Abstracts from the 53rd European Society of Human Genetics (ESHG) Conference: **Interactive e-Posters**
Volume 28 (Supplement 1), 01 Dec 2020
https://www.nature.com/articles/s41431-020-00739-z

P12.022.C

Hereditary breast and ovarian cancer: two cases of double heterozigosity for pathogenic variants in the *BRCA1* or *BRCA2* and *ATM* genes

P. Theisen[1], P. Rodrigues[1], C. Silva[2,3], D. Carpinteiro[2], L. Ribeiro[4], H. Carreiro[5], H. Gervásio[6], J. Leal da Silva[7], L. Vieira[2,3], J. Gonçalves[3]

[1]Molecular Genetics Unit, Human Genetics Department, National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal, [2]Technology and Innovation Unit, Human Genetics Department, National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal, [3]Centre for Toxicogenomics and Human Health (ToxOmics) Nova Medical School, Faculty of Medical Sciences, New University of Lisbon, Lisbon, Portugal, [4]Hematology-Oncology Service, CUF Infante Santo Hospital, Lisbon, Portugal, Lisbon, Portugal, [5]Oncological Risk Consultation, CUF Infante Santo Hospital, Lisbon, Portugal, Lisbon, Portugal, [6]Hematology-Oncology Service, CUF Viseu Hospital, Viseu, Portugal, [7]Medical Oncology Service, Luz Arrábida Hospital, Vila Nova de Gaia, Portugal

Introduction: Hereditary breast and ovarian cancer (HBOC) is estimated to represent 5-10% of all breast and ovarian cancer cases. Pathogenic germline variants in *BRCA1* and *BRCA2* account for 25% of familial cases. The identification of genetic defects in HBOC patients allows detection of carriers that can benefit from cancer risk management protocols, and predictive genetic testing to at-risk family members, after appropriate genetic counseling. Two female patients with a personal and family history of cancer were studied by next-generation sequencing (NGS).

Methods: NGS using TruSight Cancer Panel (Illumina) followed by bioinformatic analysis of 18 genes associated with HBOC was performed. Pathogenic variants were confirmed by Sanger sequencing.

Results: A rare event of double heterozigosity for pathogenic variants was identified in both patients: patient A was heterozygous for *BRCA1:*c.2037delinsCC, p.(Lys679Asn*4) and *ATM:*c.3802delG, p.(Val1268*) and patient B carried both *BRCA2:*c.6001dupT, p.(Ser2001Phefs*2) and *ATM:*3435_3436delTGinsA, p.(Asp1145Glufs*11). After genetic counseling, three relatives of patient A were analyzed: while one of her two healthy sons was heterozygous for the *ATM* variant, the other was a double heterozygote for *BRCA1:*c.2037delinsCC and *ATM:*c.3802delG; a female cousin, recently diagnosed with breast cancer, was a carrier of *ATM:*c.3802delG only.

Conclusions: The identification of these two rare cases of double heterozigosity for pathogenic variants in *BRCA1/BRCA2* and *ATM* genes, highlights the importance of using NGS-gene panel testing in HBOC. If molecular analysis had been restricted to *BRCA* genes only, the pathogenic *ATM* variants would have been missed in both families, depriving them of appropriate genetic counseling and cancer risk management.