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VARIANTES PATOGÊNICAS DO GENE *PALB2* ASSOCIADAS A DOENÇAS ONCOLÓGICAS: REVISÃO SISTEMÁTICA

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Trabalho de Conclusão de Curso apresentado no VIII Congresso de Ciência, Tecnologia e Inovação da PUC Goiás como parte dos requisitos necessários para obtenção do Grau de Bacharel em Medicina.

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RESUMO

INTRODUÇÃO: O gene *PALB2*, “parceiro” e localizador do *BRCA2*, é, frequentemente, associado à suscetibilidade ao câncer de mama, considerado um gene de moderada penetrância. Foi identificado pela primeira vez, em 2006, como gene supressor de tumor, o *PALB2* afeta, indiretamente, a expressão do *BRCA2* e as mutações de perda de função do *PALB2* causam instabilidade na via de reparo de recombinação homóloga do DNA. Mutações germinativas monoalélicas, do *PALB2*, foram descritas em estudos de câncer de mama, ovário, pâncreas e próstata. Além disso, sugere-se ainda que as neoplasias malignas da mama associadas, apresentam fenótipo mais agressivo. **OBJETIVO:** Identificar as variantes patogênicas da linhagem germinativa do gene *PALB2* mais frequentemente associadas a doenças oncológicas. **MÉTODOS:** Trata-se de revisão sistemática da literatura de publicações, em todo o mundo, acerca das variantes patogênicas do gene *PALB2* associadas a doenças oncológicas, dos últimos 5 anos (publicações entre 2017 e junho de 2022), nas bases de dados: PubMed, Science Direct e Periódico Capes. Quarenta e oito artigos foram incluídos nesta revisão. **RESULTADOS:** Um total de 129 variantes germinativas patogênicas do gene *PALB2* foi identificado neste estudo. Destas, 111 estavam associadas ao câncer de mama, 10 ao câncer de mama masculino, 10 ao câncer de pâncreas, 4 ao câncer de ovário e 4 ao câncer de próstata. A variante c.172_175delTTGT, associada aos cânceres de mama, pâncreas, ovário e próstata, foi identificada em 8/48 (16,66%) artigos, e c.509_510delGA, também, foi referida em 8 (16,66%) estudos, relacionada aos cânceres de mama e próstata. A associação entre câncer de mama feminino e masculino foi associada a c.3549C>G e a c.2257C>T. Três variantes foram relacionadas ao câncer de mama e pâncreas, sendo elas: c.2167_2168del, c.3256C>T e c.3113G>A. **CONCLUSÃO**: Mutações na linhagem germinativa do gene *PALB2* propiciam aumento no risco de desenvolvimento de neoplasias de mama, ovário, pâncreas e próstata. A identificação dos portadores das variantes patogênicas é de fundamental relevância para o acompanhamento individualizado desses indivíduos, além de possibilitar o delineamento de um tratamento específico.
Palavras-chave: PALB2; neoplasias; mutação.

ABSTRACT

INTRODUCTION: The *PALB2* gene, partner and localizer of *BRCA2*, is often associated with susceptibility to breast cancer, considered a moderate penetrance gene. First identified in 2006 as a tumor suppressor gene, *PALB2* indirectly affects *BRCA2* expression and loss-of-function mutations in *PALB2* cause instability in the DNA homologous recombination repair pathway. *PALB2* germline monoallelic mutations have been described in studies of breast, ovarian, pancreas and prostate cancer. In addition, it is also suggested that associated malignant breast neoplasms have a more aggressive phenotype. **OBJECTIVE:** To identify the pathogenic germline variants of the *PALB2* gene most frequently associated with oncological diseases. **METHODS**: This is a systematic literature review of publications, worldwide, about the pathogenic variants of the *PALB2* gene associated with oncological diseases, from the last 5 years (publications between 2017 and June 2022), in PubMed databases, Science Direct and Periódico Capes. Forty-eight articles were included in this review. **RESULTS:** A total of 129 pathogenic germline variants of the *PALB2* gene were identified in the study. Of these, 111 are associated with breast cancer, 10 with male breast cancer, 10 with pancreatic cancer, 4 with ovarian cancer and 4 with prostate cancer. The c.172_175delTTGT variant, associated with breast, pancreas, ovarian and prostate cancers, was identified in 8/48 articles (16.66%), followed by c.509_510delGA, also reported in 8 studies (16.66%). related to breast and prostate cancer. The association between female and male breast cancer was identified in c.3549C>G and c.2257C>T. Three variants were related to breast and pancreatic cancer, namely c.2167_2168del, c.3256C>T and c.3113G>A. **CONCLUSION:** Germline mutations in the PALB2 gene provide an increased risk of developing breast, ovarian, pancreas and prostate cancer. The identification of carriers of pathogenic variants is of fundamental importance for the individualized follow-up of these individuals, in addition to allowing the design of a specific treatment.

Keywords: *PALB2*; neoplasms; mutation.

SUMÁRIO

1 INTRODUÇÃO

Câncer é o nome genérico dado a um conjunto de mais de 100 doenças, caracterizadas pelo crescimento desordenado de células e pela capacidade de invadir tecidos e órgãos vizinhos (INCA, 2020). Não possuindo causa única, os canceres podem ser resultantes de fatores externos (80 a 90%) e internos (10 a 20%) (INCA, 2021). Os fatores podem interagir de diversas formas, dando início ao surgimento do câncer. Os fatores de risco ambientais de câncer são denominados cancerígenos ou carcinogênicos; esses podem alterar a estrutura genética (DNA) das células. Já as causas internas estão ligadas à capacidade do organismo de se defender das agressões externas, como: hormônios, condições imunológicas e mutações genéticas. O fator genético abrange hereditariedade familiar e aspectos étnicos que levam à predisposição à formação dos tumores (oncogênese) (INCA, 2021).

A partir de uma mutação genética, ou seja, de uma alteração no DNA da célula, essas passam a receber instruções errôneas para as suas atividades (INCA, 2021), podendo ocorrer em genes especiais, como os supressores de tumores, os quais atuam retardando a divisão celular, reparando erros do DNA ou induzindo apoptose celular (DUCY et al., 2019). Mutações nesses genes resultam em instabilidade do genoma, o que permite uma série de mudanças genéticas, incluindo: amplificações, deleções, rearranjos e substituições, que, por sua vez, possibilitam o desenvolvimento do câncer (PARK; ZHANG; PAUL, 2014).

Em 2006, Xia et al. identificaram o gene “parceiro” e localizador do *BRCA2*, o *PALB2* (do inglês, *Partner and Localizer of BRCA2*), como um gene supressor de tumor, localizado no cromossomo 16p12.2, compreendido por 13 éxons que codificam uma proteína de 1.186 aminoácidos, sendo uma das principais proteínas de interação com *BRCA1* e *BRCA2*, na manutenção da integridade do genoma.

Mutações bialélicas na linhagem germinativa do *PALB2* estão associadas à anemia de Fanconi, uma síndrome de instabilidade cromossômica, caracterizada por: insuficiência progressiva da medula óssea, anomalias congênitas e predisposição ao câncer (MACEDO; ALEMAS; ASHTON-PROLLA, 2019; ALTER; BEST, 2020). Enquanto nas mutações germinativas monoalélicas do *PALB2*, estão descritos, mais frequentemente, casos de câncer de mama, seguido de câncer de ovário, pâncreas (JANSSEN et al., 2020) e próstata (SWIFT et al., 2019).

O gene *PALB2* afeta, indiretamente, a expressão do *BRCA2* e as mutações de perda de função do *PALB2* causam instabilidade na via de reparo de recombinação homóloga do DNA, evitando o sistema de defesa, resultando em proliferação celular não controlada (DUCY et al., 2019). Além disso, sugere-se ainda que as neoplasias malignas da mama, associadas ao *PALB2*, apresentam fenótipo mais agressivo, envolvendo o imunofenótipo triplo-negativo (HEIKKINEN et al., 2009), associação com ocorrência de câncer de mama bilateral (COUCH et al., 2017), moderada penetrância (WU et al., 2020) e câncer de mama metastático (NEPOMUCENO et al., 2017). Desse modo, mostra-se como um biomarcador promissor para detecção precoce dessas neoplasias (ZHANG, 2013).

O câncer de mama, segundo dados do Globocan (2020), em ambos os sexos, é o câncer com maior incidência, em todo o mundo, ocupando o quinto lugar em mortalidade. Além disso, tem como previsão, para 2040, aumento de 33,8% na incidência e de 51,5% na mortalidade. No Brasil, os óbitos por câncer de mama ocupam o primeiro lugar, no país, representando, 16,1% do total, na mortalidade proporcional, por câncer, em mulheres (INCA, 2021).

O câncer de ovário é a segunda neoplasia ginecológica mais comum no país e tem como fator de risco principal a história familiar, especialmente, em parentes de primeiro grau, e aquelas com predisposição herdada para câncer de ovário, como mutação nos genes *BRCA1* ou *BRCA2* (INCA, 2021). No mundo, ocupa o oitavo lugar dos cânceres com maior incidência e mortalidade, em mulheres. Como também, segundo estimativas para 2040, apresentará aumento de 47,6% de mortalidade e de 36,6% de incidência (GLOBOCAN, 2020).

Já o adenocarcinoma, tipo mais comum de câncer de pâncreas, afeta, na maioria dos casos, o lado direito do órgão (cabeça). Segundo a União Internacional para o Controle do Câncer (UICC), os casos de câncer de pâncreas aumentam com o avanço da idade e têm maior incidência na população masculina. O adenocarcinoma possui alta mortalidade, pois é de difícil detecção, diagnóstico tardio e comportamento agressivo. No Brasil, é responsável por cerca de 2% de todos os tipos de câncer diagnosticados e por 4% do total de mortes causadas pela doença (INCA, 2021).

Segundo o Globocan, é esperado 61,7% de crescimento na incidência de câncer pancreático, de 2020 a 2040, e aumento de 64,2% na mortalidade. Ademais, o câncer de próstata tem altas taxas de incidência, no Brasil e no mundo, ocupando segundo lugar em incidência em homens e tendência de aumento de 58,1%, de 2020

para 2040. Além disso, está previsto crescimento de 92% em sua mortalidade, na população mundial, até 2040 (GLOBOCAN, 2020).

Diante disso, o presente estudo tem como principal objetivo identificar as variantes patogênicas do gene *PALB2* mais frequentemente associadas a doenças oncológicas.

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NOTA: Os itens **Metodologia, Resultados, Discussão e Conclusão** foram subtraídos desta versão, pois o artigo ainda não foi publicado. A versão final será disponibilizada assim que o artigo for publicado.

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ANEXO 1.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**