IMPACTS OF THE RECLASSIFICATION OF *RAD51C* AND *RAD51D* GERMLINE VARIANTS ON THE CLINICAL MANAGEMENT OF HEREDITARY BREAST AND OVARIAN CANCER PATIENTS

Thalia Rodrigues de Souza Zózimo[1,2]; Anisse Marques Chami[3]; Henrique Reis Galvão[4]; Juliana Garcia Carneiro[5]; Maira Cristina Menezes Freire[6]; Thamiris Matias Alves[7]; Agnaldo Lopes da Silva Filho[8]; Maria Raquel Santos Carvalho[1,9]; Letícia da Conceição Braga[1,2]

[1]Programa de Pós-Graduação em Genética, Departamento de Genética, Ecologia e Evolução, Universidade Federal de Minas Gerais; [2]Laboratório de Pesquisa Translacional, Instituto Mário Penna, Belo Horizonte, MG, Brazil; [3]Serviço Especial de Genética Médica do Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil; [4]Dasa Genômica, São Paulo, SP, Brazil; [5]Clínica Personal - Oncologia de Precisão e Personalizada, Belo Horizonte, MG, Brazil; [6]AstraZeneca Diagnósticos,SP, Brazil; [7]Departamento de Genética, Ecologia e Evolução, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Campus Pampulha, Belo Horizonte, MG, Brazil; [8] Programa de Pós-Graduação em Saúde da Mulher da UFMG;

INTRODUCTION

Breast cancer, the second most common cancer worldwide, causes ~700,000 annual deaths[1,2]. Although less frequent, ovarian cancer causes 140,000 annual deaths due to its late-stage diagnosis[3,4]. Approximately, 10% of cases have hereditary predisposition associated with germline variants in homologous recombination repair genes[5]. Interpreting these variants pathogenicity is crucial for improving clinical management and risk assessment[6]. *In silico* analysis of the impact of these variants on gene products is a valuable strategy for cascade screening and preventive diagnosis, aligning with public health policies priorities due to high mortality rates[7,8].

OBJECTIVE

To classify according to potential pathogenicity *RAD51C* and *RAD51D* germline variants identified in patients with breast and/or ovarian cancer mostly.

METHODOLOGY

This project was approved by the Research Ethics Committee (CAAE: 01758418.0.0000.5149) (Fig. 1)

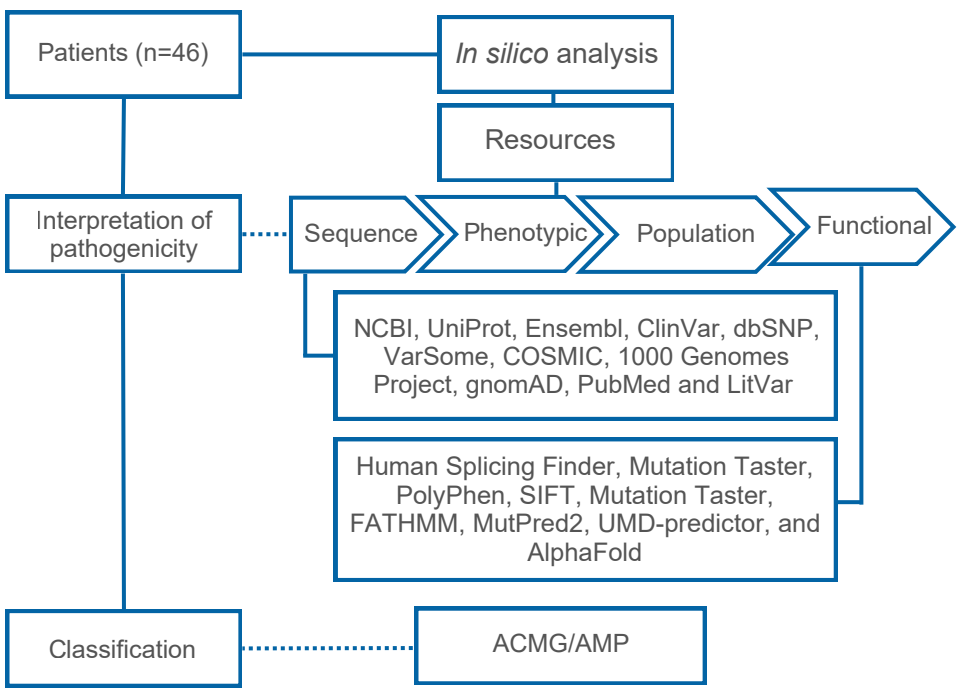

Figure 1. Germline variant analysis flowchart.

RESULTS AND DISCUSSION

Thirty-nine variants identified (*RAD51C*: 19; *RAD51D*: 20). 14 (36%) linked to breast/ovarian cancer history. Mean age at diagnosis: 41.8 years (Fig.2). Most variants were classified as VUS in ClinVar; one was novel (Fig.3).

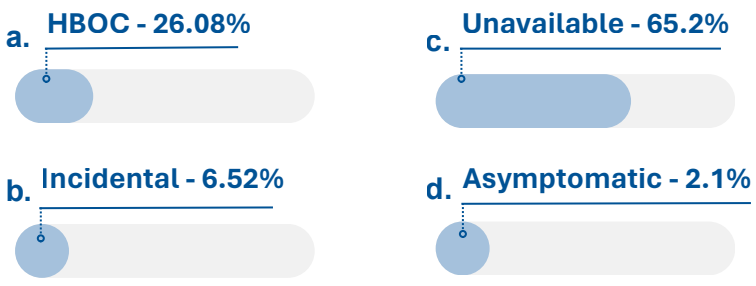

Figure 2. Clinical data

A Eleven variants were described as deleterious by predictive algorithms, showing destabilizing effects on the protein or loss of functional motifs. Furthermore, eight variants were shown to impact on splicing sites, creating new donor and acceptor sites. The RAD51C c.3G>A (p.Met1Ile) variant affects the translation initiation site (Fig.4).

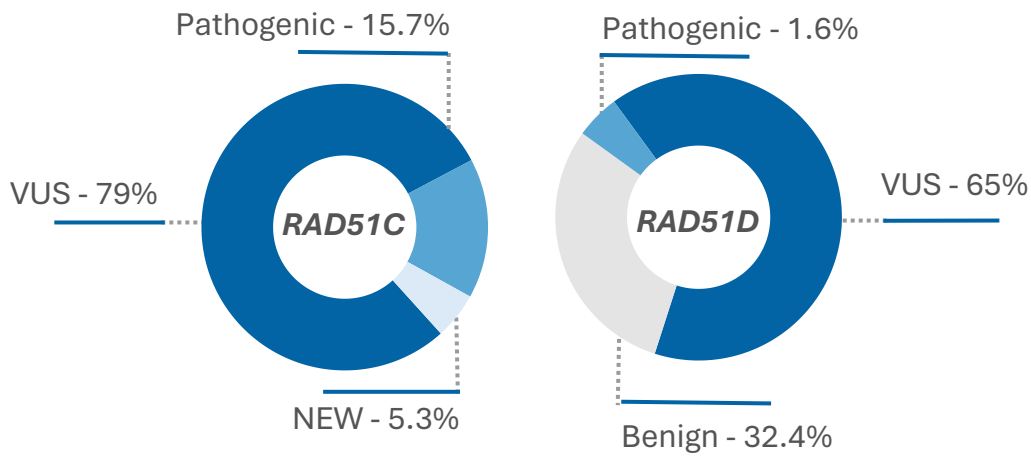

Figure 3. ClinVar classification

The reclassification was mainly based on loss-of-function criteria, low population frequency, and evidence from well-established functional studies.

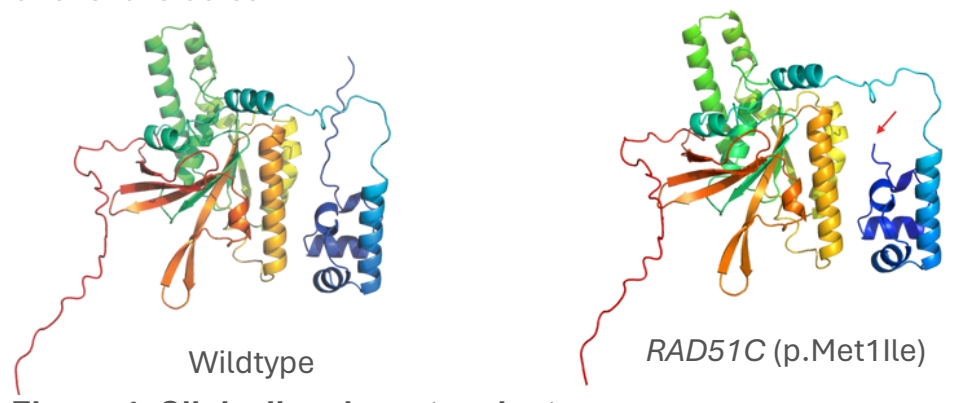

Figure 4. Clinically relevant variant

The reclassified variants were: *RAD51C* c.3G>A (p.Met1Ile), *RAD51C* c.656T>C (p.Leu219Ser), *RAD51C* c.571+4A>G, *RAD51C* c.904G>A (p.Gly302Arg), *RAD51D* c.26G>C (p.Cys9Ser) and *RAD51D* c.137C>G (p.Ser46Cys). The high proportion of VUS highlights the challenge of interpreting *RAD51C/D* variants[9,10]. Integrating predictive, splicing, and structural analyses supported reclassification of six variants as likely pathogenic, underscoring the value of combining clinical, computational, and functional evidence[11,12].

CONCLUSION

Reclassifying these variants from VUS to likely pathogenic underscores the value of genetic testing for cancer diagnosis and risk prediction. Ensuring effective return of reinterpreted results is crucial to advance oncological care and provide tangible clinical benefits for patients.

ACKNOWLEDGMENTS

We are grateful to the FAPEMIG (APQ-02856-23) and Rede Mineira de Pesquisa Translacional em Oncologia (RED 00059-23), and CAPES (Programa de Pós-Graduação em Genética, UFMG)

REFERENCES