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VARIANTES GERMINATIVAS IDENTIFICADAS POR SEQUENCIAMENTO TOTAL DE EXOMA EM FAMÍLIAS DE PACIENTES PORTADORES DE CARCINOMAS DE MAMA E COLORRETAL

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre(a) em Tocoginecologia.

Orientador(a): Prof(a). Dr(a). Silvia Regina Rogatto

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Palavras-chave: Câncer colorretal; Câncer de mama; Síndrome de predisposição ao câncer hereditário; Sequenciamento total do exoma.

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RESUMO

Introdução: Estima-se que 5 a 10% de pacientes com câncer são portadores de uma Síndrome de Predisposição Hereditária ao Câncer (SPHC). Embora uma parcela desses pacientes preencha os critérios clínicos clássicos das SPHC, vários não apresentam mutações nos principais genes já descritos nestas síndromes. **Objetivo**: Identificar variantes germinativas em pacientes com câncer de mama e colorretal com história pessoal e/ou familiar destes tumores. **Pacientes e Métodos**: O sequenciamento total do exoma foi utilizado para investigar alterações germinativas em seis pacientes que preenchem os critérios da síndrome do câncer de mama e ovário hereditário (HBOC), cinco deles também apresentaram câncer colorretal. Sete parentes de três famílias também foram incluídos no estudo. As variantes detectadas foram anotadas e filtradas usando o programa VarSeq v.2.2.2 (Golden Helix, Bozeman, MT). Variantes raras (< 1% em bancos de dados) que passaram pelos controles de qualidade e que não foram classificadas como benignas ou possivelmente benignas foram selecionadas para análises subsequentes. Foram também investigadas variantes no número de cópias (CNVs) de DNA raras (p <0,001). Os achados foram comparados com as alterações germinativas já descritas em cânceres no COSMIC (*https://cancer.sanger.ac.uk/census*). **Resultados**: Foram identificadas seis variantes patogênicas (P), cinco provavelmente patogênicas (LP), 2121 variantes de significado incerto (VUS) e 1848 CNVs. *ZDHHC11B* (c.780C>G) (P) e *XPC* c.2348C>T (VUS) presentes em membros da família 1 podem ter papel na predisposição hereditária ao câncer. Na família 2 não foram identificadas variantes candidatas à predisposição hereditária. Contudo, dois membros desta família apresentaram CNVs em *BCL3* (19q13) e *CARD11* (7p22.2), coincidentes com regiões de sítios frágeis. Todos os indivíduos testados da família 3 apresentaram a variante LP em *NOS3* (p.Pro115Glyfs*3), um gene candidato ao risco de câncer nesta família. A probanda da família 3 apresentou uma perda heterozigota nos genes *ROBO1* e *ROBO2*, os quais foram previamente descritos na síndrome do câncer de mama e colorretal hereditários. A irmã gêmea da probanda da família 3 (não afetada) apresentou perda heterozigota em *MUTYH* (patogênica), um gene associado ao risco aumentado de desenvolver câncer colorretal e pólipos adenomatosos. Os membros da Família 3 apresentaram deleções em regiões de sítios frágeis (*MACROD2*, *LRP1B*, *DMD*, *PTPRD*). Dois probandos (pacientes 11 e 13) apresentaram deleção heterozigota no gene *PMS2*, o qual está associado à Síndrome de Lynch, e ganhos em *POLE2*, um gene associado à predisposição hereditária ao câncer colorretal. A paciente 13 também era portadora da variante *PTCH1*(c.140G>T), previamente associada a HBOC. A paciente 12 apresentou a variante *WRN* c.95A>G (VUS), um candidato à predisposição hereditária ao câncer. Seis probandos apresentaram variantes em genes descritos como alvos para terapia ou associados ao prognóstico. **Conclusão**: Foram identificadas variantes e CNVs germinativas com potencial de risco ao desenvolvimento de SPHC, além de alterações em genes já descritos como marcadores prognósticos e/ou alvos acionáveis de tratamento.

Palavras-chave: câncer de mama, câncer colorretal, sequenciamento total do exoma, síndrome de predisposição ao câncer hereditário, síndrome de predisposição hereditária ao câncer de mama e ovário.

ABSTRACT

Introduction: It is estimated that 5 to 10% of cancer patients carry a hereditary predisposition to cancer syndromes (HCPS). Though a set of these patients fulfill the classic clinical criteria of HCPS, several do not present mutations in the main genes already described in these syndromes. **Objective**: Identify germline variants in patients with breast and colorectal cancer with family and/or personal history of these tumors. **Patients and Methods**: whole exome sequencing was used to investigate germline alterations in six patients that fulfill the criteria of hereditary breast and ovarian cancer (HBOC). Five patients also presented colorectal cancer. Seven relatives of three families were also included in the study. The detected variants were annotated and filtrated using the VarSeq v.2.2.2 software (Golden Helix, Bozeman, MT). Rare variants (<1% in databases) that underwent quality control and that were not classified as benign or possibly benign were selected for subsequent analyses. Rare copy number variants (CNVs) (p <0,001) were also investigated. The findings were compared with germline alterations described in cancers on COSMIC *(https://cancer.sanger.ac.uk/census*). **Results**: Six variants were pathogenic (P), alongside five probably pathogenic variants (LP), 2121 variants of uncertain significance (VUS) and 1848 CNVs. *ZDHHC11B* (c.780C>G) (P) e *XPC* c.2348C>T (VUS) present in Family 1 members may have a role in hereditary cancer predisposition. In Family 2, no candidate variants to hereditary cancer predisposition were identified. However, two members of this Family presented CNVs in *BCL3* (19q13) and *CARD11* (7p22.2), coinciding with fragile site regions. All tested individuals of Family 3 presented the LP variant in *NOS3* (p.Pro115Glyfs*3) a candidate gene to cancer risk in this Family. The Family 3 proband presented a heterozygote loss in *ROBO1* and *ROBO2* genes, which have been previously described in breast and colorectal hereditary cancer syndrome. The twin sister of family 3's proband (not affected) presented heterozygote loss in *MUTYH* (P), a gene associated with a higher risk of developing colorectal cancer and adenomatous polyps. Family 3 members presented deletions in fragile site regions (*MACROD2, LRP1B, DMD, PTPRD*). Two probands (patients 11 and 13) presented heterozygous deletion in *PMS2* gene, which is associated with Lynch Syndrome, and gains in *POLE2,* a gene associated with hereditary colorectal cancer. Patient 13 also carried variant *PTCH1*(c.140G>T), previously associated with HBOC. Patient 12 presented variant *WRN*c.95A>G (VUS), a candidate gene to hereditary cancer predisposition. Six probands presented variants in genes described as targets therapy or associated to prognosis. **Conclusion**: Germline variants and CNVs with a potential risk of developing SPHC were identified. Additionally, alterations in genes previously described as prognostic markers and/or actionable treatment targets were also identified.

Keywords: breast cancer, colorectal cancer, exome sequencing, hereditary cancer predisposition syndromes, hereditary breast and ovary cancer syndrome.

LISTA DE SIGLAS E ABREVIATURAS

ACMG*	American College of Medical Genetics and Genomics
AT	Adenocarcinoma Tubular
ºC	Grau Celsius
CA	Câncer
CCR	Câncer Colorretal
CDI-NE	Carcinoma de Mama Ductal Invasivo Tipo Não Específico
CE	Câncer de Endométrio
CEP	Comitê de Ética em Pesquisa
CG	Câncer Gástrico
ClinGen*	Clinical Genome Resource
ClinVar*	Clinical Genome Resource
cnLOH*	Copy Loss of Heterozygosity
CM	Câncer de Mama
CNVs	Variações do Número de Cópias
CONEP	Comissão Nacional de Ética em Pesquisa
COSMIC*	Catalogue of Somatic Mutations in Cancer
CP	Câncer de Próstata
Crom.	Cromossomo
CT	Quimioterapia
DGV	Database of Genomic Variants
DK*	Denmark
DNA*	Deoxyribonucleic Acid
FAP	Polipose Adenomatosa Familiar
FCCTX	Câncer Colorretal Familiar Tipo X
FS*	Strand Bias-Fisher
GQ	Qualidade dos Genótipos
HBOC*	Hereditary Breast and Ovarian Cancer Syndrome
HBCC*	Câncer de Mama e Colorretal Hereditários
HER2	Receptor do Fator de Crescimento Epidérmico Humano 2
HNPCC*	Câncer Colorretal Hereditário não Poliposo
HumCFS*	Database of Human Chromosomal Fragile Sites
IARC*	International Agency for Research on Cancer
INCA*	Instituto Nacional do Câncer
InSiGHT*	International Society of Gastrointestinal Hereditary Tumors
Kbp*	Kilo base
LFS	Síndrome de Li-Fraumeni
LoF*	Loss of Function
LoH*	Loss of heterozygosity
LP	Provavelmente Patogênicas
LR-PCR	Long Range PCR
MAP	Polipose Associada ao *MUTYH*
Mb*	Mega base
uL	Microlitros
MMR*	Mismatch Repair
MTP	Múltiplos Tumores Primários
NCCN*	National Cancer Institute

NCBI*	National Center for Biotechnology Information
ND	NanoDrop
NGS*	Next Generation Sequencing
OMS	Organização Mundial da Saúde
OV	Câncer de Ovário
P	Patogênica
pb*	Pares de Bases
PCR*	Polymerase Chain Reaction
QT	Quimioterapia
RefSeq*	Reference Sequence
RNA*	Ribonucleic Acid
ROS	Espécies Reativas de Oxigênio
RT	Radioterapia
SAV*	Software Analysis Viewer
SET	Sequenciamento Total do Exoma
SL	Síndrome de Lynch
SNP	Polimorfismos de nucleotídeos únicos
SPHC	Síndromes de Predisposição Hereditária ao Câncer
TNM	Estadiamento do Câncer
VUS	Variante de Significado Incerto
DGV*	Database of Genomic Variants

*siglas ou abreviaturas derivadas do inglês;

SUMÁRIO

1. INTRODUÇÃO

Os dados coletados pelo *Global Cancer Observatory*, da Agência Internacional de Pesquisa sobre o Câncer (IARC) (*https://gco.iarc.fr/*) reportam que o câncer foi responsável por cerca de 10 milhões de mortes no mundo em 2020 (MAO et al., 2022; PRAMESH et al., 2022; SUNG et al., 2021). Segundo os dados do INCA – Instituto Nacional do Câncer (*https://inca.gov.br/*), no Brasil estima-se 483 mil novos casos de câncer no triênio de 2023 a 2025, excluindo os casos de câncer de pele não melanoma. Espera-se um crescimento exponencial em 50% de novos casos no mundo até 2040, resultando em uma taxa de incidência significativa de aproximadamente 28,4 milhões (SUNG et al., 2021a). O câncer de mama (CM) destaca-se entre aqueles que mais preocupam a população mundial, superando o câncer de pulmão em incidência e atingindo 2,3 milhões de novos casos (11,7%) (BARRIOS, 2022; GRABINSKI; BRAWLEY, 2022). O câncer colorretal (CCR) representa 10% dos casos de câncer diagnosticados em todo o mundo, afetando principalmente homens (MORGAN et al., 2023).

Considerado um problema mundial de saúde (BRAY et al., 2018), o câncer afeta sobretudo países pobres e com poucos recursos (PRAMESH et al., 2022) sendo a principal causa de morte no mundo e um forte dilema para o aumento da expectativa de vida em todos os países (PRAMESH et al., 2022). Esses dados refletem o envelhecimento, o crescimento populacional e o desenvolvimento socioeconômico que, em suma, propiciaram a mudança na prevalência e distribuição dos principais fatores de risco para o câncer (XIA et al., 2022). Os principais fatores de risco incluem a história familiar de câncer, idade, tabagismo, obesidade, exposição a substâncias químicas e radiação, dieta pouco saudável e infecções virais (LEWANDOWSKA et al., 2019). A redução à exposição a esses fatores de risco pode ajudar a diminuir o risco geral de desenvolver a doença (GINSBURG et al., 2017; XIA et al., 2022). Deste modo, é de extrema importância o rastreamento da doença para a sua prevenção e diagnóstico precoce (GINSBURG et al., 2017; XIA et al., 2022).

O câncer é resultante do acúmulo de alterações genéticas e epigenéticas (LEWANDOWSKA et al., 2019; TAKESHIMA; USHIJIMA, 2019). Essas alterações se manifestam como aberrações cromossômicas ou em genes particulares, as quais contribuem para a instabilidade genética (TAKESHIMA; USHIJIMA, 2019). O câncer pode ser classificado em esporádico ou hereditário. Dentre esses, os esporádicos são a maioria, e os provenientes de variantes herdadas representam 5 a 10% dos casos (AKCAY et al., 2021a). As

síndromes de predisposição hereditária ao câncer (SPHC) podem ser explicadas pela presença de alterações na linhagem germinativa de genes envolvidos na regulação do ciclo celular, no sistema de reparo a erros do DNA e apoptose, entre outros (AGAOGLU; DOGANAY, 2021; CAPELLINI et al., 2021a; CAVAILLÉ et al., 2021). As SPHC são frequentemente caracterizadas por alterações genéticas que aumentam o risco de indivíduos de uma mesma família apresentarem determinados tipos tumorais. São características dos portadores de SPHC: a presença de câncer em idade jovem, histórico familiar de câncer, membros da família e caso índice (probando) apresentarem variantes patogênicas em genes supressores tumorais de alta penetrância (linhagem germinativa) e risco aumentado de desenvolvimento de múltiplos tumores (AGAOGLU; DOGANAY, 2021; VILLACIS et al., 2017b).

Dentre as SPHC mais estudadas e seus respectivos genes de alta penetrância estão incluídas a síndrome do Câncer de Mama e Ovário Hereditários (HBOC), caracterizada por variantes patogênicas principalmente nos genes *BRCA1* e *BRCA2* (FANALE et al., 2022; YOSHIDA, 2020). Estes dois genes são classificados como supressores tumorais estão envolvidos em aspectos fundamentais do metabolismo celular, como o reparo de danos ao DNA, a regulação da expressão genética e o controle do ciclo celular (PETRUCELLI; DALY; PAL, 1993). O gene *BRCA1* está mapeado no braço longo do cromossomo 17 (17q21) e codifica uma proteína com 1863 aminoácidos (CORNELISSE; CORNELIS; DEVILEE, 1996). Sua principal função é reparar o DNA por meio da recombinação homóloga por excisão de nucleotídeos, além de regular o ciclo celular (CORNELISSE; CORNELIS; DEVILEE, 1996). Devido a mutações ou inativação epigenética sua expressão é reduzida promovendo a diferenciação alterada da glândula mamária e aumentado risco de desenvolvimento de câncer de mama. Este supressor tumoral presente em todas as células é essencial para a manutenção da integridade do genoma (CORNELISSE; CORNELIS; DEVILEE, 1996). Por sua vez, o gene *BRCA2* está mapeado no braço longo do cromossomo 13 (13q12.3) e codifica uma proteína com 3428 aminoácidos (WOOSTER et al., 1994). O produto proteico do *BRCA2* interage com a proteína RAD51 para reparar as quebras na dupla fita de DNA (CRUZ et al., 2018). As mutações no gene *BRCA* são transmitidas por herança autossômica dominante (BARETTA et al., 2016). A potencialidade carcinogênica pode surgir em células germinativas quando ambas as cópias destes genes supressores, *BRCA1* e *BRCA2*, perdem sua função devido a mutações na linhagem germinativa, seguidas por um segundo evento que silencia o gene (KOTSOPOULOS, 2018). Quando esses genes perdem sua função, eles são incapazes de controlar o ciclo celular, estimular o sistema de reparo ou a apoptose, o que pode levar a efeitos carcinogênicos (BARETTA et al., 2016; KOTSOPOULOS, 2018).

Outros exemplos de SPHC incluem a Síndrome de Lynch (SL), a Polipose Adenomatosa Familiar (FAP e a Síndrome de Li Fraumeni (LFS). A SL está associada ao risco de desenvolvimento de tumores colorretais e é caracterizada pela presença de variantes patogênicas em genes do sistema de reparo a erros de pareamento do DNA (MMR – *Mismatch Repair*) (para revisão, YU et al., 2017). Os principais genes envolvidos nessa condição incluem *MLH1, MSH2, MSH6, PMS2 e EPCAM*. A FAP está associada a variantes no gene *APC*, o qual é responsável por codificar uma proteína que regula a replicação do DNA e a divisão celular (para revisão, CAPELLINI et al., 2021b; LI et al., 1988; NICHOLS et al., 2001; PIOMBINO et al., 2020). A Síndrome de Li-Fraumeni (LFS) tem herança autossômica dominante e alta penetrância, e, é caracterizada por variantes patogênicas no gene *TP53* (LI et al., 1988), O *TP53* é um supressor tumoral, responsável por codificar a proteína p53 que desempenha um papel crítico na regulação do crescimento e divisão celular, monitorando os danos ao DNA e iniciando o reparo ou induzindo a morte celular se o dano não for passível de reparo (HASSIN; OREN, 2023). Em células saudáveis a proteína induz a expressão dos genes *GADD45*, *WAF1/p21/CIP1*, *cyclinG*, *Bax* e *MDM2*) que regulam a parada do ciclo celular e a apoptose (HONDA; TANAKA; YASUDA, 1997). Além disso, os níveis de proteína p53 são mantidos baixos por meio da degradação proteassômica constitutiva, instruída pelo MDM2, que é o principal inibidor de p53 (HONDA; TANAKA; YASUDA, 1997). A função da p53 pode ser interrompida devido a mutações no gene *TP53*, levando ao surgimento de diversos tipos de câncer (DE ANDRADE et al., 2021). As variantes de *TP53* podem ser agrupadas em três categorias principais com base em suas consequências funcionais: 1) variantes que levam à perda de função (LOF) e resultam em haploinsuficiência; 2) variantes que conferem ganhos de função (GOF); e 3) variantes que comprometem as atividades de transativação e apresentam efeito dominante negativo (DE ANDRADE et al., 2021). Tumores que possuem mutações no *TP53* tendem a se desenvolver mais rapidamente, responder inadequadamente aos tratamentos antitumorais e apresentar um prognóstico desfavorável (HU et al., 2021a). Assim, a utilização de terapias direcionadas ao *TP53* é uma estratégia promissora no combate ao câncer (OLIVIER; HOLLSTEIN; HAINAUT, 2010).

Embora muitos pacientes se enquadrem nos critérios clínicos das SPHC, um número significativo não apresentam variantes patogênicas nos genes de alta penetrância ou em genes já descritos anteriormente como associados a tais síndromes (GARBER; OFFIT, 2005a; VILLACIS et al., 2017b). Este fato dificulta o diagnóstico preciso de um câncer hereditário (GARBER; OFFIT, 2005b). Estudos apontam que cerca de 30% dos pacientes com LFS não possuem variantes no gene *TP53* (VARLEY et al., 1997). Em um estudo envolvendo 2.365

indivíduos, pertencentes a 116 famílias brasileiras distintas com suspeita de SL, 61,2% dos casos não apresentaram variantes nos genes de reparo a erros de pareamento (CARNEIRO DA SILVA et al., 2015). Em um estudo com 21.401 famílias alemãs, aproximadamente 76% dos pacientes analisados com HBOC não apresentaram variantes patogênicas nos genes *BRCA1* e *BRCA2* (KAST et al., 2016). Os avanços na tecnologia de sequenciamento têm permitido a identificação de variantes funcionais em outros genes associados ao risco de desenvolvimento das SPHC. Estes achados contribuem para o aconselhamento genético e adoção de medidas de rastreamento precoce, os quais permitem o desenvolvimento de estratégias de redução de risco mais efetivas (FELICIO et al., 2021) a fim de detectar o tumor em estágio inicial e, assim, receber o tratamento adequado (HUANG et al., 2021).

5. CONCLUSÃO

No presente estudo, utilizando os critérios estabelecidos pelo ACMG e ClinVar, foram detectadas cinco variantes P, 39 LP e 2.161 VUS. Não foram observadas variantes em genes clássicos associadas ao fenótipo das famílias aqui estudadas, como *BRCA1* e *BRCA2*. Entretanto, este estudo permitiu a identificação de novos genes potenciais na predisposição hereditária ao câncer de mama e câncer colorretal assim como marcadores prognósticos e alvos acionáveis de drogas. A seguir, serão listadas as variantes mais relevantes identificadas.

Foram identificadas variantes em supressores tumorais e oncogenes que podem ter atuar como um fator de risco ou terem papel prognóstico. Todos os membros investigados da família 1 apresentaram as variantes em *XPC* c.2348C>T (probanda e filha III-1), *EP300* c.6418G>A (probanda e filha III-1) e *ZDHHC11B* c.780C>G. A família 2 não apresentou variantes relacionadas ao risco da doença. Na família 3, foram identificadas as variantes em *NOS3* p.Pro115Glyfs*3 (probanda IV-1, mãe III-2 e irmã IV-II), *XPA* c.89G>A (NM_000380.4) (probanda e mãe IV-2) e *NOTCH2* c.4922A>C (NM_024408.4) (probanda e mãe (IV-2). A paciente 12 apresentou uma variante em *WRN* c.95A>G e a paciente 13 apresentou a variante em *PTCH1* c.140G>T. Estes achados destacam a importância desses genes na predisposição ao câncer nessas famílias e sugerem a necessidade de investigações adicionais para compreender melhor o seu impacto e possíveis implicações clínicas.

Ao todo, foram identificadas 20 variantes em marcadores prognósticos. Esses resultados fornecem informações valiosas sobre o perfil genético dos pacientes, ajudando a direcionar o tratamento de forma mais individualizada e a melhorar as perspectivas de sobrevivência e a sua qualidade de vida. Além disso, 13 variantes ocorrem em genes candidatos a alvos acionáveis de tratamento.

A presença de CNVs raras foi um achado frequente na maioria dos pacientes do estudo. Interessantemente, membros das famílias 2 e 3 apresentaram CNVs em genes que se mapeiam em regiões de sítios frágeis. Estas regiões são propensas a alta instabilidade genética, podendo ser uma possível explicação para o risco aumentado de tumores nestas famílias. Essa hipótese é reforçada pelo fato de que regiões de sítios frágeis serem herdadas. A presença de CNVs nessas regiões específicas fornece uma explicação alternativa para o fenótipo observado nos pacientes, ampliando nosso entendimento sobre os mecanismos genéticos subjacentes ao desenvolvimento tumoral.

Adicionalmente, a análise das CNVs revelou alterações nos genes *PMS2* e *POLE2*.O gene *PMS2* é um componente fundamental do sistema de reparo a erros de pareamento do DNA.

Foi identificada uma deleção heterozigota no gene *PMS2* nas pacientes 11 e 13 e um ganho significativo na paciente 12. A primeira pode estar associada à predisposição ao câncer, entretanto o ganho em *PMS2* está localizado em uma região de sobreposição com o pseudogene e, portanto, não podemos afirmar se há relevância para o fenótipo. O ganho em *POLE2* nas pacientes 11 e 13 é um achado significativo, pois mutações nesse gene estão associadas a síndrome de predisposição ao câncer colorretal e câncer de endométrio.

Um dos grandes dilemas do sequenciamento é a identificação de VUS e seu papel no risco da doença. Neste estudo foram identificadas várias VUS em genes com relevância para o fenótipo em estudo. Entretanto, há a necessidade de análises adicionais, como ensaios funcionais para confirmar sua associação ou especificidade com o fenótipo acrescida de novos dados que possam ser disponibilizados em literatura.

A análise do sequenciamento do exoma em famílias com câncer de mama e colorretal permitiu identificar variantes de potencial significado para o fenótipo além de alterações que podem contribuir como marcadores prognósticos e alvos terapêuticos.

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