosomal protein S5
EIF5A	Eukaryotic translation initiation factor 5A
HELZ2	Helicase with zinc finger 2
POLR2A	DNA-directed RNA polymerase II subunit RPB1
TXNDC	Thioredoxin domain-containing protein
GPX4	Glutathione peroxidase 4
EGS	Likely eukaryotic translation elongation factor
CDK2	Cyclin-dependent kinase 2
CTSH	Cathepsin H
ACADVL	Very long-chain specific acyl-CoA dehydrogenase
SDF4	Stromal cell-derived factor 4
FAH	Fumarylacetoacetate hydrolase
GOLGA3	Golgin subfamily A member 3
IZUMO4	Izumo sperm-egg fusion protein 4
LSM14A	Sm-like protein LSM14A
VMD1	Not clearly identified; possibly VMD2 (Bestrophin-1-like)
A1BG	Alpha-1B-glycoprotein
GABRD	Gamma-aminobutyric acid receptor subunit delta
ELANE	Neutrophil elastase
PDGFRD	Platelet-derived growth factor receptor delta
PI3GFA	Phosphoinositide-3-kinase catalytic subunit alpha isoform
COL6A2	Collagen alpha-2(VI) chain
COL6A1	Collagen alpha-1(VI) chain
OGN	Osteoglycin
ASPN	Asporin
FLCH2	Filaggrin-2-like (low-confidence annotation)
ENSFCAP00000012586	Predicted feline protein (uncharacterized)
ENSFCAP00000017147	Predicted feline protein (uncharacterized)
ENSFCAP00000010380	Predicted feline protein (uncharacterized)
ENSFCAP00000012595	Predicted feline protein (uncharacterized)

Figure 5. Protein-protein interaction network indicating the top 30 proteins interactions. Node = protein; closely connected nodes = similar biological pathways or functional group; node color = clusters/interaction groups; colored lines/strings = interaction evidence (red = gene fusions; blue = gene co-occurrence across genomes; light blue = curated pathway knowledge; green = genomic proximity; purple = similar sequences or domains; pink = biochemical data).

The variable importance in projection (VIP) score identified 15 proteins contributing mainly to feline mammary carcinoma with 14 of the proteins having higher abundance in cribiform tumors as compared with only 1 protein in higher abundance in tubulopapillary tumor (Figures 6).

For both cribiform and tubulopapillary subtypes of the feline mammary carcinoma, similar alterations were observed in KEGG pathways enrichment such as the estrogen signalling pathway, protein processing in endoplasmic reticulum, antigen processing and presentation, carbon metabolism, ribosome, lysosome, spliceseosome and glycolysis/gluconeogenesis pathways involved in which have significant implications for tumor development, progression and evasion. Proteins identified in the fold change analysis were used to construct a Sankey plot, allowing visualization of the key pathways associated with the differentially abundant proteins in two groups (Figure

7). Pathway differences for certain proteins between the two subtypes were also observed, in the protein processing in the endoplasmic reticulum and lysosome pathways (Figures 8 and 9).

Evaluation of total proteins obtained from both feline carcinoma subtypes and compared with human breast cancer using The Human Protein Atlas showed the presence of 2 proteins indicative of poor prognosis; and 4 proteins specific to either of cribiform and tubulopappilary feline carcinoma, with additional evidence of common proteins shared cross human and feline carcinoma groups (Supplemental Table 1).

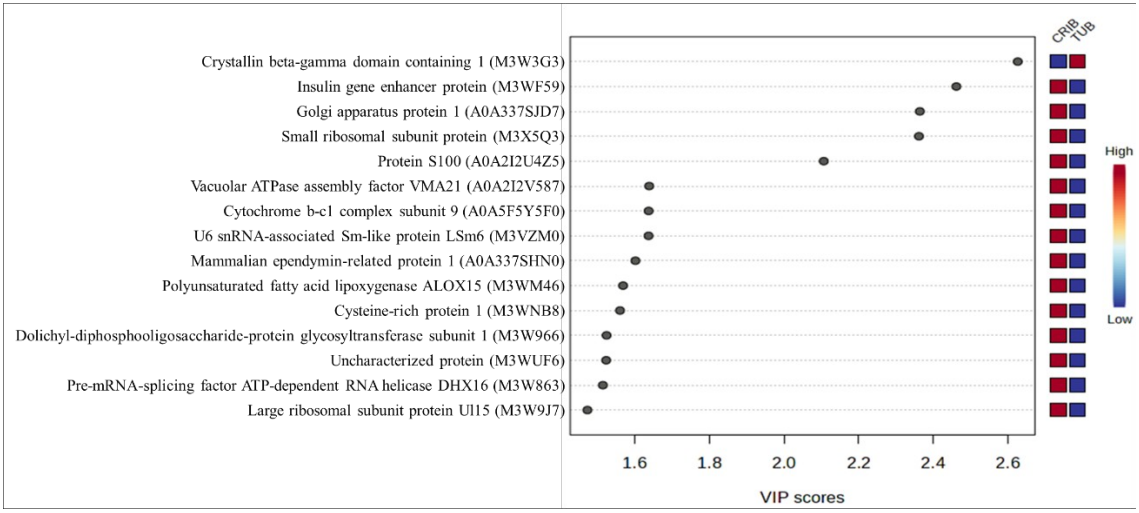


Figure 6. Differentially abundant proteins in the VIP score of cribiform and tubulopapillary subtypes of feline mammary carcinoma.

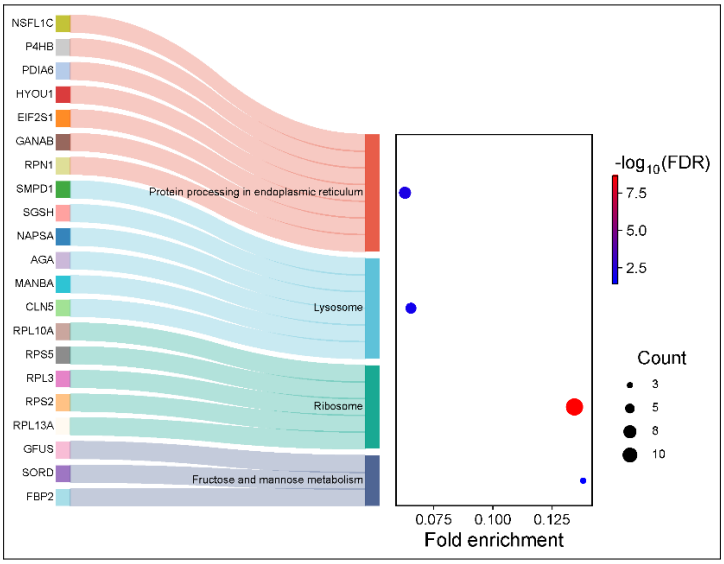
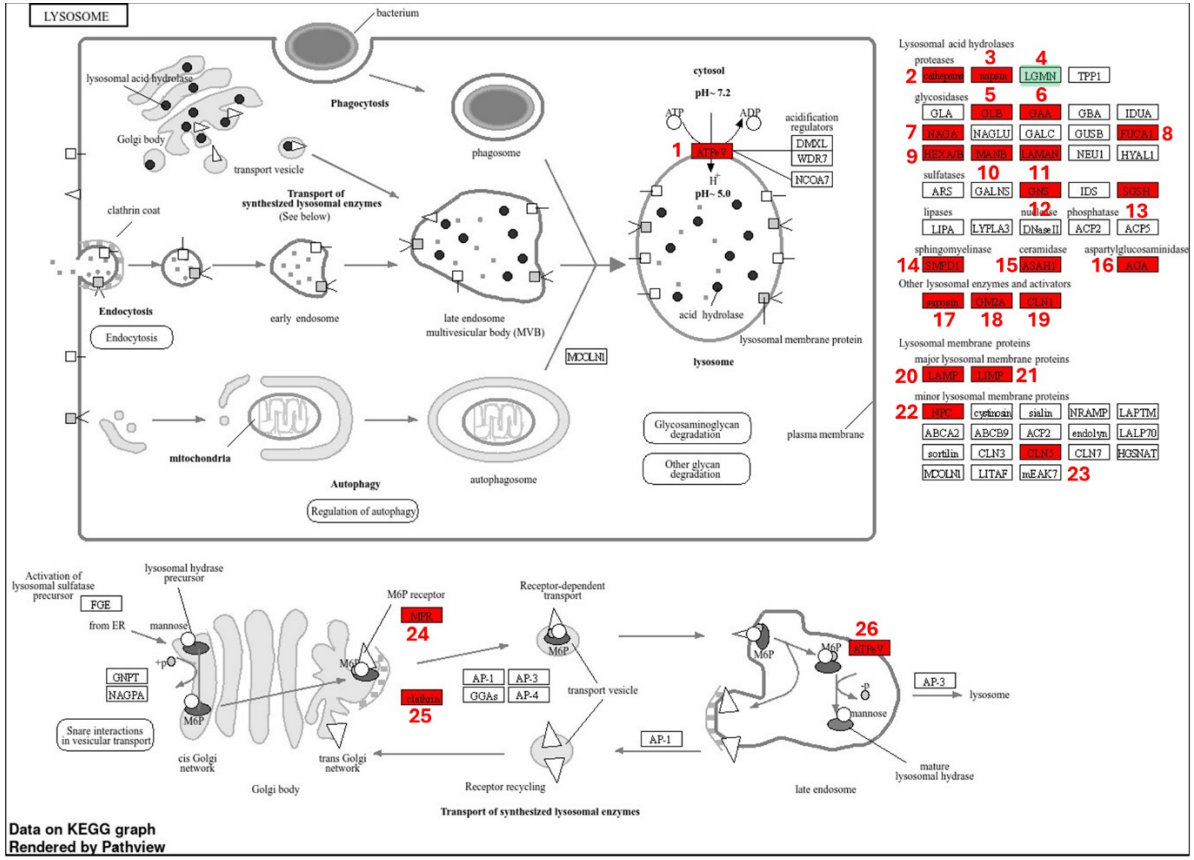
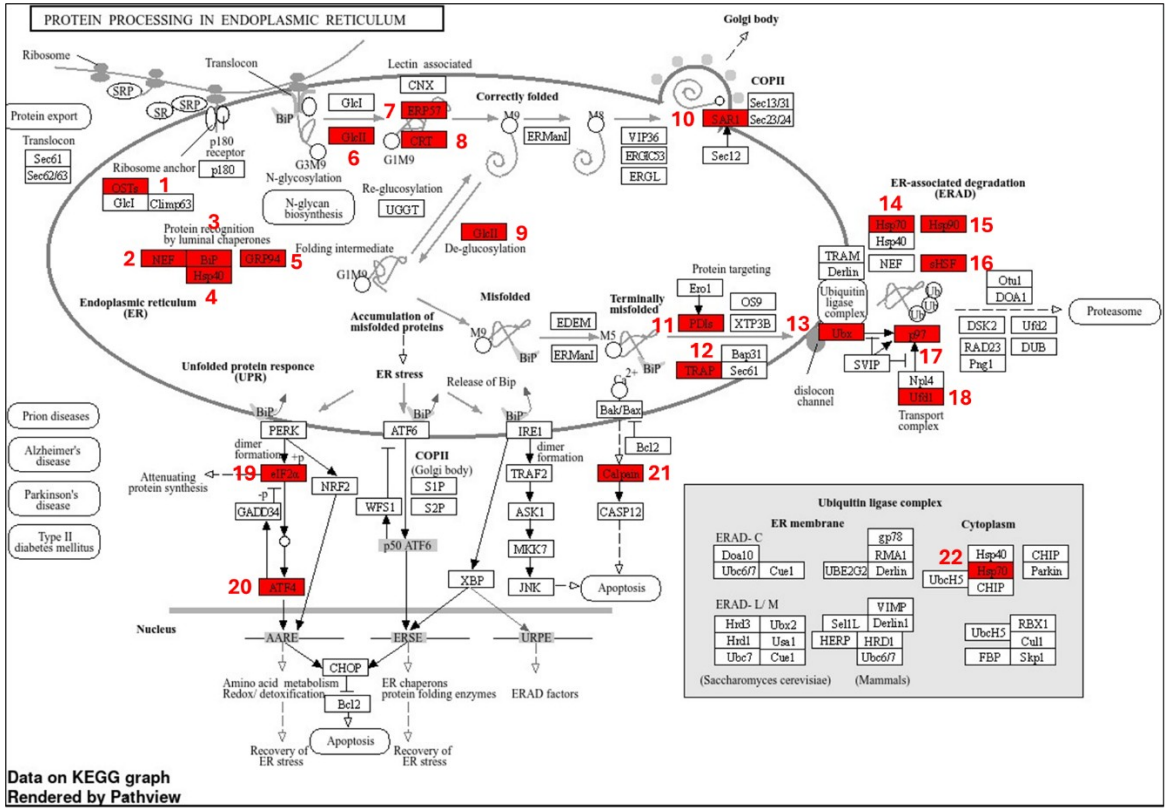


Figure 7. Pathway fold enrichment of proteins differentially abundant in the fold change analysis.



N	Protein name (*Gene*)	Cribiform	Tubulopapillary
1	Tripeptidyl-peptidase 1 (TPP1, CLN2)	X	--
2	Cathepsin A (*CTSA, CPY*)	X	X
3	Napsin-A (*NAPSA*)	X	X
4	V-type H+-transporting ATPase subunit a (ATPeV0A, ATP6N)	--	X
5	Beta-galactosidase (*GLB1, ELNR1*)	X	X
6	Lysosomal alpha-glucosidase (*GAA*)	X	X
7	Alpha-N-acetylgalactosaminidase (*NAGA*)	X	X
8	Alpha-L-fucosidase (*FUCA*)	X	X
9	Hexosaminidase (*HEXA_B*)	X	X
10	Beta-mannosidase (*MANBA, mnB*)	X	X
11	Lysosomal alpha-mannosidase (*MAN2B1, LAMAN*)	X	X
12	N-acetylglucosamine-6-sulfatase (*GNS*)	X	X
13	N-sulfoglucosamine sulfohydrolase (*SGSH*)	X	X
14	Sphingomyelin phosphodiesterase (*SMPD1, ASM*)	X	X
15	Acid ceramidase (*ASAH1*)	X	X
16	N4-(beta-N-acetylglucosaminyl)-L-asparaginase (*AGA, aspG*)	X	X
17	Saposin (*PSAP, SGP1*)	X	X
18	Ganglioside GM2 activator (*GM2A*)	X	X
19	Palmitoyl-protein thioesterase (*PPT*)	X	X
20	Lysosomal-associated membrane protein 1/2 (*LAMP1_2, CD107*)	X	X
21	CD63 antigen (*CD3, MLA1, TSPAN30*)	X	X
22	Niemann-Pick C1 protein (*NPC1*)	X	X
23	Ceroid-lipofuscinosis neuronal protein 5 (*CLN5*)	X	X
24	Insulin-like growth factor 2 receptor (*IGF2R, CD222*)	X	X
25	Clathrin light chain A (*CLTA, LCA*)	X	X
26	V-type H+-transporting ATPase subunit a (*ATPeV0A, ATP6N*)	X	--

Figure 8. KEGG pathway enrichment (LYSOSOME) of the cribiform and tubulopapillary subtypes from feline mammary carcinoma. The table on the right indicates the proteins and locations in the lysosome pathway, indicating the presence (X) and absence (--) in each group. Protein highlighted in green (4) was absent in the cribiform, and other two proteins (1 and 26) were absent in the tubulopapillary subtype.



N	Protein name (*Gene*)	Cribiform	Tubulopapillary
1	Dolichyl-diphosphooligosaccharide---protein glycosyltransferase subunit 1 (ribophorin I) (*RPN1, OST1*)	X	X
2	Hypoxia up-regulated 1 (*HYOU1*)	--	X
3	Endoplasmic reticulum chaperone BiP (*HSPA5, BIP*)	X	X
4	DnaJ homolog subfamily B member 11 (*DNAJB11*)	--	X
5	Heat shock protein 90kDa beta (*HSP90B, TRA1*)	X	X
6	Mannosyl-oligosaccharide alpha-1,3-glucosidase (*GANAB*)	X	X
7	Protein disulfide-isomerase A3 (*PDIA3, GRP58*)	X	X
8	Calreticulin (*CALR*)	X	X
9	Mannosyl-oligosaccharide alpha-1,3-glucosidase (*GANAB*)	X	X
10	GTP-binding protein SAR1 (*SAR1*)	X	X
11	Protein disulfide-isomerase A1 (*PDIA1, P4HB*)	X	X
12	Translocon-associated protein subunit alpha (*SSR1*)	X	X
13	UBX domain-containing protein 1/4 (*UBXN1_4*)	X	X
14	Heat shock 70kDa protein 1/6/8 (*HSPA1_6_8*)	X	X
15	Molecular chaperone HtpG (*HSP90A, htpG*)	X	X
16	Crystallin, alpha A (*CRYAA*)	X	X
17	Transitional endoplasmic reticulum ATPase (*VCP, CDC48*)	X	X
18	Ubiquitin fusion degradation protein 1 (*UFD1*)	X	X
19	Translation initiation factor 2 subunit 1 (*EIF2S1*)	X	X
20	Cyclic AMP-dependent transcription factor ATF-4 (*ATF8, CREB2*)	X	X
21	Calpain-1 (*CAPN1*)	X	X
22	Heat shock 70kDa protein 1/6/8 (*HSPA1_6_8*)	X	X

Figure 9. KEGG pathway enrichment (PROTEIN PROCESSING IN ENDOPLASMIC RETICULUM) of the cribiform and tubulopapillary subtypes from feline mammary carcinoma. The Table on the right indicates the proteins and locations in the protein processing in endoplasmic reticulum pathway, indicating the presence (X) and absence (--) in each group. Two proteins were absent in the cribiform (2 and 4) subtype.

4. DISCUSSION

This present study highlights the innovative application of proteomic analysis to formalin-fixed, paraffin-embedded (FFPE) feline mammary carcinoma samples. While FFPE tisssue is abundant in veterinary pathology archives, its use for large-scale proteomic profiling remains limited due to challenges associated with protein cross-linking and degradation. By successfully applying advanced shotgun LC-MS/MS proteomics to this material, our study demonstrates that FFPE samples can yield comprehensive protein profiles capable of revealing tumor-specific alterations. This methodological approach not only leverages existing histological repositories but also maximises the scientific value of archived specimens, thereby overcoming a major barrier in comparative oncology research.

Moreover, the ability to characterize tumor heterogeneity and identify subtype-specific biomarkers from FFPE samples underscore the translational potential of this work. Unlike previous studies that relied primarily on fresh or frozen tissue, our findings show that routinely collected clinical material can be repurposed to uncover molecular drivers of aggressiveness and prognosis in feline mammary carcinoma. This establishes a practical and cost-effective pipeline for biomarker discovery that can be extended to other tumor types and species, including humans, thereby bridging veterinary and human oncology. Such novelty strenghtens the role of feline mammary carcinoma as a comparative model for breast cancer and demonstrates the feasibility of FFPE proteomics in advancing diagnostic and therapeutic research.

As demonstrated by our results, both cribiform and tubulopapillary subtypes of the feline mammary carcinoma are associated with common and distinct metabolic and molecular features that influence progression and clinical outcomes (8). Venn diagram analysis of the total proteins returned after LC-MS/MS and compared with human breast cancer proteins indicated specific proteins within each of the subtypes, such as an uncharacterized protein (A0A337S6M6), AHNAK nucleoprotein (A0A337S8X8), glycerol kinase (A0A337SAZ0), and myosin-2 (A0A337SF79), for cribiform carcinoma; and glucosylceramidase beta 3 (A0A2I2UCJ0), beta-2-glycoprotein 1 (M3WH75), SEA domain-containing protein (M3WNR4), and EF-hand domain-containing protein (A0A337SCP2), in tubulopapillary carcinoma that play roles in regulating cell proliferation, apoptosis, invasion and immune evasion. However, two proteins like T-complex protein 1 subunit alpha (M3VZ89) and reticulon 3 (A0A5F5XKU7) are commonly expressed in human breast cancer and were found in

cribiform and tubulopapillary subtypes of feline mammary carcinoma. These proteins are indicative of poor prognosis (30).

4.1. Proteins contributing to cribiform and tubulopapillary feline mammary carcinoma

Fifteen proteins showed differential abundance between the groups in VIP scores matrix ($\alpha > 1.5$); however, in comparison, only one was more abundant in the TUB group: the crystallin beta-gamma domain-containing protein 1 (M3W3G3). The following proteins were more abundant in the CRIB group: insulin gene enhancer protein (M3WF59), Golgi apparatus protein 1 (A0A337SJD7), small ribosomal subunit protein (M3X5Q3), S100 protein (A0A2I2U4Z5), vacuolar ATPase assembly factor VMA21 (A0A2I2V587), cytochrome b-c1 complex subunit 9 (A0A5F5Y5F0), U6 snRNA-associated Sm-like protein LSm6 (M3VZM0), mammalian ependymin-related protein 1 (A0A337SHN0), polyunsaturated fatty acid lipoxygenase ALOX15 (M3WM46), cysteine-rich protein 1 (M3WNB8), dolichyl-diphosphooligosaccharide–protein glycosyltransferase subunit 1 (M3W966), uncharacterized protein (M3WUF6), pre-mRNA-splicing factor ATP-dependent RNA helicase DHX16 (M3W863), and large ribosomal subunit protein uL15 (M3W9J7).

The protein *crystallin beta-gamma domain-containing 1* (M3W3G3), also detected in human breast cancer, belongs to the beta-gamma crystallin family and exhibits calcium-binding capacity (31). While traditionally known as a structural component of the ocular lens, its interaction with trefoil factors has been implicated in mucosal healing and tumorigenesis (32). Although the precise mechanisms underlying its role in tumorigenesis remain unclear, calcium-binding proteins are widely recognized for their involvement in tumor progression and metastasis (33). Several studies have proposed a potential link between calcium metabolism and tumor development, suggesting that alterations in tissue calcium concentrations may disrupt key molecular pathways, depending on the tissue's physiological and histological context (34). Recent evidence indicates that cancer cells modulate the expression and activity of calcium transport regulators—including Ca^{2+} pumps, channels, and exchangers—impacting the homeostasis of organelles central to calcium regulation, such as the endoplasmic reticulum (a major Ca^{2+} reservoir), lysosomes, and mitochondria (35). The higher abundance of this protein in TUB group may contribute to the aggressive behavior observed in this tumor subtype.

The insulin gene enhancer protein ISL-1 (M3WF59) is a LIM-homeodomain transcription factor involved in insulin secretion and metabolic regulation, which has been linked to several tumor types (36). Knockdown of ISL-1 has been shown to reduce glucose uptake and inhibit tumor cell proliferation both *in vivo* and *in vitro*, particularly in gastric cancer, by regulating *GLUT4* expression through direct promoter binding - supporting its role as a driver of glycolysis and energy acquisition in tumor cells (37,38). Although ISL-1 was detected in both tumor subtypes in our study, its higher abundance in the CRIB group suggests a potential role in enhancing glucose uptake, thereby fueling rapid cellular proliferation and possibly contributing to the metastatic potential of this tumor form.

The protein small ribosomal subunit protein uS7 (M3X5Q3) is an important part of the translation process and is a primary ribosomal RNA (rRNA) binding protein involved in RNA folding and the binding of other proteins during small unit assembly in all species (39,40). It functions within the cell by binding to CDK6, a cyclin-dependent kinase critical for cell proliferation and development especially in the cribiform carcinoma as demonstrated by the VIP score. Knockdown of the small ribosomal subunit protein uS7 has been shown to induce G1 cell cycle arrest and downregulate CDK6 expression in colon cancer cells (38). The depletion of uS7 leads to the degradation of CDK6. The implication is that, since CDK4/6-cyclin D complexes are involved in the phosphorylation of the tumor suppressor RB protein in the G1 phase of the cycle, resulting in its inactivation and the acceleration of cancer cell proliferation, the overabundance of this protein in any tumor is an indication of aggressive growth, reflective of its presence in two tumor subtypes in our samples, but in cribiform carcinoma it was more abundant (41) since it is more aggressive neoplasia.

The other protein contributing to great abundance in cribiform subtype is serine protease subtilisin family (A0A212U4Z5) is involved in tissue remodelling and cell signalling processes (42). This serine protease improves the proliferation of cancer cells by activation of signalling pathways, enhancement in DNA repair mechanisms, and drug-induced apoptosis reduction which are hallmarks of cancer (42). It can either have tumor-promoting or suppressing effect depending on the cellular context by influencing proteolytic networks, extracellular matrix remodelling, cytokine signalling and regulation of growth factors, and immunosuppressive effects (43). Besides, stromal-cell derived serine proteases have been associated with tumor development and metastasis

based on their high and selective expression in tumor-associated stromal cells with the potential of inhibiting them by active-site targeting using small molecules to treat cancer (44–46). Therapeutic inhibition to counteract drug resistance often observed in tumor chemotherapy in feline mammary carcinoma would be greatly enhanced by blocking this overabundant protein as detected in our study.

Vacuolar ATPase assembly factor VMA21 (A0A212V587) is an assembly factor that plays a critical role in intracellular pH homeostasis with a perceived role in cancer therapy, as previous *in vivo* and *in vitro* assessment demonstrated that patients with a higher expression of this protein had higher differentiation grade and longer disease-specific survival at stages I–III disease as its overexpression decreased colorectal cancer growth (47–49). Interestingly, previous research data have established that tubular carcinoma have a better overall survival and breast cancer-specific survival of 94.4% and 99.4% compared with cribiform carcinoma, of 91.6% and 98.4% respectively (50), corresponding to their less and more aggressive natures. These data were seemingly validated by our results, and this may be probably due to a higher abundance of the 14 contributing proteins out of the 15 differentially abundant proteins in cribiform carcinoma listed above, and as demonstrated by the VIP score as compared with only 1 protein with higher differential abundance in tubulopapillary carcinoma.

Another small ribosomal subunit protein uS14 (A0A337SCP7) acting by different pathway, plays an important role in maintaining the integrity of protein synthesis, but accumulating evidence suggests its role in tumorigenesis and cancer progression, including in mammary carcinomas (51–53). Various human cancers show an aberrant expression of ribosomal proteins such as uS14 which is linked to disrupted cell-cycle regulation and p-53 mediated apoptosis, processes that are critically relevant to tumor incidence (54–56). The presence of this protein in both carcinomas under study supports an underlying role of this protein in human and veterinary mammary carcinoma. The observed dysregulation of this protein could be implicated in the malignant transformation of the feline mammary tissue by impairing ribosomal biogenesis stress response, thus allowing abnormal cells to evade p53-dependent tumor suppression mechanisms (2,57). Furthermore, the proteomics of the cribiform and tubuloppapillary tumor in our study identifies ribosomal protein abundance as a potential diagnostic marker that correlates with aggressive tumor behaviour and reduced survival (58,59). The upregulation of this protein in CRIB group may indicate enhanced

translational capacity and cellular proliferation, which are features associated with high grade malignancies (60,61). These findings indicate that monitoring small ribosomal subunit protein uS14 (A0A337SCP7) expression, especially in feline cribiform carcinoma, where it is more abundant in our study could assist in stratifying tumor aggressiveness and proffer therapeutic interventions targeting ribosome biogenesis or translational control in feline oncology (54,62).

The complex molecular mechanisms involved in the development and progression of feline mammary carcinoma which also includes the dysregulation of various proteins involves the pivotal role played by ubiquinol-cytochrome c reductase complex III subunit X (A0A5F5Y5F0) in mitochondria electron transport and ATP synthesis (63,64). Components of this protein complex such as the ubiquinol-cytochrome c reductase (UQCRFS1), can be altered, and have been associated with an aggressive tumor phenotype in human breast cancer (65,66), with its upregulation in both tumor samples under study suggesting a parallel in feline mammary carcinoma. This is because disruptions in mitochondrial function can lead to increased reactive oxygen species (ROS) production, contributing to genomic instability and tumor progression (63). In addition, the suppression of ubiquinol-cytochrome c reductase complex III subunit X (A0A5F5Y5F0) inhibits cancer cell growth by blocking binding to p53 (a prominent cancer inhibitor) in the nucleus, causing its ubiquitination and degradation, leading to tumorigenesis (67). The more abundant presence of this protein in felines within the cribiform subtype, could equate to the aggressive nature of these tumors.

The LSM6 homolog U6 small nuclear RNA and mRNA degradation associated V (M3VZMO) protein is part of the LSM protein family responsible for forming stable heteromers that bind specifically to the 3'-terminal oligo (U) tract of U6 snRNA and may play a role in pre-mRNA splicing by mediating U4/U6 snRNP formation and facilitating various aspects of RNA metabolism (68). It has been predicted to be in cytoplasm and nucleus and a part of several cellular components involved in mRNA splicing, via spliceosome and maturation of SSU-rRNA, acting upstream of or within mRNA catabolic process. An upregulation of this protein has been associated with a role in cellular transformation and the progression of several malignancies including human breast cancer (69). Interestingly, it was both present in feline tumor subtypes, with greater abundance in the cribiform carcinoma where it most likely plays a similar

role in human breast cancer, facilitating cellular transformation and tumor cell progression.

Arachidonate lipoxygenase (M3WM46) is an enzyme involved in the metabolism of arachidonic acid to bioactive lipid mediators such as leukotrienes and hydroxyeicotetraenpoic acids (HETEs) (70). These metabolites can modulate inflammation, cell proliferation, and angiogenesis, processes that are often co-opted during tumor development (71). In human cancers, lipoxygenases have been implicated in tumor growth and metastasis, suggesting a similar role in feline mammary carcinoma (72), since the protein is likewise expressed in both tumor subtypes in our study, but in greater abundance in more aggressive tumor, CRIB group.

The protein cysteine rich protein 1 (M3WNB8) is known for its role in cytoskeletal organization and cell differentiation (73). Its altered expression has been observed in many human cancers where it has been suggested to influence tumor cell motility and invasiveness (74). Given its role in maintaining cellular integrity and architecture, its dysregulation could be a contributory factor to the metastatic potential of feline mammary carcinoma cells (74). We recorded a high abundance of this protein in cribiform carcinoma relative to tubulopappilary carcinoma and suggest its contribution to the tumor cell motility and invasiveness of these tumor subtypes, like the situation in human breast cancer.

Dolichyl-diphosphooligosaccharide -protein glycosyltransferase subunit 1 (M3W966) is a component of the oligosaccharyl transferase complex, essential for N-linked glycosylation of proteins which is critical for proper protein folding and function (75,76). Aberrations in glycosylation pathways have been linked to cancer progression, as they can affect cell to cell adhesion, immune recognition and receptor signalling, all which can influence tumorigenesis (77,78). The presence of this protein in both cribiform and tubulopapillarey samples in our study is an indication of enhanced protein production necessary for tumor progression. Similarly, its higher abundance in cribiform carcinoma in our study demonstrates its contribution to the greater aggression of this subtype.

The role of RNA helicase (M3W863) which are molecules involved various aspects of RNA metabolism includes, transcription, splicing and translation (79). It has been implicated in cancer cell propagation where it may influence cell cycle regulation and apoptosis (80). Our results show its abundant expression in both tumor subtypes,

evidence of its role in tumor cell evasion of apoptosis.

Mammalian ependymin-related protein 1 (A0A337SHN0) also upregulated in cribiform and tubulopapillary feline mammary carcinoma is associated with cell growth, differentiation, adhesion and migration (81). It has been associated with tumor growth and metastasis in human cancers (82). Its role in cell-to-cell interactions implies that its aberrant expression, especially as indicated in our results, where although present in both tumor samples, is more abundant in cribiform subtype could facilitate the dissemination of feline mammary carcinoma cells.

4.2. Proteins specific for cribiform and tubulopapillary feline mammary carcinoma

The cribiform feline mammary histological carcinoma subtype is marked by organized epithelial structures that mimic glandular architecture (83). Our proteomic studies based on comparison with human breast cancer and feline tubulopapillary proteins, identified four proteins specific to it, namely, AHNAK nucleoprotein (A0A337S8X8), glycerol kinase (A0A337SAZ0), Myosin-2 (A0A337SF79), and an uncharacterized protein (A0A337S6M6) which may influence tumorigenesis and prognosis.

AHNAK nucleoprotein (A0A337S8X8) is a large scaffold protein involved in cellular architecture and signal transduction and has been implicated in reduced tumor suppression and regulation of epithelial to mesenchymal transition (EMT) (84). It is associated with the production and release of extracellular vesicles that cause disruption of the stroma by surrounding fibroblasts, thereby promoting cancer in the human breast cancer microenvironment (85). Its upregulation in feline mammary carcinoma could facilitate tumor invasiveness and dissemination via loss of cytoskeletal integrity and heightened cell motility (84). Moreover, high AHNAK expression as observed in our results has been associated with short disease-free survival and poor overall survival in pancreatic ductal adenocarcinoma, modulation of the TGF-β signalling pathway, further connecting it to oncogenic epithelial to mesenchymal transition (EMT) events (86). This exact role in human breast cancer by this protein could be responsible for the tumor progression and aggression in the cribiform subtype as reflected in our study.

The phosphotransferase enzyme, glycerol kinase (A0A337SAZ0) is central to lipid and energy metabolism involved in triglycerides and glycerophospholipid synthesis, playing a dual role in oncogenesis (87,88). Its increased expression in

cribiform carcinoma as evident in our results can enhance membrane synthesis and conversion of glycerol into glycerol-3- phosphate, fuelling anabolic pathways critical for rapid tumor growth (87). Additionally, altered glycerolipid metabolism is associated with more aggressive tumor phenotypes, suggesting that glycerol kinase could serve as a metabolic biomarker of malignancy and a potential therapeutic target (89–91).

Myosin-2 (A0A337SF79), a non-muscle myosin involved in cytoskeletal remodelling and cell migration plays a pivotal role in cancer cell invasiveness (92,93). Its overexpression as observed from our results may contribute to the mechanical force generation required for cellular movement through the extracellular matrix – a key feature of metastasis in mammary carcinoma. Its upregulation as noted could correlate to higher metastatic potential and poorer prognosis due to its involvement in motility and cell contractility mechanisms (94–96). Furthermore, Myosin-2 may influence integrin-mediated signalling, impacting cell adhesion and communication within the tumor environment (97–99), enhancing feline mammary tumor cell resilience and capacity for metastasis as it is both present both samples under study, more so in cribiform carcinoma

We detected an uncharacterized protein (A0A337S6M6), found in the cytosol, but also present in the hair cortex and embedded in the interfilamentous matrix, consisting of hair-keratin associated proteins (KTRAP) essential for the formation of a rigid and resistant hair shaft through their extensive di-sulphide bond cross-linking with abundant cysteine residues of hair keratin. Additionally, it also constitutes a part of the intermediate filament, which is a cytoskeletal structure with distinct elongated structure, characteristically 10 nm in diameter in the cytoplasms of eukaryotic cells (UniProtKB). Since intermediate filament proteins are key part of the cytoskeleton, contributing to the maintenance of cellular shape, mechanical resilience, and spatial organization of organelles, the enhanced expression of this uncaharacterized protein (A0A337S6M6), may be indicative of alterations in filament dynamics to support physical adaptability of tumor cells, promoting tumor growth, and increased resistance to stress within tumor microenvironment. The enhancement of this protein within our feline cribiform carcinoma subtype, and in tubuloppapillary samples to a lesser degree, signals not just tumoral structural adaptation, but deeper biological changes associated with aggressiveness, metastatic potential and treatment resistance, paralleling known mechanisms in human breast cancer (100).

In all, the proteins identified in cribiform feline mammary carcinoma reflect a diverse set of biological functions implicated in its tumorigenesis, ranging from effect on cytoskeletal integrity (AHNAK, myosin-2) to metabolic adaptation (glycerol kinase) to the yet to be discovered but potentially novel roles by uncharacterized protein (A0A337S6M6). Their specific expression patterns may contribute to the distinct behaviour of cribiform tumors, which includes lower differentiation and higher invasiveness (101,102).

Tubular and papillary epithelial structures characterize tubulopapillary carcinoma histological subtype, which is often associated with moderate to high malignancy (103), and understanding the biological mechanisms governing its tumor initiation, progression and metastasis is based upon understanding its unique protein profile (104). We identified four proteins specific to tubulopapillary carcinoma tumorigenesis, including, Glucosylceramidase beta 3 (A0A2I2UCJ0), Beta-2-glycoprotein 1 (M3WH75), SEA domain-containing protein (M3WNR4), and EF-hand domain-containing protein (A0A337SCP2) which may be potentially significant contributors to the pathophysiology of this carcinoma.

Glucosylceramidase beta 3 is a cytosolic β-glucosidase mostly present in the kidney, liver, spleen, intestine and lymphocytes of mammals (105). It is an enzyme involved in the degradation of glycosphingolipids, thereby playing a crucial role in lipid metabolism (102). Glycosphingolipids are in the plasma membrane domains and play significant roles in regulating membrane fluidity, while also serving as key bioeffector of diverse cellular functions such as differentiation, proliferation, apoptosis, and senescence (106,107). Alteration in glycosphingolipids levels have been linked to drug resistance and metastatic potential in various cancers due to its modifying effect on cell membrane properties and intracellular signalling (108–110). In the context of tubulopapillary feline mammary carcinoma, upregulation of glucosylceramidase beta 3 can lead to increased ceramide, a product of glucosylceramide breakdown, a process associated with anti-apoptosis and increased cell survival (111–113).

The protein beta-2-glycoprotein 1 (M3WH75) is a plasma protein involved in lipid transport and immune regulation (114). It is involved as a major player in tumor cell migration and invasion by binding apoptotic cells and potentially shielding tumor cells from immune surveillance, especially in a microenvironment with high immune infiltration. This immune evasion mechanism may aid tumor progression and correlate

with poor prognosis, especially in aggressive subtypes such as tubulopapillary carcinoma (115).

As a diverse multifaceted protein with various biological functions involving triglyceride metabolism, blood coagulation, and homeostasis; it plays a significant role in anti-migration of human aortic endothelial vascular cells via NF-κB/eNOS/NO signalling pathway (116). Endothelial cells migration is involved in vascular physiology and pathology, such as angiogenesis and tumorigenesis, thus underscoring its role in the regulation of tumor cell migration and invasion (116). Additionally, high plasma levels of beta-2-glycoprotein 1 have been associated with higher overall survival (OS) and disease-free survival in hepatocarcinoma patients validating the possibility that activating its levels in high-risk patients could play a role in mitigating cancer progression (117). Their presence in our tumor samples may represent an attempt by the feline immune system at containing tumor spread, thereby improving prognosis.

Another protein, SEA domain-containing protein (M3WNR4) are ubiquitous protein modules important for the structure and function of a wide range of membrane-associated and secreted proteins in organisms from yeast to humans (118,119). It is involved in the formation of mucins and glycoproteins associated with cell adhesion and protection, glycosylation and implicated in the proteolytic cleavage processes that activate signalling cascades (120,121). In mammary carcinomas, they may facilitate the dynamic changes in cell adhesion, allowing for increased epithelial-to-mesenchymal transition (EMT), a hallmark of cancer metastasis (122,123). Their presence in tubulopapillary feline mammary carcinoma samples may thus be associated with a potential for invasiveness and metastatic dissemination.

EF-hand domain-containing protein (A0A337SCP2) is a helix-loop-helix structural motif, capable of binding calcium ions, essential for various cellular functions such as proliferation, motility, and apoptosis (124,125). They act as calcium sensors or buffers, regulating the downstream signaling pathways (126). Breast cancer cells manipulate cellular circuitry by taking advantage of calcium signalling for survival and progression by modulating intracellular calcium concentrations, evidenced by the increased expression of calcium channels, pumps, effectors and enzymes, culminating in high calcium or elevated calcium mobilizing capacity required for malignant functions like migration, invasion, proliferation, tumorigenesis and metastasis (127). Conversely, depending on the calcium context, they could also contribute to apoptosis

resistance, both of which are indicative of poor prognosis as is the case in tubulopapillary feline carcinoma (128).

The expression of these four proteins may collectively contribute to a more malignant phenotype in tubulopapillary feline mammary carcinoma. Alterations in lipid metabolism (GBA3), immune modulation (β2GP1), cell adhesion (SEA domain-containing protein), and calcium signalling (EF-hand domain-containing protein) represent a multifaceted oncogenic program. These pathways are commonly co-opted in human breast cancer too, suggesting that similar mechanisms might be at play in feline carcinomas, with prognostic and therapeutic implications (129). Moreover, profiling these proteins in clinical cases may help to stratify patients based on risk, and inform more precise treatment approaches, as their specificity to feline tubulopapillary tumor further enhance their utility as sub-type specific molecular markers.

4.3. Common proteins reflecting poor prognosis in humans, cribiform and tubulopapillary feline carcinoma

From the total proteins recovered after LC-MS/MS and compared with human breast cancer based on data from Human Protein Atlas, two proteins were identified in both cribiform and tubulopapillary feline mammary carcinoma, and associated with poor prognosis in human breast cancer, namely, T-complex protein 1 subunit alpha (M3VZ89)and Reticulon-3 (A0A5F5XKU7). The underlying effects of these proteins may provide insights into the shared traits of these carcinomas.

T-complex protein 1 subunit alpha (M3VZ89), located in the plasma membrane, is a component of the chaperonin-containing *TCP1 complex* (CCT or TRiC), and is critical for the folding of cytoskeletal proteins like actin and tubulin, a number of proteins linked to cancer like KRAS, p53 and STAT3 (130–133). The protein folding process is essential for maintaining cell structure and function, particularly in proliferative cells like cancer cells (128). In human breast cancer, TCP1 is overexpressed and promotes cell proliferation and resistance to apoptosis, which are hallmark features of aggressive tumors (30). It regulates Wnt7b/beta-catenin pathway through p53 to influence the proliferation and migration of hepatocellular carcinoma cells (134). In feline mammary carcinomas, particularly cribiform and tubulopapillary subtypes, elevated expression of TCP1 likely supports cytoskeletal reorganization, allowing tumor cells to migrate to and invade surrounding tissues.

Studies in human oncology have demonstrated that high TCP1 expression correlates with shortened disease-free survival and overall poor prognosis in breast cancer (135). In addition, the chaperonin complex plays a role in cell cycle progression by regulating the folding of cyclins and other mitotic proteins, thus its upregulation in feline tumors may drive unchecked cell division, contributing to higher-grade malignancies and metastatic potential (136). TCP1´s role in maintaining protein homeostasis under stress may also confer resistance to chemotherapy, making it a marker for poor treatment response (133,137). The protein has been implicated in promoting cells survival under stressful such as nutrient deprivation and hypoxia, both common in tumor microenvironments (130). In breast cancer, its expression has been linked to increased tumor cell resistance to apoptosis and enhanced metastatic behaviour (138).

In the context of feline mammary carcinomas, overabundance of RTN3, could enhance tumor cell survival via modulation of unfolded protein response (UFR) pathways and autophagy, allowing cancer cells to escape autophagy (139,140). It may also promote the maintenance of cancer stem-like cells, which are known for their roles in tumor relapse and therapy resistance (140). In tubulopapillary tumors, often characterized by glandular-like structures, Reticulon-3´s role in vesicle trafficking and endoplasmic reticulum morphology may be especially important secretory functions and sustaining tumor metabolism (141).

Combined, T-complex protein 1 subunit alpha and Reticulon-3 represent synergistic contributors to poor prognosis in mammary carcinoma. While T-complex protein 1 subunit alpha drives proliferation and cytoskeletal dynamics, Reticulon-3 sustains survival under stress, providing dual advantage to cancer cells. Their co-upregulation in cribiform and tubulopapillary subtypes could explain the aggressive biological behaviours often observed in these tumors. Furthermore, as previously noted, both proteins are implicated in resistance to apoptosis, which may be the underlying reason for response failure to conventional therapies (30). Their identification in our samples strengthen their translational relevance to human breast cancer and highlights the feline mammary carcinoma model as valuable platform for drug discovery.

4.4. Protein and enzyme augmentation in metabolic pathways

In our study, various metabolic pathways, common to both cribiform and tubulopapillary feline carcinomas had specific protein and enzyme upregulation. While similar proteins were augmented in both carcinoma subtypes in the same metabolic pathways, there were occasional disparities in the enzyme and or protein augmentation in the same metabolic pathways between the two carcinoma subtypes. The metabolic pathways demonstrating protein and enzyme upregulation include carbon metabolism, estrogen, antigen processing and presentation, lysosome, protein processing in endoplasmic reticulum, glycolysis/gluconeogenesis and spliceseosome pathways.

Similarly, distinct protein and enzyme upregulation across certain metabolic pathways were observed, with signatures for either cribibiform or tubulopapillary also occurring in the same metabolic pathways. The pathways act by aiding tumor cell progression, endoplasmic reticulum stress, immune recognition, metabolic reprogramming and enhanced protein expression to support rapid tumor growth tumor, autopahgy modulation, evasion of apoptosis and acidification of the tumor microenvironment.

The enzymes hexokinase [EC:2.7.1.1], glucose-6-phosphate isomerase [EC:5.3.1.9], fructose-1,6-bisphosphatase [EC:3.1.3.11, triose-phosphate isomerase [EC:5.3.1.1], glyceraldehyde-3-phosphate dehydrogenase [EC:1.2.1.12], phosphoglycerate kinase [EC:2.7.2.3], phosphoglycerate mutase [EC:5.4.2.11], phosphopyruvate hydratase [EC4.2.1.11], pyruvate kinase [EC:2.7.1.40], dihydrolipoyl dehydrogenase [EC:1.8.1.4], and aldehyde dehydrogenase (NAD(+)[EC:1.2.1.3] were all augmented in glycolysis/gluconeogenesis pathway, indicating rapid glucose metabolism and energy turnover (142). Since cancer cells undergo metabolic reprogramming to support rapid growth and proliferation, it is no wonder therefore that there was upregulation in the various key enzymes involved in glycolysis/gluconeogenesis, as it reflects the need to meet increased energy requirements of the rapidly dividing tumor cells (143–145).

The altered metabolism necessary to support the rapid, unregulated proliferation of cancer cells, reflecting a corresponding need for more nucleotides often involves one-carbon (1C) metabolism, which is particularly important for its role in DNA synthesis (146,147), validating the observed upregulation of proteins in our carcinoma samples. Apart from its role in DNA synthesis, altered carbon metabolism, particularly is one-

carbon (1C) metabolism is important in methylation processes related to cancer cell survival and proliferation through alteration of DNA transcription to mRNA which also results in the modification of biological process regulation (148,149).

In estrogen pathway, we observed upregulation in similar proteins and enzymes between cribiform and tubulopapillary groups, namely, heat shock protein 70, heat shock protein 90 [EC:3.6.4.10], KRT19, Cathepsin D [EC:3.4.23.5], Protein Kinase A [EC:2.7.11.11], phosphorylated CREB, calmodulin, indicating their respective roles as molecular protein chaperone, non-chaperonin molecular chaperone ATPase, a lysosomal aspartic endopeptidase, cellular processes and gene transcription and calcium-dependent signalling.

The estrogen pathway enrichment in both cribiform and tubuloppapilary carcinoma suggest shared hormonal influence during early tumor development but does not necessarily reflect differences in aggressiveness or prognosis, It might also suggest both tumors are comparably advanced where other pathways – such as immune immune evasion, rewiring, or proteostasis disruption, may play more prominent roles in their aggressiveness (150-152).

The cellular mechanism that determines the direct interaction between cancer and the immune system, by which tumor cells register their intracellular changes on their surface, to be subsequently sensed by T-lymphocytes is the antigen presentation and processing pathway (153,154). The selective augmentation of specific proteins within this pathway may influence cancer-immunoediting, and promote tumor progression through selective pressures (155,156). Similar altered protein and enzyme augmentation patterns were observed in antigen processing and presentation pathways between cribiform and tubulopapillary samples, namely heat shock protein 70, heat shock protein 90 [EC:3.6.4.10], Binding Immunoglobulin Protein or 78 kDa Glucose-regulated Protein [EC:3.6.4.10], Major Histocompatibility Complex (MHC) class I, ERp57 [EC:5.3.4.1], Calreticulin, Beta-2-microglobulin, Cathepsin B [EC:3.4.22.1] and HLA-DM. They function as molecular chaperones, a non-chaperonin molecular chaperone ATPase in energy-dependent protein folding and stabilization, catalysation of phosphate groups and rearrangement of disulphide bonds in proteins, and peptide exchange, a critical step in antigen presentation (157,158), all processes which may aid immune evasion and resilience of cancer cells.

5. CONCLUSION

The observed overlap in proteomics between feline and human tumors in our study, including shared markers indicative of poor prognosis, reinforces the biological parallels between the two species. The identification of subtype specific proteins and functional pathways differences, such as those related to cellular architecture, antigen presentation, ovarian steroidogenesis, and metabolic processes, highlight tumor-specific alterations in both carcinoma subtypes under study. Although principal component analysis revealed some overlap in the global abundance patterns between cribiform and tubulopapillary feline carcinoma subtypes, VIP scoring and Venn analysis demonstrated distinct molecular signatures, suggesting that feline mammary carcinoma recapitulate the heterogeneity and key molecular features of human breast cancer.

The various molecular and metabolic underpinnings of these proteins demonstrate their distinctive roles, but collectively, they are important to various cellular processes including cellular structure and metabolism, RNA processing, protein synthesis, cell adhesion, immune evasion or signalling, with their dysregulation possibly contributing to the initiation and progression of feline mammary carcinoma, potentially impacting prognosis. Despite the valuable insights provided by this study, we acknowledge certain limitations. The relatively small sample size and restriction to only two histological subtypes may limit the generalizability of the findings across the broader spectrum of feline mammary carcinoma. In addition, the use of FFPE material, although practical and widely available, may have introduced protein cross-linking and degradation that could reduce proteome coverage and quantification accuracy. Finally, the proteomic approach applied here was discovery-based and did not include functional and clinical validation, which is necessary to confirm the biological and diagnostic relevance of the identified proteins. Future proteogenomic integration and validation studies of the most promising candidate biomarkers using larger, independent sample cohorts and complemetary assays and targeted proteomics will be necessary to establish these relationships and explore their potential as prognostic markers or therapeutic targets in feline mammary oncology. Expanding the analysis to additional FMC subtypes and integrating proteomic data with trancsriptomic, genomic, and metabolomic approaches would also help to provide a systems-level understanding of tumor biology.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

OOA, GMC, MIMM, and GWDS contributed to the acquisition of data, data interpretation, technical procedures and critical revision of this study. FFS contributed to the conceptualization, acquisition of data, technical procedures, the intellectual, scientific content of the study, and approved the final manuscript. PBG and LAA contributed to bench work procedures. All authors read and approved the final manuscript.

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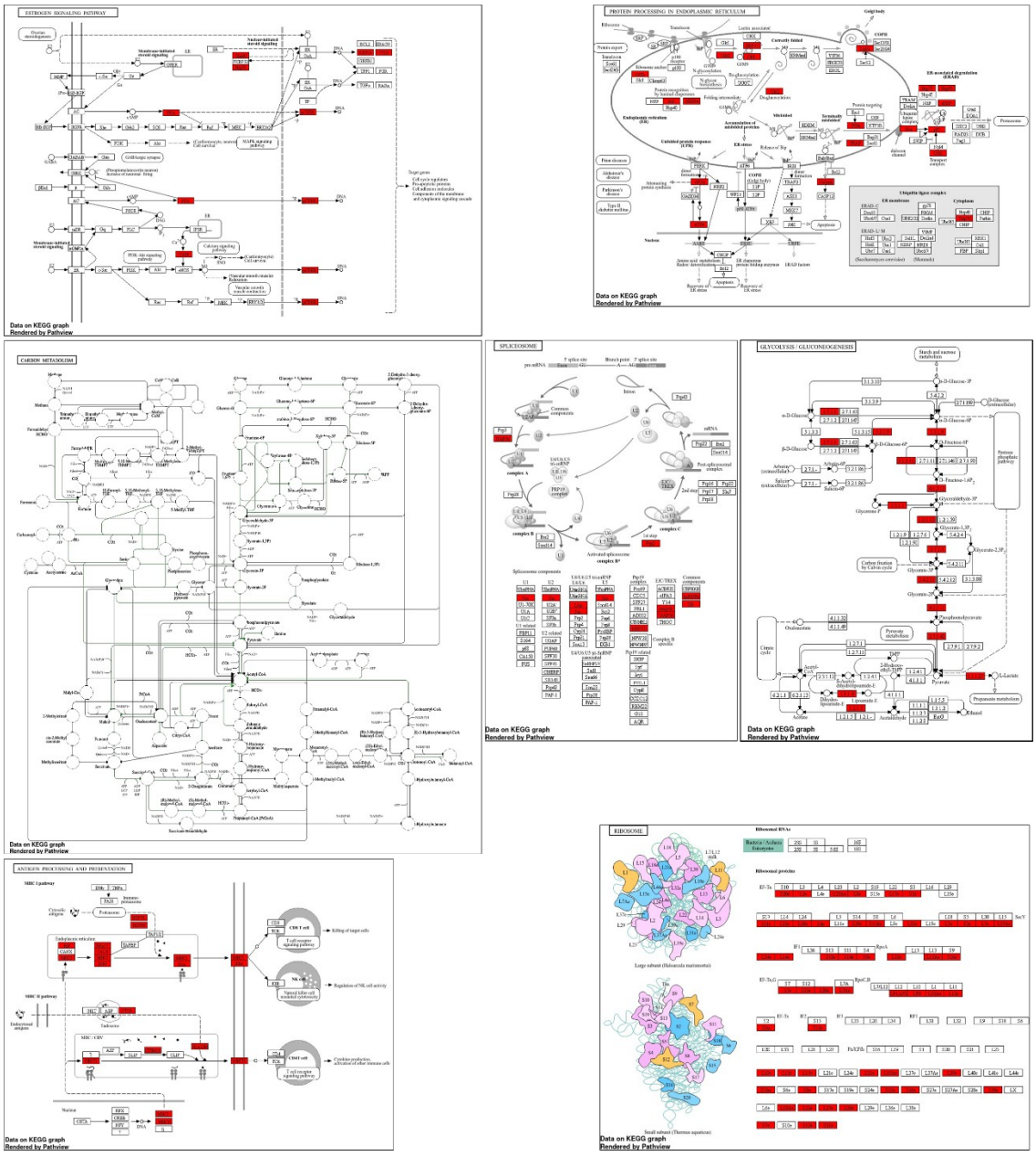
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Enrichment pathways

Supplemental Table 1.

Proteins found in cribiform and tubulopapillary feline mammary carcinoma compared with human breast cancer proteins.

Protein name	UniProtKB ID	Gene name	Group		
			Human	Feline	
				CRIB	TUB
10 kDa heat shock protein, mitochondrial	A0A337SEI8	HSPE1	X	X	X
14-3-3 domain-containing protein	A0A2I2ULR9	--	--	X	X
14-3-3 domain-containing protein	M3WVC7	YWHAZ	X	X	X
1-phosphatidylinositol-3-phosphate 5-kinase	A0A2I2UHL8	PIKFYVE	X	X	X
2-iminobutanoate/2-iminopropanoate deaminase	A0A2I2UD52	RIDA	X	X	X
40S ribosomal protein S12	A0A2I2U1K1	RPS12	X	X	X
40S ribosomal protein S21	A0A2I2V3D5	RPS21	X	X	X
40S ribosomal protein S25	M3VW27	RPS25	X	X	X
40S ribosomal protein S26	M3WJU8	RPS26	X	X	X
40S ribosomal protein S8	M3XE20	RPS8	X	X	X
45 kDa calcium-binding protein	M3W808	SDF4	X	X	X
5'-3' exonuclease PLD3	A0A5F5XE59	PLD3	X	X	X
5'-nucleotidase	M3W6Q5	NT5E	X	X	X
5'-nucleotidase, cytosolic IB	A0A337S927	NT5C1BA	X	X	X
60 kDa heat shock protein, mitochondria	M3WXZ4	HSPD1	X	X	X
60S acidic ribosomal protein P0	M3WIQ1	RPLP0	X	X	X
60S ribosomal protein L13	M3W059	RPL13	X	X	X
60S ribosomal protein L27	M3WIA8	RPL27	X	X	X
60S ribosomal protein L7a	A0A2I2U4W2	RPL7A	X	X	-
78 kDa glucose-regulated protein	M3WFT4	HSPA5	X	X	X
A0A5F5XKU7	A0A5F5XKU7	RTN3	X	X	X
Abhydrolase domain containing 18	M3WW68	ABHD18	X	X	X
ABI family member 3 binding protein	M3WLN8	ABI3BP	X	X	X
Acid ceramidase	A0A2I2V0N3	ASAH1	X	X	X
Acid phosphatase	M3W7V9	ACP3	X	X	X
Acidic leucine-rich nuclear phosphoprotein 32 family member	A0A2I2UW24	ANP32A	X	X	X
Aconitate hydratase, mitochondrial	M3WP87	ACO2	X	X	X
Acrosin	A0A337RXU2	ACR	X	X	X
Acrosin-binding protein	M3W6N5	ACRBP	X	X	X
Actin alpha 2, smooth muscle	M3W7A1	ACTA2	X	X	X
Actin gamma 1	M3W6I2	ACTG1	X	X	X
Actinin alpha 4	A0A2I2U3E4	ACTN4	X	X	X
Actin-related protein 2/3 complex subunit 3	M3W1M4	ARPC3	X	X	X
Actin-related protein 2/3 complex subunit 4	M3WSL5	ARPC4	X	X	X
Actin-related protein 2/3 complex subunit 5	M3WMY0	ARPC5	X	X	X
Activated RNA polymerase II transcriptional coactivator p15	A0A2I2UN36	SUB1	X	X	X
Acyl-CoA-binding protein	A0A2I2U6R0	DBI	X	X	X
Acylphosphatase	M3WWT9	ACYP1	X	X	X
Adenine phosphoribosyltransferase	A0A2I2UMH4	APRT	X	X	X
Adenosylhomocysteinase	A0A2I2U551	AHCY	X	X	X
Adenylate kinase isoenzyme 1	M3WX07	AK1	X	X	X
ADF-H domain-containing protein	A0A5F5XRM0	COTL1	X	X	X
Adiponectin, C1Q and collagen domain containing	M3WJN6	ADIPOQ	X	X	X
ADP ribosylation factor 6	A0A5F5XYI9	--	--	X	X
ADP ribosylation factor like GTPase 8A	A0A337SXE8	ARL8A	X	X	X
ADP/ATP translocase	M3VW78	LOC101095941	--	X	X
ADP/ATP translocase	M3W759	SLC25A31	--	X	X
ADP-ribosylation factor	M3X7Y7	ARF1	X	X	X
Afamin	A0A2I2U1Z3	AFM	--	X	X
Aggrecan core protein	A0A5F5XE37	ACAN	X	X	X
AHNAK nucleoprotein	A0A337S8X8	--	--	X	X
AHNAK nucleoprotein	A0A337S8X8	--	--	X	--
A-kinase anchoring protein 4	M3WZ40	AKAP4	--	X	X
Albumin	P49064	ALB	X	X	X
Aldehyde dehydrogenase (NAD(+))	M3XAZ0	ALDH7A1	X	X	X
Aldehyde dehydrogenase 2 family member	M3X7B5	ALDH2	X	X	X
Aldehyde dehydrogenase 9 family member A1	M3W1Z4	ALDH9A1	X	X	X
Aldo-keto reductase family 1 member B	M3WHU0	AKR1B1	X	X	X
Alpha-1-B glycoprotein	M3W0W4	A1BG	X	X	X
Alpha-2-HS-glycoprotein	A0A5F5Y4L1	AHSG	--	X	X

Alpha-2-macroglobulin	M3WMA9	A2M	X	X	X
Alpha-2-macroglobulin like 1	A0A337SNL8	A2ML1	X	X	X
Alpha-amylase	M3X5H0	AMY2B	X	X	X
Alpha-crystallin B chain	M3WT79	CRYAB	X	X	X
Alpha-fetoprotein	M3X557	AFP	X	X	X
Alpha-galactosidase	A0A5F5XU62	NAGA	X	X	X
Alpha-mannosidase	A0A2I2UJS0	MAN2B1	X	X	X
Aminopeptidase	M3VU18	ENPEP	X	X	X
Anaphylatoxin-like domain-containing protein	A0A5F5XM97	--	--	X	X
Angiotensin-converting enzyme	A0A2I2UTZ7	ACE	X	X	X
Angiotensinogen	A0A2I2UUP6	AGT	X	X	X
Ankyrin 3	M3XEN9	ANK3	X	X	X
Annexin	A0A2I2UN04	ANXA7	X	X	X
Annexin	A0A337SCD2	ANXA2	X	X	X
Annexin	A0A5F5Y7J8	ANXA5	X	X	X
Annexin	M3WIJ2	ANXA4	X	X	X
Annexin	M3WM96	ANXA1	X	X	X
Annexin	M3XFZ3	ANXA11	X	X	X
Antithrombin-III	M3WLL8	SERPINC1	X	X	X
Apolipoprotein A-I	M3WPG6	APOA1	X	X	X
Apolipoprotein A-IV	M3W955	APOA4	--	X	X
Apolipoprotein B	M3X9R6	APOB	--	X	X
Apolipoprotein D	M3X8P7	APOD	X	X	X
Arachidonate 12-lipoxygenase, 12R type	M3WM43	ALOX12B	X	X	X
Arachidonate lipoxygenase 3	M3WM46	ALOXE3	X	X	X
Arginase	M3VXU3	ARG1	X	X	X
Armadillo repeat containing 6	M3WC30	ARMC6	X	X	X
Aspartate aminotransferase	M3X6W4	GOT1	X	X	X
Aspartylglucosaminidase	M3X0F1	AGA	X	X	X
Asporin	M3WWN6	ASPN	X	X	X
ATP synthase subunit alpha	M3WZB0	ATP5F1A	X	X	X
ATP synthase subunit beta	M3WG78	ATP5F1B	X	X	X
ATP synthase subunit d, mitochondrial	A0A337SD82	ATP5PD	X	X	-
ATP synthase subunit e, mitochondrial	A0A337SK34	ATP5ME	X	X	X
Autophagy related 2A	M3WGK5	ATG2A	X	X	X
Autophagy-related protein 9	M3WIE1	ATG9B	X	X	-
Barrier-to-autointegration factor	A0A2I2UEU9	BANF1	X	X	X
Basigin	A0A5F5Y008	BSG	X	X	X
Bassoon presynaptic cytomatrix protein	M3XCH9	BSN	X	X	X
Beta-1,4-galactosyltransferase	M3W8S5	B4GALT4	X	X	X
Beta-2-glycoprotein 1	M3WH75	APOH	--	--	X
Beta-2-microglobulin	A0A0A0MQ10	B2M	X	X	X
Beta-casein	M3VV53	CSN2	--	X	X
Beta-galactosidase	M3WZ71	GLB1	X	X	X
Beta-galactoside alpha-(2,6)-sialyltransferase	M3WJN7	ST6GAL1	X	X	X
Beta-hexosaminidase	A0A0A0MQ23	HEXB	--	X	X
Beta-hexosaminidase	M3X8Q6	HEXA	X	X	X
Beta-lactoglobulin-1	P33687	LGB1	X	X	X
Beta-lactoglobulin-3	P33688	LGB3	--	X	X
Beta-mannosidase	M3W7X6	MANBA	X	X	X
Beta-nerve growth factor	A0A337SBN0	NGF	X	X	X
Biogenesis of lysosome-related organelles complex 1 subunit 6	A0A337S6D6	BLOC1S6	X	X	X
Bis(monoacylglycero)phosphate synthase CLN5	A0A2I2UWU9	CLN5	X	X	X
Bleomycin hydrolase	M3W1G9	BLMH	X	X	X
BPI fold containing family A member 2	A0A337S0F0	BPIFA2	--	X	X
Bromodomain containing 4	A0A337S3L5	BRD4 BRD3	X	X	X
C1GALT1 specific chaperone 1	M3WD96	C1GALT1C1	X	X	X
C1q and TNF related 5	M3XCZ4	C1QTNF5	X	X	X
C1q and TNF related 8	A0A2I2V2K9	C1QTNF8	--	X	X
Cadherin 11	M3W046	CDH11	X	X	X
Cadherin-1	A0A337SG59	CDH1	X	X	X
Calcium homeostasis modulator family member 4	M3W5I9	CALHM4	--	X	X
Calcium/calmodulin-dependent protein kinase	A0A2I2U0V7	CAMKK2	X	X	X
Calcium/calmodulin-dependent protein kinase	A0A5F5XSX8	CAMK2A	X	X	X
Calicin	M3WTE9	CCIN	X	X	X
Calmodulin 2	M3WQA1	CALM2	X	X	X
Calmodulin like 3	A0A2I2U5U0	CALML3	X	X	X
Calmodulin-lysine N-methyltransferase	M3WDV6	CAMKMT	X	X	X
Calpain small subunit 1	M3WK60	CAPNS1	X	X	X
Calpain-1 catalytic subunit	A0A337RXK3	CAPN1	X	X	X

Calreticulin	M3VUU7	CALR	X	X	X
Calsequestrin	M3XE43	CASQ2	X	X	X
Calumenin	A0A5F5XF37	CALU	X	X	X
cAMP-dependent protein kinase catalytic subunit beta	A0A2I2UFW9	PRKACB	X	X	X
cAMP-dependent protein kinase type I-alpha regulatory subunit	A0A337STX8	PRKAR1A	X	--	X
Canopy FGF signaling regulator 2	M3WG69	CNPY2	X	X	X
Carboxylesterase 5A	Q8I034	CES5A	--	X	X
Carboxymethylenebutenolidase homolog	M3X3U3	CMBL	X	X	X
Carboxypeptidase A4	M3WB83	CPA4	X	X	X
Carboxypeptidase M	M3WKG9	CPM	X	X	X
Carboxypeptidase Q	M3WQN1	CPQ	X	X	X
Carnitine O-acetyltransferase	A0A2I2UP24	CRAT	X	X	--
Caspase 14	M3W8J6	CASP14	--	X	X
Catalase	M3VXR8	CAT	X	X	X
Catenin beta 1	M3W0E4	CTNNB1	X	X	X
Catenin delta 2	A0A337RZS0	CTNND2	X	X	X
Cathelicidin	F1C962	CAMP	X	X	X
Cathepsin B	M3WLU0	CTSB	X	X	X
Cathepsin D	M3W8G3	CTSD	X	X	X
Cathepsin F	M3W7M8	CTSF	X	X	X
Cathepsin G	A0A337SS37	CTSG	X	X	X
Cathepsin H	M3WGI2	CTSH	X	X	X
Cathepsin K	M3W0Q2	CTSK	X	X	X
Cathepsin L1-like	M3VX87	LOC101087880	--	X	X
Cathepsin X	M3VVI7	CTSZ	X	X	X
CCR4-NOT transcription complex subunit 1	M3X382	CNOT1	X	X	X
CCR4-NOT transcription complex subunit 11	M3W6R7	CNOT11	X	X	--
CD166 antigen	M3W6Y7	ALCAM	X	--	X
CD177 molecule	A0A2I2UYP6	CD177	X	X	X
CD34 molecule	A0A5F5Y5V1	CD34	X	--	X
CD44 antigen	A0A337S5E8	CD44	X	X	X
CD48 molecule	A0A337SSQ8	CD48	X	X	X
CD58 molecule	A0A5F5Y1Y8	CD58	X	X	X
CD68 molecule	A0A5F5XIA7	CD68	X	--	X
Chaperonin containing TCP1 subunit 6A	A0A5F5XMX0	CCT6A	X	X	X
Chloride intracellular channel protein	M3WNY6	CLIC1	X	X	X
Chromosome B1 C4orf3 homolog	A0A337S5Z7	CB1H4orf3	--	X	X
Chromosome D1 C11orf54 homolog	A0A5F5Y4Z5	CD1H11orf54	--	X	X
Ciliary neurotrophic factor receptor subunit alpha	A0A337RVG5	CNTFR	X	X	X
Citrate synthase	M3WG68	CS	X	X	X
Clathrin heavy chain	M3X4Z2	CLTC	X	X	X
Clathrin light chain	A0A5F5XUC1	CLTA	X	X	X
Clusterin	M3WKP2	CLU	X	X	X
Coatomer subunit beta'	M3VWP9	COPB2	X	X	X
Cofilin 1	M3WIJ6	CFL1	X	X	X
Coiled-coil domain containing 85B	A0A337SJP2	CCDC85B	X	X	X
Coiled-coil domain-containing protein 89	M3VUP8	CCDC89	X	X	X
Collagen type I alpha 1 chain	M3W2F5	COL1A1	X	X	X
Collagen type I alpha 2 chain	A0A5F5XYM1	COL1A2	X	X	X
Collagen type III alpha 1 chain	M3WL90	COL3A1	X	X	X
Collagen type VI alpha 1 chain	M3WLD9	COL6A1	X	X	X
Collagen type VI alpha 2 chain	A0A2I2UQI3	COL6A2	X	X	X
Collagen type VI alpha 3 chain	M3WHG4	COL6A3	X	X	X
Collagen type XII alpha 1 chain	A0A2I2U432	COL12A1	X	X	X
Collagen type XIV alpha 1 chain	M3VWP6	COL14A1	X	X	X
Collagen type XV alpha 1 chain	A0A337RV83	COL15A1	X	X	X
COMM domain containing 8	A0A5F5XS47	COMMD8	X	X	X
Complement component 1 Q subcomponent-binding protein, mitochondrial	M3WS12	C1QBP	X	X	X
Complement factor B	M3W2B8	CFB	X	X	X
Complex III assembly factor LYRM7	M3X3E3	LYRM7	X	X	X
Condensin complex subunit 1	A0A5F5Y4G8	NCAPD2	X	X	X
Copine 1	A0A2I2V326	CPNE1	X	X	X
Copine 3	A0A337SJW2	CPNE3	X	X	X
Core histone macro-H2A	M3X3U0	MACROH2A1	X	X	X
Corneodesmosin	M3X143	CDSN	X	X	X
Coronin	A0A2I2U047	CORO1C	X	X	X
Creatine kinase B-type	M3W8P6	CKB	X	X	--
Creatine kinase M-type	M3VYX8	CKM	X	X	X
Creatine kinase U-type, mitochondrial	A0A337SPH8	CKMT1B	X	X	X

Crystallin beta-gamma domain containing 1	M3W3G3	CRYBG1	X	X	X
C-type lectin domain containing 11A	A0A2I2U6F0	CLEC11A	X	X	X
C-type natriuretic peptide	M3WH43	NPPC	X	X	X
CutA divalent cation tolerance homolog	A0A2I2UJG2	CUTA	X	X	X
Cyclic AMP-dependent transcription factor ATF-4	M3WB57	ATF4	X	X	X
Cyclin C	A0A2I2UJ30	CCNC	X	X	X
Cyclin dependent kinase 3	M3W4N5	CDK3	X	X	X
Cystatin A	A0A0A0MPZ8	CSTA	X	X	X
Cystatin domain-containing protein	A0A337SE08	CSTB	X	X	X
Cystatin E/M	M3WIK5	CST6	X	X	X
Cysteine rich protein 1	M3WNB8	CRIP1	X	X	X
Cysteine-rich and transmembrane domain-containing protein 1	M3VWB9	CYSTM1	X	X	X
Cytochrome b5 type A	M3X9M9	CYB5A	X	X	X
Cytochrome b5 type B	A0A2I2UMU3	CYB5B	X	X	X
Cytochrome c domain-containing protein	A0A2I2U526	LOC109503558	X	X	--
Cytochrome c oxidase subunit	A0A2I2UCG4	LOC101100266	--	X	X
Cytochrome c oxidase subunit 2	P48890	MT-CO2	X	X	X
Cytochrome c oxidase subunit 5A, mitochondrial	A0A5F5Y4I7	LOC101081808	-	X	X
Cytochrome c oxidase subunit 7A2, mitochondrial	A0A2I2V489	COX7A2	X	X	X
Cytosol aminopeptidase	M3WRM3	LAP3	X	X	X
D-3-phosphoglycerate dehydrogenase	M3WF60	PHGDH	X	X	X
DDAH family member 2, ADMA-independent	M3XC02	DDAH2	X	X	X
D-dopachrome decarboxylase	M3WBD6	DDT	X	X	X
Decaprenyl diphosphate synthase subunit 1	M3WGD6	PDSS1	X	X	X
Decorin	M3X0W2	DCN	X	X	X
Delta-aminolevulinic acid dehydratase	M3WB25	ALAD	X	X	X
Deoxyribonuclease 1L3	M3W621	DNASE1L3	X	X	X
Dermatopontin	M3XE34	DPT	X	X	X
Desmocollin 1	A0A2I2UZT4	DSC1	X	X	X
Desmoglein 1	A0A337SP25	DSG1	X	X	X
Desmoglein 4	M3WTD0	DSG4	--	X	X
Desmoplakin	M3WCK3	DSP	X	X	X
Destrin, actin depolymerizing factor	A0A2I2UFE0	DSTN	X	X	X
Diacylglycerol kinase	M3WJU2	DGKA	X	X	X
Dihydrolipoyl dehydrogenase	M3W291	DLD	X	X	X
Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	M3W5T1	DLST	X	X	X
Dipeptidyl peptidase 1	M3W9M0	CTSC	X	X	X
Dipeptidyl peptidase 4	A0A5S7SG08	DPP4	X	X	X
Dipeptidyl peptidase 7	A0A5F5XVS8	DPP7	X	X	X
DLA class II histocompatibility antigen, DR-1 beta chain-like	A0A5F5XSC6	LOC111558969	--	X	X
DNA replication licensing factor MCM3	M3X046	MCM3	X	X	X
DNA-directed RNA polymerase subunit	A0A2I2V2C9	POLR2A	--	X	X
DnaJ heat shock protein family (Hsp40) member C13	A0A2I2UK41	DNAJC13	X	X	X
DnaJ homolog subfamily C member 3	M3WSH1	DNAJC3	X	--	X
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	M3VVE9	DDOST	X	X	X
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	M3W966	RPN1	X	X	X
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit DAD1	M3X9E1	DAD1	X	X	X
Dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit TMEM258	M3WJA9	TMEM258	X	X	X
Dual specificity phosphatase 14	M3WDI6	DUSP14	X	X	X
Dynein axonemal assembly factor 1	M3WFB2	DNAAF1	X	X	X
Dynein light chain	A0A2I2V4P1	DYNLL2	X	X	X
Dynein light chain roadblock	M3VY92	DYNLRB1	X	X	X
EF-hand domain-containing protein	A0A2I2U8F9	CAPS	X	X	X
EF-hand domain-containing protein	A0A2I2U998	--	--	X	X
EF-hand domain-containing protein	A0A337SCP2	--	--	--	X
EF-hand domain-containing protein	A0A337SKT0	--	--	X	X
EH domain containing 4	M3WXE7	EHD4	X	X	X
Elastase, neutrophil expressed	M3XDQ5	ELANE	X	X	X
Elongation factor 1-alpha 1	Q66RN5	EEF1A1	X	X	X
Elongation factor 1-beta	M3WCX7	EEF1B2	X	X	X
Elongation factor 1-delta	M3XFH0	EEF1D	X	X	X
Elongation factor 1-gamma	M3WAC5	EEF1G	X	X	X
Elongation factor 2	M3VVM1	EEF2	X	X	X

Elongation factor Tu	M3VZQ3	TUFM	X	X	X
Elongin B	M3W2P5	ELOB	X	X	X
Endothelial differentiation related factor 1	M3VUN3	EDF1	X	X	X
Engulfment and cell motility 3	A0A337SDU3	ELMO3	X	X	X
Enhancer of rudimentary homolog	M3WAD9	ERH	X	X	X
Epiplakin 1	A0A5F5XL62	EPPK1	--	X	X
Epithelial membrane protein 1	A0A2I2UYU0	EMP1	X	X	X
Epoxide hydrolase 1	A0A2I2UMU7	EPHX1	X	X	X
Ethylmalonyl-CoA decarboxylase	M3W8C4	ECHDC1	X	X	--
Eukaryotic translation initiation factor 2 subunit 1	M3WYU5	EIF2S1	X	X	X
Eukaryotic translation initiation factor 6	M3W5W5	EIF6	X	X	X
Exportin-2	M3VWN2	CSE1L	X	X	X
Extracellular matrix protein 1	M3X2V7	ECM1	X	X	X
F-actin-capping protein subunit alpha	M3W7D2	CAPZA3	X	X	X
F-actin-capping protein subunit alpha	M3WIM3	CAPZA1	X	X	X
F-actin-capping protein subunit beta	A0A337S8B2	CAPZB	X	X	X
FAM3 metabolism regulating signaling molecule C	M3WVJ8	FAM3C	X	--	X
FAM3 metabolism regulating signaling molecule D	M3W626	FAM3D	X	X	X
Family with sequence similarity 131 member B	A0A337SJ50	FAM131B	X	X	--
Fanconi-associated nuclease	A0A5F5Y5S4	FAN1	X	X	X
Far upstream element binding protein 1	A0A337S476	FUBP1	X	X	X
Fascin	A0A2I2U7R8	FSCN1	X	X	X
FAT atypical cadherin 2	M3XCA4	FAT2	X	--	X
Fatty acid binding protein 3	M3X9Z0	FABP3	X	X	X
Fatty acid binding protein 4	M3WSU7	FABP4	X	X	X
Fatty acid binding protein 5	M3W564	FABP5	X	X	X
Fc gamma receptor IIb	A0A2I2U0C2	FCGR2B	X	X	X
Ferric chelate reductase 1	M3XEV8	FRRS1	X	X	X
Ferritin	A0A0A0MPZ6	FTH1	X	X	X
Ferritin heavy chain	Q2MHN2	FTH1	X	X	X
Ferritin light chain	Q2MHN1	FTL	X	X	X
Fetuin B	M3WG98	FETUB	--	X	X
Fibrillin 1	M3WMG2	FBN1	X	X	X
Fibrinogen alpha chain	M3W022	FGA	X	X	X
Fibrinogen beta chain	M3WII3	FGB	X	X	X
Fibromodulin	A0A2I2UMT4	FMOD	X	X	X
Fibronectin	A0A2I2U011	FN1	X	X	X
Fibulin 5	M3WFS9	FBLN5	X	X	X
Fibulin-1	A0A337SRF9	FBLN1	X	X	X
Filamin A	A0A2I2V3V8	FLNA	X	X	X
Filamin A interacting protein 1 like	M3X039	FILIP1L	X	X	X
Filamin B	M3W620	FLNB	X	X	X
Focal adhesion kinase 1	A0A2I2UMM7	PTK2	X	X	X
Folate gamma-glutamyl hydrolase	M3WHF8	GGH	X	X	X
Folate receptor-like domain-containing protein	A0A337SLR6	--	--	X	X
Folate receptor-like domain-containing protein	M3W6W1	LOC101084733	--	X	X
Fructose-1,6-bisphosphatase isozyme 2	M3VXP7	FBP2	X	X	X
Fructose-bisphosphate aldolase	M3WK75	ALDOA	X	X	X
FRY microtubule binding protein	M3X419	FRY	X	X	X
Fumarylacetoacetase	A0A5F5XFP7	FAH	X	X	X
FYVE and coiled-coil domain autophagy adaptor 1	A0A5F5XCH0	FYCO1	X	X	X
G protein-coupled receptor 179	M3W4R4	GPR179	X	X	X
G protein-coupled receptor class C group 5 member A	M3WJV7	GPRC5A	X	--	X
GABA type A receptor associated protein like 2	M3W9J5	GABARAPL2	X	X	X
Galectin	A0A337S4Q5	LGALS3	X	X	X
Galectin	A0A337SP31	--	--	X	X
Galectin	M3W9D5	LGALS1	X	X	X
Galectin-3-binding protein	A0A2I2U679	CANT1	X	X	X
Gamma-aminobutyric acid type A receptor subunit delta	A0A337S5Q8	GABRD	X	X	X
Gamma-glutamylcyclotransferase	M3WBE2	GGCT	X	X	X
Ganglioside GM2 activator	M3WHT1	GM2A	X	X	X
Gasdermin A	M3WLQ9	GSDMA	X	X	X
GDP-L-fucose synthase	M3VVW7	GFUS	X	X	X
Gelsolin	A0A5F5XIG6	GSN	X	X	X
General vesicular transport factor p115	A0A337S5Y6	USO1	X	X	X
GIY-YIG domain-containing protein	A0A337RWX2	SLX1A	X	X	--
Glucose-6-phosphate isomerase	A0A337S9I7	GPI	X	X	X
Glucosidase 2 subunit beta	M3W340	PRKCSH	X	X	X
Glucosidase II alpha subunit	M3WAD1	GANAB	X	X	X
Glucosylceramidase	M3VVL7	GBA1	X	X	X

Glucosylceramidase beta 3	A0A2I2UCJ0	GBA3	--	--	X
Glutaminyl-peptide cyclotransferase	M3WST2	QPCT	X	X	X
Glutaredoxin 3	A0A337S755	GLRX3	X	X	X
Glutaredoxin 3	A0A337S755	GLRX3	X	X	--
Glutathione peroxidase	A0A2I2V5E5	GPX3	X	X	X
Glutathione peroxidase	M3X766	GPX4	X	X	X
Glutathione S-transferase	M3WMX0	GSTM3	X	X	X
Glutathione S-transferase omega	M3W556	GSTO2	X	X	--
Glutathione synthetase	A0A337SJ23	GSS	X	X	X
Glutathione transferase	A0A5F5XTS9	GSTP1	X	X	X
Glyceraldehyde-3-phosphate dehydrogenase	A0A5F5Y264	--	--	X	X
Glyceraldehyde-3-phosphate dehydrogenase	M3W5S9	GAPDHS	X	X	X
Glyceraldehyde-3-phosphate dehydrogenase	Q9N2D5	GAPDH	X	X	X
Glycerol kinase	A0A337SAZ0	GK2	--	X	--
Glycine--tRNA ligase	M3WF28	GARS1	X	X	--
Glycogenin glucosyltransferase	A0A337S2C5	GYG1	X	X	X
Glycoprotein IX platelet	M3WWM7	GP9	--	X	X
Glycoprotein nmb	M3XBW8	GPNMB	X	X	X
Glyoxalase domain containing 4	A0A2I2V038	GLOD4	X	X	X
Golgi apparatus protein 1	A0A337SJD7	GLG1	X	X	X
Golgin A3	M3VYM4	GOLGA3	X	X	X
Growth/differentiation factor 8	M3WPT7	MSTN	X	X	-
GTP-binding nuclear protein Ran	M3WXV4	RAN	X	X	X
H1.4 linker histone, cluster member	A0A5F5XKM9	H1-4	X	X	X
H1.5 linker histone, cluster member	M3W584	H1-5	X	X	X
H2B.L variant histone 1	M3X5W1	H2BL1	--	X	X
Haptoglobin	E3UTY9	HP	X	X	X
Heat shock 70 kDa protein 13	M3X6Z7	HSPA13	X	X	X
Heat shock protein 90 alpha family class A member 1	A0A337S6T1	HSP90AA1	X	X	X
Heat shock protein 90 beta family member 1	M3WK11	HSP90B1	X	X	X
Heat shock protein beta-1	M3WWP2	HSPB1	X	X	X
Heat shock protein family A (Hsp70) member 1B	A0A337RXE8	--	--	X	X
Heat shock protein family A (Hsp70) member 2	M3W8G1	HSPA2	X	X	X
Heat shock protein family A (Hsp70) member 8	A0A2I2UZM2	HSPA8	X	X	X
Helicase with zinc finger 2	A0A5F5XRJ1	HELZ2	X	X	X
Heme binding protein 2	A0A2I2V4X4	HEBP2	X	X	X
Hemoglobin subunit alpha	P07405	HBA	X	X	X
Hemoglobin subunit beta-A/B	P07412	HBB	X	X	X
Heparan sulfate proteoglycan 2	A0A5F5Y6R8	HSPG2	X	X	X
Heterogeneous nuclear ribonucleoprotein A1	A0A337S498	HNRNPA1	X	X	X
Heterogeneous nuclear ribonucleoprotein K	M3WLH7	HNRNPK	X	X	X
Heterogeneous nuclear ribonucleoproteins A2/B1	M3XCQ1	HNRNPA2B1	X	X	X
Heteroous nuclear ribonucleoprotein H1	A0A5F5XXJ0	HNRNPH1	X	X	X
Heteroous nuclear ribonucleoprotein R	A0A2I2UFR7	HNRNPR	X	X	--
Hexokinase	A0A2I2U1D6	HK1	X	X	X
High affinity immunoglobulin epsilon receptor subunit gamma	A0A2I2V145	FCER1G	X	X	X
Histidine ammonia-lyase	M3W406	HAL	X	X	X
Histidine kinase/HSP90-like ATPase domain-containing protein	A0A5F5Y0E9	HSP90AB1	X	X	X
Histidine triad nucleotide binding protein 2	M3WHJ0	HINT2	X	--	X
Histidine--tRNA ligase, cytoplasmic	M3VWD2	HARS1	X	X	X
Histone H2A	M3X2B2	H2AJ	X	X	X
Histone H2A/H2B/H3 domain-containing protein	A0A337S574	--	--	X	X
Histone H2B	A0A2I2U8P7	--	--	X	X
Histone H2B	A0A2I2USF3	H2BC17	X	X	X
Histone H4	M3WSM7	H4C4	X	X	X
Homeobox protein Nkx-2.5	M3VUY6	NKX2-5	--	X	X
HtrA serine peptidase 1	M3W0Q9	HTRA1	X	--	X
Hyaluronan and proteoglycan link protein 4	A0A2I2UM20	HAPLN4	X	X	X
Hydroxymethylglutaryl-CoA lyase, mitochondrial	A0A5F5XXK7	FUCA1	X	X	X
Hydroxysteroid 17-beta dehydrogenase 4	M3W9K8	HSD17B4	X	X	X
Hypoxia up-regulated protein 1	M3VW30	HYOU1	X	-	X
IF rod domain-containing protein	A0A337SCP9	KRT13	X	X	X
IF rod domain-containing protein	A0A337SVY6	--	--	X	X
IF rod domain-containing protein	M3VUF2	KRT86	X	X	X
IF rod domain-containing protein	M3VUG4	LOC101097497	--	X	X
IF rod domain-containing protein	M3WGY5	--	--	X	X
IF rod domain-containing protein	M3WQ25	KRT41	--	X	X
IF rod domain-containing protein	M3WZD7	KRT89	--	X	X
Ig-like domain-containing protein	A0A2I2U1K0	--	--	X	X

Ig-like domain-containing protein	A0A2I2U5M6	--	--	X	X
Ig-like domain-containing protein	A0A2I2UI16	--	--	X	X
Ig-like domain-containing protein	A0A2I2USM8	--	--	X	X
Ig-like domain-containing protein	A0A2I2UUB6	LOC101088734	--	X	X
Ig-like domain-containing protein	A0A2I2V189	--	--	X	X
Ig-like domain-containing protein	A0A337S014	LOC105259814	--	X	X
Ig-like domain-containing protein	A0A337S1X7	--	--	X	X
Ig-like domain-containing protein	A0A337S2C9	CEACAM1	X	X	X
Ig-like domain-containing protein	A0A337S7W6	--	--	X	X
Ig-like domain-containing protein	A0A337SA19	--	--	X	X
Ig-like domain-containing protein	A0A337SA21	--	--	X	X
Ig-like domain-containing protein	A0A5F5XD04	LOC105259618	--	X	X
Ig-like domain-containing protein	A0A5F5XKU3	--	--	X	X
Ig-like domain-containing protein	A0A5F5XZ27	--	--	X	X
Ig-like domain-containing protein	M3WAZ6	LOC111556169	--	X	X
Ig-like domain-containing protein	M3WNZ4	LOC105260551	--	X	X
Ig-like domain-containing protein	M3WR78	--	--	X	X
Ig-like domain-containing protein	M3WX06	--	--	X	X
Ig-like domain-containing protein	M3X1A8	--	--	X	X
Ig-like domain-containing protein	M3X4T8	--	--	X	X
Ig-like domain-containing protein	M3XD51	--	--	X	X
Ig-like domain-containing protein	M3XG22	--	--	X	X
Immunoglobulin C1-set domain-containing protein	A0A5F5XWQ4	--	--	X	X
Importin 11	M3VZZ6	IPO11	X	X	X
Importin 5	M3WXS9	IPO5	X	X	X
Inorganic diphosphatase	M3WTQ9	PPA1	X	X	X
Inosine-5'-monophosphate dehydrogenase	M3WC84	IMPDH2	X	X	X
Inositol-1-monophosphatase	A0A5F5XBU4	IMPA1	X	X	X
inositol-phosphate phosphatase	A0A5F5Y040	--	--	X	X
Insulin degrading enzyme	M3XDA5	IDE	X	X	X
Insulin gene enhancer protein ISL-1	M3WF59	ISL1	X	X	X
Insulin-like growth factor-binding protein 5	M3WQ08	IGFBP5	X	X	X
Inter-alpha-trypsin inhibitor heavy chain 4	A0A5F5Y7V2	ITIH4	X	X	X
Inter-alpha-trypsin inhibitor heavy chain H1	M3WN59	ITIH1	--	X	X
Inter-alpha-trypsin inhibitor heavy chain H3	M3WN60	ITIH3	X	-	X
Intercellular adhesion molecule 1	M3WBF1	ICAM1	X	X	X
Intercellular adhesion molecule 3	M3WYZ5	ICAM3	X	X	X
Interleukin 4 induced 1	A0A337SS87	IL4I1	X	X	X
Interleukin enhancer binding factor 2	A0A337RWC2	ILF2	X	X	-
Interleukin enhancer binding factor 3	M3W314	ILF3	X	X	X
IQ motif containing F1	M3WAV6	IQCF1	--	X	--
Isocitrate dehydrogenase [NADP]	M3W1B8	IDH1	X	X	X
IZUMO family member 4	M3WGB4	IZUMO4	X	X	X
Janus kinase and microtubule interacting protein 2	M3WP74	JAKMIP2	X	X	X
Janus kinase and microtubule interacting protein 3	M3VUC8	JAKMIP3	X	X	X
Joining chain of multimeric IgA and IgM	M3XBL5	JCHAIN	X	X	X
Junction plakoglobin	A0A2I2UBN8	JUP	X	X	X
Kallikrein related peptidase 7	A0A5F5XDU3	KLK7	X	X	X
Katanin p60 ATPase-containing subunit A-like 2	A0A5F5XNK1	KATNAL2	X	X	X
Keratin 12	M3VXR2	KRT12	X	X	X
Keratin 23	M3VXR4	KRT23	X	X	X
Keratin 24	M3VXQ9	KRT24	X	X	X
Keratin 26	M3X826	KRT26	--	X	X
Keratin 28	A0A337RW34	KRT28	--	X	X
Keratin 3	M3VUG8	KRT3	--	X	X
Keratin 32	A0A2I2USJ2	KRT32	--	X	X
Keratin 36	A0A2I2U4F0	KRT36	X	X	X
Keratin 39	M3VXR5	KRT39	X	X	X
Keratin 74	A0A2I2V546	KRT74	--	X	X
Keratin 76	M3VUG7	KRT76	--	X	X
Keratin 77	M3XG51	KRT77	--	X	X
Keratin 78	M3VUH1	KRT78	--	X	X
Keratin 79	M3VUH0	KRT79	X	X	X
Keratin 80	M3X1L9	KRT80	X	X	X
Keratin 82	M3VUF5	KRT82	--	X	X
Keratin 84	M3VUF7	KRT84	--	X	X
Keratin, type I cytoskeletal 10	M3VXR1	KRT10	X	X	X
Keratin, type I cytoskeletal 14	A0A337SM15	KRT17	X	X	X
Keratin, type I cytoskeletal 19	M3VXK3	KRT19	X	X	X
Keratin, type I cytoskeletal 27	A0A2I2UVW3	KRT25	--	X	X
Keratin, type II cytoskeletal 71	E1AB55	KRT71	X	X	X

Keratin, type II cytoskeletal 8	A0A337SEH4	--	--	X	X
Kinesin-like protein	A0A5F5XE91	KIF12	X	X	X
Kinetochore scaffold 1	A0A5F5XCV6	KNL1	X	X	X
Kininogen 1	A0A5F5XVF5	KNG1	--	X	X
KPRP N-terminal and LCE C-terminal like protein	A0A2I2UGM3	KPLCE	--	X	X
Kremen protein	M3W1U0	KREMEN1	X	X	X
Lactotransferrin	M3WKU0	LTF	X	X	X
Lactoylglutathione lyase	M3X4B1	GLO1	X	X	X
Lamin A/C	M3WFR2	LMNA	X	X	X
Lamin B1	M3VZT0	LMNB1	X	X	-
Laminin subunit beta 1	M3W292	LAMB1	X	X	X
Large ribosomal subunit protein eL14	A0A337SCP5	RPL14	X	X	X
Large ribosomal subunit protein eL20	A0A5F5XEC0	RPL18A	X	X	X
Large ribosomal subunit protein eL22	A0A2I2UNG3	RPL22	X	X	X
Large ribosomal subunit protein eL28	M3W4G0	RPL28	X	X	X
Large ribosomal subunit protein eL30	A0A5F5XFW3	RPL30	X	X	X
Large ribosomal subunit protein eL31	A0A2I2V0T7	RPL31	X	X	X
Large ribosomal subunit protein eL33	A0A337SK14	RPL35A	X	X	X
Large ribosomal subunit protein eL34	M3WMR1	RPL34	X	X	X
Large ribosomal subunit protein eL38	M3WE21	RPL38	X	X	X
Large ribosomal subunit protein eL39	A0A2I2UY38	RPL39	X	X	X
Large ribosomal subunit protein P2	M3W9K1	RPLP2	X	X	X
Large ribosomal subunit protein uL11	M3WD17	RPL12	X	X	X
Large ribosomal subunit protein uL13	M3WAY9	RPL13A	X	X	X
Large ribosomal subunit protein uL14	M3WKT7	RPL23	X	X	X
Large ribosomal subunit protein uL15	M3W9J7	RPL27A	X	X	X
Large ribosomal subunit protein uL15/eL18 domain-containing protein	A0A2I2V180	RPL18	X	X	X
Large ribosomal subunit protein uL18	A0A5F5Y2G3	RPL5	X	X	X
Large ribosomal subunit protein uL2	M3WRT2	RPL8	X	X	X
Large ribosomal subunit protein uL22	Q5XTY7	RPL17	X	X	X
Large ribosomal subunit protein uL23	M3W1E8	RPL23A	X	X	X
Large ribosomal subunit protein uL3	A0A337SEG6	RPL3	X	X	X
Large ribosomal subunit protein uL30	A0A337S2E2	RPL7	X	X	X
Lebercilin LCA5	A0A2I2UNY5	LCA5	X	X	X
Leucine rich repeat containing 15	M3X588	LRRC15	X	X	X
Leucine rich repeat containing 25	M3WC03	LRRC25	X	X	X
Leucine rich repeat containing 75B	M3VWS8	LRRC75B	X	X	X
Leucine rich repeats and calponin homology domain containing 2	M3WJQ6	LRCH2	X	X	X
L-Fucosyltransferase	A0A337S584	FUT1	X	X	X
LIM and SH3 domain protein 1	M3X768	LASP1	X	X	X
Lipocalin/cytosolic fatty-acid binding domain-containing protein	A0A5F5XI37	LOC109496317	--	X	X
Lipocalin/cytosolic fatty-acid binding domain-containing protein	M3VU75	LOC100144393	--	X	X
Lipocalin/cytosolic fatty-acid binding domain-containing protein	M3WIS7	LOC101098498	--	X	X
Lipocalin/cytosolic fatty-acid binding domain-containing protein	M3X0N6	BLGIII	--	X	X
L-lactate dehydrogenase	A0A2I2U9C6	LDHB	X	X	X
L-lactate dehydrogenase	A0A337S8L1	LDHA	X	X	X
Loricrin	A0A2I2UFW4	LORICRIN	--	X	X
Low affinity immunoglobulin gamma Fc region receptor III-A	Q9N2I5	FCGR3A	X	X	X
LSM6 homolog, U6 small nuclear RNA and mRNA degradation associated	M3VZM0	LSM6	X	X	X
LSM7 homolog, U6 small nuclear RNA and mRNA degradation associated	M3W0C9	LSM7	X	X	X
Luc7-like protein	M3WGR7	LUC7L3	X	X	--
Lumican	M3W0X1	LUM	X	X	X
L-xylulose reductase	M3WFI7	DCXR	X	X	X
Lymphocyte antigen 6 family member D	A0A337SJ42	LY6D	X	X	X
Lymphocyte antigen 6 family member G6C	M3WX31	LY6G6C	X	X	X
Lysophosphatidylcholine acyltransferase 4	M3VX71	LPCAT4	X	X	X
Lysosomal alpha-glucosidase	M3W981	GAA	X	X	X
Lysosomal associated membrane protein 1	C6GGN9	LAMP1	X	X	X
Lysosomal associated membrane protein 2	A0A337STH0	LAMP2	X	X	X
Lysozyme	M3W413	LYZ	X	X	X
Lysozyme g-like protein	M3W055	LYG2	X	X	X
Mab-21 domain containing 2	A0A337SA27	MB21D2	X	X	X

MAC-inhibitory protein	A0A5F5XQT8	CD59	X	X	X
Macrophage migration inhibitory factor	M3W1I3	MIF	X	X	X
Maestro heat like repeat family member 2A	M3WP81	MROH2A	--	X	X
Mago homolog, exon junction complex subunit	M3X9V4	MAGOH	X	X	X
Major allergen I polypeptide chain 1	P30438	CH1	X	X	X
Major allergen I polypeptide chain 2	P30440	CH2	X	X	X
Mal, T cell differentiation protein 2	A0A2I2UQT9	MAL2	X	X	X
Malate dehydrogenase, cytoplasmic	Q7YRU4	MDH1	X	X	X
Malate dehydrogenase, mitochondrial	K0J107	MDH2	X	X	X
Malic enzyme	A0A2I2UHG8	ME1	X	X	X
Mammalian ependymin-related protein 1	A0A337SHN0	EPDR1	X	X	X
Mannose-6-phosphate receptor, cation dependent	A0A5F5XZT8	M6PR	X	X	X
Mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase	A0A5F5XUP4	ENGASE	X	X	X
Marginal zone B and B1 cell specific protein	M3X8R2	MZB1	X	X	X
MARVEL domain-containing protein	M3WRE2	SYPL1	X	X	X
Maspardin	M3WF48	SPG21	X	X	X
Matrilin 4	A0A337SJ17	MATN4	X	X	X
Matrix Gla protein	A0A2I2V3J5	MGP	X	X	X
Melanotransferrin	M3W126	MELTF	X	X	X
Membrane-associated progesterone receptor component 1	M3WUA3	PGRMC1	X	X	X
Mesencephalic astrocyte derived neurotrophic factor	A0A2I2ULZ5	MANF	X	X	X
MET transcriptional regulator MACC1	A0A5F5Y1A1	MACC1	X	X	X
Metallo-beta-lactamase domain-containing protein 1	A0A337SM68	MBLAC1	X	X	X
Metalloproteinase inhibitor 1	M3W949	TIMP1	X	X	X
Metalloproteinase inhibitor 2	A0A337SHQ6	TIMP2	X	X	X
Meteorin-like protein	M3XFR1	METRNL	X	--	X
Methanethiol oxidase	M3VXE7	SELENBP1	X	X	X
MHC class I-like antigen recognition-like domain-containing protein	A0A2I2U6W9	--	--	X	X
Microfibril associated protein 5	M3WRG6	MFAP5	X	X	X
Microtubule associated protein 1 light chain 3 alpha	M3XB56	MAP1LC3A	X	X	X
Migration and invasion enhancer 1	M3WPV6	MIEN1	X	X	X
Milk fat globule EGF and factor V/VIII domain containing	M3W678	MFGE8	X	X	X
Mimecan	M3VVG9	OGN	X	X	X
Mitochondrial carrier 2	M3X0I4	MTCH2	X	X	X
Mitochondrial import inner membrane translocase subunit	A0A337SU38	TIMM13	X	X	X
Mitochondrial import inner membrane translocase subunit	A0A5F5XLE4	TIMM10B	X	X	X
Mitochondrial import receptor subunit TOM22 homolog	M3VZ70	TOMM22	X	X	X
Monocyte differentiation antigen CD14	M3VWC6	CD14	X	X	X
Mothers against decapentaplegic homolog	A0A2I2UFR8	SMAD4	X	X	X
MPV17 mitochondrial inner membrane protein like 2	A0A2I2U077	MPV17L2	X	X	X
Mucin 4, cell surface associated	M3WF35	MUC4	X	X	X
Multifunctional methyltransferase subunit TRM112-like protein	M3WWU1	TRMT112	X	X	X
Myelin basic protein	A0A2I2V1G2	MBP	X	--	X
Myeloid derived growth factor	A0A2I2V0Q8	MYDGF	X	X	X
Myeloperoxidase	M3WGL9	MPO	X	X	X
Myocilin	A0A2I2UIM0	MYOC	-	X	X
Myosin light chain 1/3, skeletal muscle isoform	A0A2I2U0Y6	MYL1	X	X	X
Myosin light chain 12A	A0A337S230	MYL12A	X	X	X
Myosin light chain 9	A0A337S1U2	MYL9	X	X	--
Myosin light polypeptide 6	A0A2I2UHR0	MYL6	X	X	X
Myosin-2	A0A337SF79	MYH2	--	X	--
NAC-A/B domain-containing protein	A0A2I2UG75	LOC101093299	--	X	X
N-acetylglucosamine-6-sulfatase	M3VUR6	GNS	X	X	X
N-acylethanolamine-hydrolyzing acid amidase	A0A2I2V455	NAAA	X	X	X
NADH-cytochrome b5 reductase	A0A337RZ16	CYB5R3	X	X	X
NADH-cytochrome b5 reductase	M3WI84	CYB5R1	X	X	X
Napsin A aspartic peptidase	A0A5F5XWA2	NAPSA	X	X	X
NCCRP1, F-box associated domain containing	M3W7Q3	NCCRP1	X	X	X
Nephronectin	A0A337SNS5	NPNT	X	X	X
Neudesin neurotrophic factor	A0A337SAE3	NENF	X	X	X
Neuroplastin	M3W5R1	NPTN	X	X	X
NHL repeat containing 3	A0A2I2UPA5	NHLRC3	X	X	--
Nicastrin	A0A337S9P8	NCSTN	X	X	X

N-myc downstream regulated 1	M3VZX9	NDRG1	X	X	X
Non-selective voltage-gated ion channel VDAC1	A0A2I2UXU4	VDAC1	X	X	X
Non-selective voltage-gated ion channel VDAC2	M3X2J1	VDAC2	X	X	X
Non-selective voltage-gated ion channel VDAC3	M3WCM7	VDAC3	X	X	X
Non-specific serine/threonine protein kinase	A0A2I2UU64	CDC42BPA	X	X	X
Non-specific serine/threonine protein kinase	A0A337S886	CSNK1D	X	X	X
Non-specific serine/threonine protein kinase	M3WKI0	TSSK6	X	X	X
NPC intracellular cholesterol transporter 2	M3X1L5	NPC2	X	X	X
NSF attachment protein alpha	M3W5E1	NAPA	X	X	X
NSFL1 cofactor p47	A0A337SQ94	NSFL1C	X	X	X
N-sulfoglucosamine sulfohydrolase	M3VVP5	SGSH	X	X	X
Nuclear transport factor 2	M3X0F5	NUTF2	X	X	X
Nucleobindin 2	M3W7H2	NUCB2	X	X	X
Nucleobindin-1	M3W064	NUCB1	X	X	X
Nucleophosmin	A0A2I2V1F6	NPM1	X	X	X
Nucleoside diphosphate kinase	A0A2I2U4B5	NME2	X	X	X
Nucleoside diphosphate kinase	A0A337SIM6	NME1	X	X	X
Nudix hydrolase 5	A0A5F5XK35	NUDT5	X	X	X
Olfactomedin like 3	M3WB23	OLFML3	X	X	X
Oligodendrocyte myelin glycoprotein	M3WAC2	OMG	X	--	X
Outer dense fiber protein 1	M3W6P2	ODF1	--	X	X
Outer dense fiber protein 2	A0A337SPH7	ODF2	X	X	X
Palmitoyl-protein thioesterase 1	M3X4P7	PPT1	X	X	X
Palmitoyltransferase	A0A337SM53	ZDHHC15	X	X	X
Pantetheinase	A0A5F5XLV1	VNN1	X	X	X
Parathymosin	M3W6N9	PTMS	X	X	X
Pentraxin family member	A0A5F5XWB9	CRP	X	X	X
Peptidase M20 domain containing 1	M3W6E4	PM20D1	X	X	X
Peptidase S1 domain-containing protein	A0A5F5XFA7	--	--	X	X
Peptidase S1 domain-containing protein	M3W2K3	--	--	X	X
Peptidyl-prolyl cis-trans isomerase	A0A2I2UBH3	PPIB	X	X	X
Peptidyl-prolyl cis-trans isomerase	A0A5F5XQ37	--	--	X	X
Peptidyl-prolyl cis-trans isomerase	A0A5F5XQZ5	PPIA	--	X	X
Peptidylprolyl isomerase	A0A2I2UG00	FKBP1A	X	X	X
Periostin	A0A2I2U6U3	POSTN	X	X	X
Peroxiredoxin-2	M3VUU2	PRDX2	X	X	X
Peroxiredoxin-5	M3X1J5	PRDX5	X	X	X
Peroxiredoxin-6	A0A2I2UL25	PRDX6	X	X	X
Peroxisome proliferator activated receptor delta	A0A337SGM7	PPARD	X	X	X
Phosphatidylethanolamine-binding protein 1	A0A2I2ULZ1	PEBP1	X	X	X
Phosphoglycerate kinase	A0A2I2UJH0	PGK1	X	X	X
Phosphoglycerate kinase	M3X166	PGK2	--	X	X
Phosphoglycerate mutase	A0A337S2Y5	PGAM1	X	X	X
Phosphoglycerate mutase	M3WYZ8	PGAM2	X	X	X
Phosphoinositide phospholipase C	A0A337RV53	PLCH2	X	X	X
Phosphoinositide phospholipase C	A0A337SD30	PLCD1	X	X	X
Phospholipase B1, membrane-associated	M3W3L4	PLB1	X	X	--
Phospholipase B-like	A0A2I2UDS4	PLBD2	X	X	X
Phospholipase B-like	M3WDG7	PLBD1	X	X	X
Phosphopyruvate hydratase	A0A2I2UTE6	ENO1	X	X	X
PITH domain containing 1	A0A337SAH5	PITHD1	X	X	X
Piwi like RNA-mediated silencing 4	M3WE65	PIWIL4	X	X	--
Plakophilin 1	M3W2I5	PKP1	X	X	X
Plakophilin 3	M3W7Z1	PKP3	X	X	X
Plasminogen	M3X3T9	PLG	--	X	X
Plastin-3	A0A2I2UIE1	PLS3	X	X	X
Platelet-activating factor acetylhydrolase	M3WAT6	PLA2G7	X	X	X
Platelet-activating factor acetylhydrolase IB subunit alpha2	M3XFC9	PAFAH1B2	X	X	--
Platelet-activating factor acetylhydrolase IB subunit beta	B0LSW3	PAFAH1B1	X	X	X
Platelet-derived growth factor D	M3WUD8	PDGFD	X	X	X
Platelet-derived growth factor subunit A	A0A337SRH5	PDGFA	X	X	X
Plectin	A0A337S671	PLEC	X	X	X
Plexin domain containing 2	M3WE03	PLXDC2	X	X	--
Podocan	M3WQJ6	PODN	X	X	X
Podoplanin	M3W7Y4	PDPN	X	X	X
POF1B actin binding protein	M3WY81	POF1B	X	X	X
Poly(rC) binding protein 1	M3WS36	PCBP1	X	X	X
Poly(rC) binding protein 2	A0A337SP10	PCBP2	X	X	X
Polyadenylate-binding protein	A0A337RXS6	PABPC1	X	X	X

Polymeric immunoglobulin receptor	M3W5Z6	PIGR	X	X	X
Polypeptide N-acetylgalactosaminyltransferase	A0A337SHB3	GALNT10	X	--	X
Polypeptide N-acetylgalactosaminyltransferase	A0A5F5XHE5	GALNT13	X	X	X
Polypeptide N-acetylgalactosaminyltransferase	M3W8C0	GALNT2	X	X	X
Polypeptide N-acetylgalactosaminyltransferase	M3WMF2	GALNT17	X	X	X
Potassium channel tetramerization domain containing 12	A0A337RZ36	KCTD12	X	X	X
Potassium voltage-gated channel subfamily C member 1	M3W381	KCNC1	X	X	X
Pregnancy zone protein-like	A0A5F5XG49	LOC101080976	--	X	X
Prenylcysteine oxidase 1	M3WSQ5	PCYOX1	X	X	X
Pro-adrenomedullin	A0A337S6E3	ADM	X	X	X
Procollagen C-endopeptidase enhancer	A0A5F5XK05	PCOLCE	X	X	X
Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1	M3VU17	PLOD1	X	X	X
Profilin	M3WEL8	PFN1	X	X	X
Programmed cell death 6	A0A2I2UD44	PDCD6	X	X	X
Prohibitin	A8WA76	PHB1	X	X	X
Prolactin-induced protein	A0A337SBR4	PIP	X	X	X
Proliferation-associated 2G4	M3WLH5	PA2G4	X	X	X
Proline and arginine rich end leucine rich repeat protein	M3WQY0	PRELP	X	X	X
Proline-serine-threonine phosphatase interacting protein 1	M3WE88	PSTPIP1	X	X	--
Prolyl endopeptidase	M3W3E3	PREP	X	X	--
Prosaposin	M3WI47	PSAP	X	X	X
Prostaglandin reductase 1	A0A2I2V040	PTGR1	X	X	X
Prostate stem cell antigen	A0A2I2UM62	PSCA	X	X	X
Proteasome 20S subunit alpha 2	A0A2I2V2W1	PSMA2	X	X	X
Proteasome 20S subunit alpha 7	A0A5F5XRW3	PSMA7	X	X	X
Proteasome 26S subunit, non-ATPase 6	M3VV10	PSMD6	X	X	X
Proteasome activator subunit 4	M3X2F4	PSME4	X	X	X
Proteasome subunit alpha type	A0A2I2UNM4	PSMA5	X	X	X
Proteasome subunit alpha type	A0A337SD26	PSMA3	X	X	X
Proteasome subunit alpha type	A0A337SKX0	PSMA4	X	X	X
Proteasome subunit alpha type	M3WF05	PSMA1	X	X	X
Proteasome subunit alpha type	M3WV20	PSMA6	X	X	X
Proteasome subunit beta	A0A2I2U3F3	PSMB6	X	X	X
Proteasome subunit beta	A0A337SNC1	PSMB5	X	X	X
Proteasome subunit beta	M3VXE9	PSMB4	X	X	X
Proteasome subunit beta	M3WKT6	PSMB3	X	X	X
Proteasome subunit beta	M3WKX9	PSMB7	X	X	X
Proteasome subunit beta	M3X6T9	PSMB1	X	X	X
Proteasome subunit beta	M3XCX1	PSMB2	X	X	X
Protein deglycase	M3WYR7	PARK7	X	X	X
Protein disulfide-isomerase	M3W668	PDIA3	X	X	X
Protein disulfide-isomerase	M3XCN6	P4HB	X	X	X
Protein disulfide-isomerase A6	M3WB33	PDIA6	X	X	X
Protein kinase C	M3WIY6	PKN1	X	X	X
Protein kish	A0A337RXP3	TMEM167A	X	X	X
Protein S100	A0A2I2U4Z5	S100A16	X	X	X
Protein S100	A0A2I2URR0	S100A6	X	X	X
Protein S100	A0A5F5XHL3	S100A4	X	X	X
Protein S100	M3VWD6	S100A8	X	X	X
Protein S100	M3VZX1	S100A9	X	X	X
Protein S100-A11	A0A337SDR6	--	--	X	X
Protein-arginine deiminase	A0A2I2U4T3	PADI3	--	X	X
Protein-glutamine gamma-glutamyltransferase K	M3W4C6	TGM1	X	X	X
Protein-glutamine gamma-glutaNyl transferase 2	M3W2W5	TGM2	X	X	X
Proteolipid protein 2	M3W114	PLP2	X	X	X
Prothrombin	M3WSI8	F2	--	X	X
Pterin-4-alpha-carbinolamine dehydratase	A0A5F5XDD6	PCBD1	X	X	X
PTPRF interacting protein alpha 4	M3WI86	PPFIA4	X	X	X
Purine nucleoside phosphorylase	M3W6S5	PNP	X	X	X
Putative hydroxypyruvate isomerase	A0A5F5Y491	HYI	X	X	X
Putative protein-lysine deacylase ABHD14B	A0A337RXE3	ABHD14B	X	X	X
Pyruvate kinase	A0A337S4I7	PKM	X	X	X
Queuosine 5'-phosphate N-glycosylase/hydrolase	A0A2I2U1N7	QNG1	X	X	X
Rab GDP dissociation inhibitor	M3WHB4	GDI2	X	X	X
RAB11B, member RAS onco family	M3WM66	RAB11B	X	X	X
RAB1B, member RAS oncogene family	A0A2I2UQJ5	RAB1B	X	X	--
RAB2A, member RAS onco family	M3WVD4	RAB2A	X	X	X

RAB35, member RAS onco family	A0A337ST24	RAB35	X	X	X
RAB5A, member RAS oncogene family	A0A337SHI5	RAB5A	X	X	X
RAB6A, member RAS onco family	A0A337S9B8	RAB6A	X	X	X
Radixin	A0A2I2UJB3	RDX	X	X	X
Ragulator complex protein LAMTOR3	A0A2I2U2H8	LAMTOR3	X	X	X
Ral transcription factor IIIC subunit 4	M3XFX4	GTF3C4	X	X	X
Ras-related protein Rab-14	M3WTD7	RAB14	X	X	X
Ras-related protein Rab-7a	M3WRD9	RAB7A	X	X	X
Receptor protein-tyrosine kinase	A0A2I2UV62	EPHA4	X	X	X
Receptor protein-tyrosine kinase	M3WLY6	TIE1	X	X	X
Renin receptor	M3XEW0	ATP6AP2	X	X	X
Replication protein A3	A0A2I2UN78	RPA3	X	X	X
Reticulocalbin 2	A0A337SFQ9	RCN2	X	-	X
Reticulon	A0A5F5XCI4	RTN4	X	X	X
Reticulon 4 receptor	A0A2I2U7X2	RTN4R	X	X	X
Rho GDP dissociation inhibitor beta	A0A2I2UL98	ARHGDIB	X	X	X
Rho GDP-dissociation inhibitor 1	A0A2I2UBL3	ARHGDIA	X	X	X
Rho guanine nucleotide exchange factor 15	M3VX24	ARHGEF15	X	X	X
Rhophilin associated tail protein 1	M3W1M0	ROPN1	X	X	X
Ribonuclease 4	A0A5F5XYN1	RNASE4	X	X	X
Ribosomal protein	M3WHU6	RPL10A	X	X	X
Ribosomal protein L15	M3X6G6	RPL15	X	X	X
Ribosomal protein L26	M3WES0	RPL26	X	X	X
Ribosomal protein L32	A0A2I2U6Z1	RPL32	X	X	X
RIC3 acetylcholine receptor chaperone	A0A337SEY3	RIC3	X	X	X
RING-type E3 ubiquitin transferase	A0A5F5Y2A3	MKRN3	--	X	X
RNA binding motif protein 41	M3VXN6	RBM41	X	X	X
RNA exonuclease 2	M3WPD6	REXO2	X	X	X
RNA helicase	A0A2I2U6G2	DDX39B	X	X	X
RNA helicase	M3W863	DHX16	X	X	X
RNA helicase	M3XBC3	EIF4A1	X	X	X
RRM domain-containing protein	A0A337SDT4	HNRNPC	X	X	X
RRM domain-containing protein	M3VVZ2	SRSF3	X	X	X
RUN and TBC1 domain-containing protein 3	A0A337SLV9	SGSM3	X	X	X
S100 calcium binding protein A12	M3WK02	S100A12	X	X	X
S100 calcium binding protein A14	A0A2I2ULR1	S100A14	X	X	X
Saoe class I histocompatibility antigen, A alpha chain-like	A0A337SDQ4	FLAI-K	--	X	X
Scavenger receptor class B member 2	M3VW08	SCARB2	X	X	X
SEA domain-containing protein	A0A5F5XMZ4	--	--	X	X
SEA domain-containing protein	M3WNR4	--	--	--	X
Secreted phosphoprotein 1	A0A337SJI4	SPP1	X	X	X
Semaphorin-3C	M3WV31	SEMA3C	X	X	X
Sepiapterin reductase	A0A2I2UR05	SPR	X	X	X
Serine and arginine rich splicing factor 11	A0A5F5XPS2	SRSF11	X	X	X
Serine and arginine rich splicing factor 7	M3WYE6	SRSF7	X	X	X
Serine and arginine rich splicing factor 9	M3WEB9	SRSF9	X	X	X
Serine protease 22	A0A337RTP4	PRSS22	X	X	X
Serine/arginine-rich splicing factor 1	M3VY56	SRSF1	X	X	X
Serine/arginine-rich splicing factor 2	A0A337SID0	SRSF2	X	X	X
Serine/threonine kinase 35	M3X2P6	STK35	X	X	X
Serine/threonine-protein phosphatase	A0A2I2V1P8	PPP2CA	X	X	X
Serine/threonine-protein phosphatase	M3WEL4	PPP1CC	X	X	X
Serine/threonine-protein phosphatase with EF-hands	M3W5Y3	PPEF2	X	X	X
Serpin B10	M3W9H4	SERPINB10	--	X	X
Serpin B5	M3W9H2	SERPINB5	X	X	X
Serpin family A member 1	M3WCX1	SERPINA1	X	X	X
Serpin family A member 3	M3WCX6	SERPINA3	X	X	X
Serpin family B member 12	A0A2I2UMR7	SERPINB12	--	X	X
Serpin family B member 13	A0A337SB03	SERPINB13	--	X	X
Serpin family B member 2	M3X3Q3	SERPINB2	X	X	X
Serpin family B member 7	A0A2I2V0E8	SERPINB7	X	X	X
Serpin family B member 8	M3WTG3	SERPINB8	X	X	X
Serpin family E member 2	A0A337SQV7	SERPINE2	X	X	X
Serum amyloid A protein	A0A337SUS3	SAA1	X	--	X
SET nuclear proto-oncogene	A0A5F5XDZ6	LOC101093782	X	X	X
SH3 domain-binding glutamic acid-rich-like protein	M3X5I6	SH3BGRL	X	X	X
SH3 domain-binding glutamic acid-rich-like protein 3	M3WHM8	SH3BGRL3	X	X	X
Short chain dehydrogenase/reductase family 9C member 7	A0A2I2UG01	SDR9C7	--	X	X
Signal peptidase complex catalytic subunit SEC11	M3X3W0	SEC11A	X	X	X

Signal recognition particle 9	A0A2I2U1G7	SRP9	X	X	X
SLIT and NTRK like family member 5	A0A2I2UBS9	SLITRK5	X	X	X
Sm protein F	M3X1K2	SNRPF	X	X	X
Small monomeric GTPase	A0A2I2UDJ9	RAB27A	X	X	X
Small monomeric GTPase	M3VUK3	SAR1B	X	X	X
Small monomeric GTPase	M3X4J3	RAP1A	X	X	X
Small nuclear ribonucleoprotein E	A0A5F5XWP9	SNRPE	X	X	X
Small nuclear ribonucleoprotein Sm D2	M3X0Z8	SNRPD2	X	X	X
Small nuclear ribonucleoprotein Sm D3	A0A337SKF2	SNRPD3	X	X	X
Small nuclear ribonucleoprotein-associated protein	A0A2I2V053	SNRPB SNRPN	X	X	X
Small ribosomal subunit protein eS1	A0A0A0MQ24	RPS3A	X	X	X
Small ribosomal subunit protein eS28	M3X2Q9	RPS28	X	X	X
Small ribosomal subunit protein eS4	P62705	RPS4X	X	X	X
Small ribosomal subunit protein eS7	Q5RT64	RPS7	X	X	X
Small ribosomal subunit protein RACK1	A0A337SB80	RACK1	X	X	X
Small ribosomal subunit protein uS10	A0A337S771	RPS20	X	X	X
Small ribosomal subunit protein uS12	M3WAB5	RPS23	X	X	X
Small ribosomal subunit protein uS13	A0A2I2UWM9	RPS18	X	X	X
Small ribosomal subunit protein uS14	A0A337SCP7	RPS29	X	X	X
Small ribosomal subunit protein uS15	A0A2I2U4A9	RPS13	X	X	X
Small ribosomal subunit protein uS17	M3WAZ1	RPS11	X	X	X
Small ribosomal subunit protein uS2	M3VZ17	RPSA	X	X	X
Small ribosomal subunit protein uS3	M3WG22	RPS3	X	X	X
Small ribosomal subunit protein uS4	M3WJZ7	RPS9	X	X	X
Small ribosomal subunit protein uS5	A0A337SF71	RPS2	X	X	X
Small ribosomal subunit protein uS7	M3X5Q3	RPS5	X	X	X
Small ribosomal subunit protein uS8	M3WDL6	RPS15A	X	X	X
Small ribosomal subunit protein uS9	M3WDU7	RPS16	X	X	X
Sodium/hydrogen exchanger	A0A337S8U5	SLC9A7	X	X	X
Solute carrier family 2, facilitated glucose transporter member 3	A0A2I2UUL1	SLC2A3	X	X	X
Solute carrier family 25 member 3	A0A2I2UUV9	SLC25A3	X	X	X
Sorbitol dehydrogenase	A0A2I2V1M2	SORD	X	X	X
Spectrin beta chain	M3VZY4	SPTB	X	X	X
Spen family transcriptional repressor	A0A5F5XZS4	SPEN	X	X	X
Sperm associated antigen 6	M3W458	SPAG6	X	X	X
Sperm microtubule inner protein 9	A0A5F5XN33	SPMIP9	--	X	X
Sperm-tail PG-rich repeat containing 3	M3X7U7	STPG3	X	X	X
Sphingomyelin phosphodiesterase	M3X374	SMPD1	X	X	X
SPHK1 interactor, AKAP domain containing	A0A5F5XJN0	SPHKAP	X	X	X
Splicing factor proline and glutamine rich	A0A337SJM7	SFPQ	X	X	X
SRC kinase signaling inhibitor 1	M3W4R7	SRCIN1	X	X	X
ST13 Hsp70 interacting protein	A0A2I2V252	ST13	X	X	X
Stratifin	A0A5F5Y312	SFN	X	X	X
Sulfhydryl oxidase	A0A5F5XIH0	QSOX1	X	X	X
Sulfotransferase	A0A2I2UVG5	LOC101088902	--	X	X
Superoxide dismutase [Cu-Zn]	A0A2I2UPH5	SOD1	X	X	X
Superoxide dismutase [Cu-Zn]	A0A337SS20	SOD3	X	X	X
Suprabasin	A0A5F5XKD6	SBSN	X	X	X
Sushi domain containing 2	M3WBD8	SUSD2	X	X	X
Synaptogyrin	A0A2I2U9G9	SYNGR2	X	X	X
Synemin	A0A5F5XIK5	SYNM	X	X	X
Syntaxin binding protein 3	M3WQB8	STXBP3	X	X	X
Syntaxin-7	A0A2I2UJ09	STX7	X	X	X
Tax1-binding protein 3	A0A2I2U8E9	TAX1BP3	X	X	X
TBC1 domain family member 32	A0A337SNU3	TBC1D32	X	--	X
T-complex protein 1 subunit alpha	M3VZ89	TCP1	X	X	X
T-complex protein 1 subunit beta	M3VWY7	CCT2	X	-	X
T-complex protein 1 subunit delta	M3WRA1	CCT4	X	X	X
T-complex protein 1 subunit epsilon	M3VZR8	CCT5	X	X	X
T-complex protein 1 subunit eta	M3WJC5	CCT7	X	X	X
T-complex protein 1 subunit gamma	A0A2I2V532	CCT3	X	X	X
T-complex protein 1 subunit theta	A0A2I2U221	CCT8	X	X	X
Tenascin C	M3W358	TNC	X	X	X
Testis expressed 15, meiosis and synapsis associated	A0A5F5Y2W8	TEX15	--	X	X
Thioredoxin domain-containing protein	M3W2V1	TXN	X	X	X
Thioredoxin domain-containing protein 17	M3WT37	TXNDC17	X	X	X
Thioredoxin like 1	A0A337S744	TXNL1	X	X	--
Thioredoxin reductase 1, cytoplasmic	A0A5F5Y4A1	TXNRD1	X	X	X
Thioredoxin related transmembrane protein 1	A0A2I2V3M4	TMX1	X	X	X
Thioredoxin-dependent peroxide reductase,	M3WDP0	PRDX3	X	X	X

mitochondrial					
Thioredoxin-dependent peroxiredoxin	A0A2I2UQ65	PRDX1	X	X	X
Thioredoxin-dependent peroxiredoxin	A0A5F5XS51	PRDX4	X	X	X
Thrombospondin 1	M3WF45	THBS1	X	X	X
Thy-1 membrane glycoprotein	A0A2I2UGV7	THY1	X	X	X
Thymocyte selection associated	M3WD74	THEMIS	X	X	X
Tissue factor pathway inhibitor	M3X7K4	TFPI2	X	X	X
Transaldolase	M3W800	TALDO1	X	X	X
Transcobalamin-2	M3W1K0	TCN2	X	-	X
Transcription initiation factor TFIID subunit	A0A337SJ21	TAF1	X	X	X
Transcriptional adapter	M3WRJ9	TADA2B	X	X	X
Transferrin	M3X260	TF	X	X	X
Transgelin	A0A2I2UZE2	SIDT2	X	X	X
Transgelin	A0A5F5XQX5	TAGLN2	X	X	X
Transglutaminase 5	A0A2I2UX75	TGM5	X	X	X
Transitional endoplasmic reticulum ATPase	M3VW05	VCP	X	X	X
Transketolase	A0A5F5Y605	TKT	X	X	X
Translation elongation factor IF5A C-terminal domain-containing protein	A0A337RZ59	EIF5A	X	X	X
Translationally-controlled tumor protein	M3VXX1	TPT1	X	X	X
Translocase of outer mitochondrial membrane 5	A0A2I2UNL5	TOMM5	X	X	X
Translocator protein	M3X9H1	TSPO	X	X	X
Translocon-associated protein subunit alpha	A0A337SD08	SSR1	X	X	X
Translocon-associated protein subunit delta	M3W1G5	SSR4	X	X	X
Transmembrane 9 superfamily member	A0A5F5XIC8	TM9SF4	X	X	X
Transmembrane p24 trafficking protein 10	M3VWQ5	TMED10	X	X	X
Transmembrane p24 trafficking protein 2	M3W0X6	TMED2	X	X	X
Transmembrane p24 trafficking protein 7	A0A2I2UKF8	TMED7	X	X	X
Transmembrane p24 trafficking protein 9	A0A2I2UFI9	TMED9	X	X	X
Transmembrane protein 109	M3XFK8	TMEM109	X	X	X
Transmembrane protein 132B	M3WQ37	TMEM132B	X	X	X
Transmembrane protein 33	A0A5F5XQR2	TMEM33	X	X	X
Transmembrane protein 63C	M3WFM6	TMEM63C	X	X	X
Transthyretin	M3WEV9	TTR	--	X	X
Trimethylguanosine synthase	M3WF64	TGS1	X	X	X
Triosephosphate isomerase	M3X9A1	TPI1	X	X	X
Tripartite motif containing 29	A0A337S2K3	TRIM29	X	X	X
Tripartite motif containing 75	A0A337RX39	TRIM75	--	X	X
Tripeptidyl-peptidase 1	A0A2I2V5I2	TPP1	X	--	X
Tropomodulin 4	M3W499	TMOD4	X	X	X
Tropomyosin 4	M3WAL8	TPM4	X	X	X
Trypsin	M3WP64	LOC101085453	--	X	X
Tryptophan--tRNA ligase, cytoplasmic	A0A2I2UA14	WARS1	X	X	X
Tubulin alpha chain	A0A2I2UZ20	TUBA4A	X	X	X
Tubulin alpha chain	M3W119	LOC101090556	--	X	X
Tubulin alpha chain	M3WDV2	TUBA5	--	X	X
Tubulin alpha chain	M3WER4	TUBA1A	X	X	X
Tubulin beta chain	M3W0Z9	TUBB4B	X	X	X
Tubulin beta chain	M3WL16	TUBB2A	X	X	X
Tubulin beta chain	M3X7Z9	TUBB	X	X	X
Tubulin gamma chain	A0A341ZMI1	TUBG1	X	X	X
Tubulin polymerization promoting protein family member 2	M3WLJ3	TPPP2	--	X	X
Tubulin tyrosine ligase like 3	M3WNJ6	--	--	X	X
Tubulointerstitial nephritis antigen like 1	A0A337S5K9	TINAGL1	X	--	X
Tumor protein p53 binding protein 1	M3WYM9	TP53BP1	X	X	X
Twisted gastrulation BMP signaling modulator 1	M3X4Y2	TWSG1	X	--	X
Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta	M3WFK3	YWHAB	X	X	X
Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	M3WEZ7	YWHAE	X	X	X
Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma	M3VWG1	YWHAG	X	X	X
U6 snRNA-associated Sm-like protein LSm3	A0A2I2US81	LSM3	X	X	X
U6 snRNA-associated Sm-like protein LSm8	A0A2I2UY34	LSM8	X	X	X
UBC core domain-containing protein	M3W806	LOC123385946	--	X	X
Ubiquinol-cytochrome c reductase core protein 1	M3VXW7	UQCRC1	X	X	X
Ubiquinol-cytochrome c reductase, complex III subunit X	A0A5F5Y5F0	UQCR10	X	X	X
Ubiquitin conjugating enzyme E2 N	M3W1V6	UBE2NL	X	X	X
Ubiquitin conjugating enzyme E2 QL1	A0A337SG23	UBE2QL1	X	X	X

Ubiquitin recognition factor in ER associated degradation 1	M3W1Y3	UFD1	X	X	X
Ubiquitin thioesterase	M3XBE5	OTUB1	X	X	X
Ubiquitin-fold modifier 1	A0A2I2USD4	UFM1	X	X	X
Ubiquitin-like domain-containing protein	A0A2I2UE49	--	--	X	X
Ubiquitin-like domain-containing protein	A0A337SE67	SUMO2	X	X	X
Ubiquitin-like domain-containing protein	M3VWM9	FAU	X	X	X
Ubiquitinyl hydrolase 1	A0A337SI75	USP24	X	X	X
UDP-N-acetylglucosamine transferase subunit ALG13	A0A2I2U8L0	--	--	X	X
Uncharacterized protein	A0A337S6M6	--	--	X	--
Uncharacterized protein	A0A5F5XFU6	LOC101094346	--	X	X
Uncharacterized protein	A0A5F5XPG6	--	--	X	X
Uncharacterized protein	A0A5F5Y6S4	--	--	X	X
Uncharacterized protein	M3WF14	RPL10	X	X	X
Uncharacterized protein	M3WUF6	--	--	X	X
Unconventional myosin-Id	A0A337SUP0	MYO1D	X	X	X
UPAR/Ly6 domain-containing protein	A0A2I2U8K1	ACRV1	X	X	X
Urocanate hydratase	M3WN75	UROC1	--	X	X
Vacuolar ATPase assembly factor VMA21	A0A2I2V587	VMA21	X	X	X
Vacuolar protein sorting 13 homolog C	A0A337SER1	VPS13C	X	X	X
Vacuolar protein sorting-associated protein 16 homolog	M3VXC7	VPS16	X	X	X
Vacuolar proton pump subunit B	M3WIR6	ATP6V1B2	X	X	X
Vasoactive intestinal peptide	M3VY16	VIP	X	X	X
Versican core protein	A0A2I2UH10	VCAN	X	X	X
Very long-chain specific acyl-CoA dehydrogenase, mitochondrial	A0A337SL36	ACADVL	X	X	--
Vesicle amine transport 1	M3WIA9	VAT1	X	X	X
Vesicle associated membrane protein 3	M3W6N1	VAMP3	X	X	X
Vimentin	A0A2I2U8W9	VIM	X	X	X
Vinculin	M3XCV3	VCL	X	X	X
Vitamin D-binding protein	M3W2Z1	GC	--	X	X
Vitelline membrane outer layer 1 homolog	M3W8U6	VMO1	X	X	X
VPS26, retromer complex component A	A0A337S4V0	VPS26A	X	X	X
V-set and immunoglobulin domain containing 8	M3W9R6	VSIG8	X	X	X
V-type proton ATPase catalytic subunit A	M3X6U5	ATP6V1A	X	X	X
V-type proton ATPase subunit	A0A337SG88	ATP6V0D1	X	X	--
WAP four-disulfide core domain protein 2	A0A337SCH3	WFDC2	X	--	X
Wiskott-Aldrich syndrome protein family member	M3W8J1	WASF2	X	X	X
WW domain binding protein 2	A0A337SAP2	WBP2	X	X	--
Xaa-Pro dipeptidase	M3W8R0	PEPD	X	X	X
Zona pellucida binding protein	A0A2I2UDE6	ZPBP	--	X	X
Zymogen granule protein 16B	A0A5F5XBP5	ZG16B	X	--	X

CAPÍTULO 3

FINAL CONSIDERATIONS

I observed in many dealings as a black foreign student that certain factors impact profoundly on the success and emotional well-being of students. One is that to be a professor and a top administrator simultaneously is both a huge responsibility and almost too much power that can be devolved to great advantage and benefit of many, especially in the academic community. I have been fortunate to enjoy the benevolence, support and protection of such powers in FMVZ.

Another is that there is a very thin line between miscommunication and subtle maltreatment of foreign students. It takes sensitive and observant professors to maintain balance in the laboratory. I have also been blessed with such an advisor.

In all, the professors here at UNESP, Botucatu were generally amazing and profound. The level of commitment to excellence is very remarkable.