Discordancy in interpretation of a BRCA1 variant in the Belgian population

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INTRODUCTION

An accurate classification of BRCA variants is essential for an adapted genetic counselling and management of the patient. The classification of the BRCA1 c.5071A>G or p.(Thr1691Ala) variant remains unclear as it has been classified as variant of unknown significance, likely pathogenic, and more recently as likely benign.

METHODS

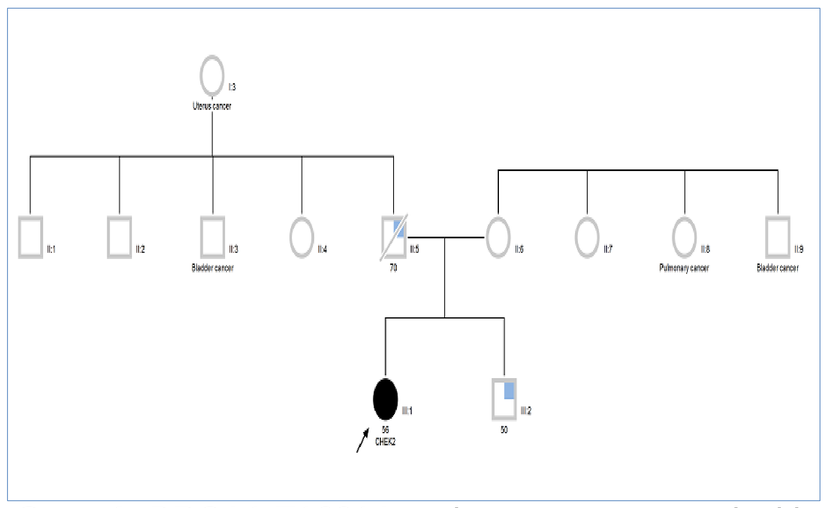
We used ACMG 2015, ACGS 2020, and UK canVIG-UK 2020 assessment methods to classify the variant. We reviewed the personal history and pedigrees of all the carriers included in the CHU de Liège database as of February 2023. We evaluated if the variant segregated with BRCA1 related cancers following an autosomal dominant inheritance.

RESULTS

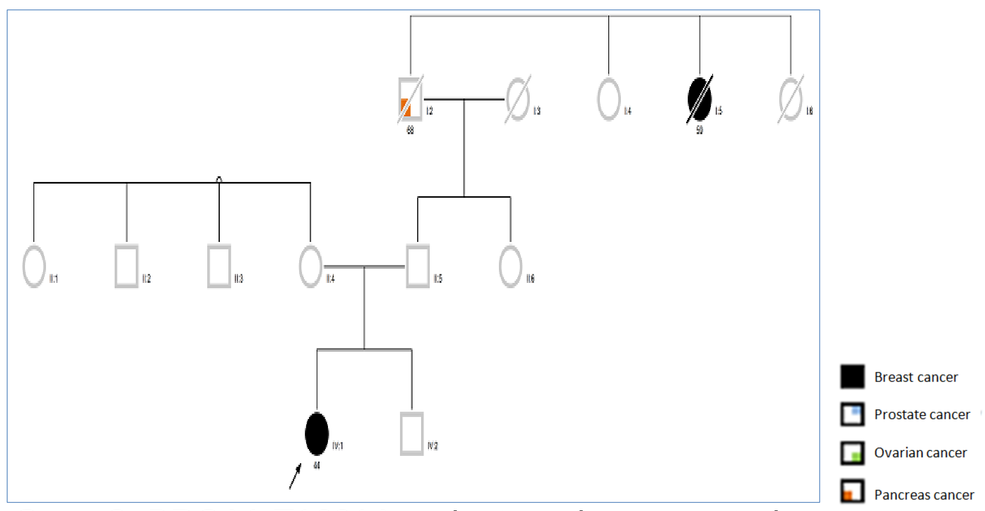
Classifying BRCA1 T1691A variant

This variant consists in a substitution of one nucleotide in a highly conserved amino acid. The physicochemical difference between threonine and alanine is small. It is predicted to be deleterious to protein function by in silico analyses. One functional study[1] reports four different assays in which this variant does not impact protein function. A second functional study[2] suggests this variant as deleterious in one of their three assays, and neutral or intermediate in the other two. It is also described with an intermediate impact on cell survival in another functional study[3].
This variant was described in a patient with ovarian cancer. This variant is absent from control databases.
We classified this variant as **a variant of unknown significance**.
ACMG criteria : PM2_mod, PP3_sup, BS3_supp*.*

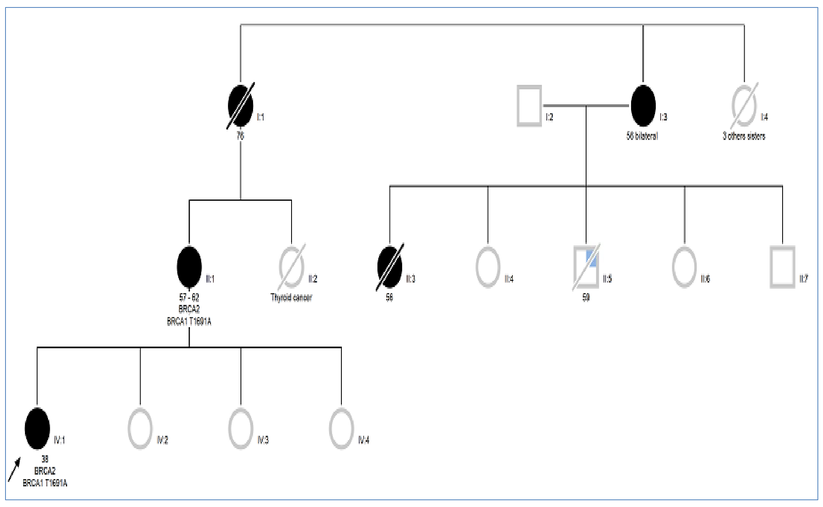
Five probands from CHU de Liège database



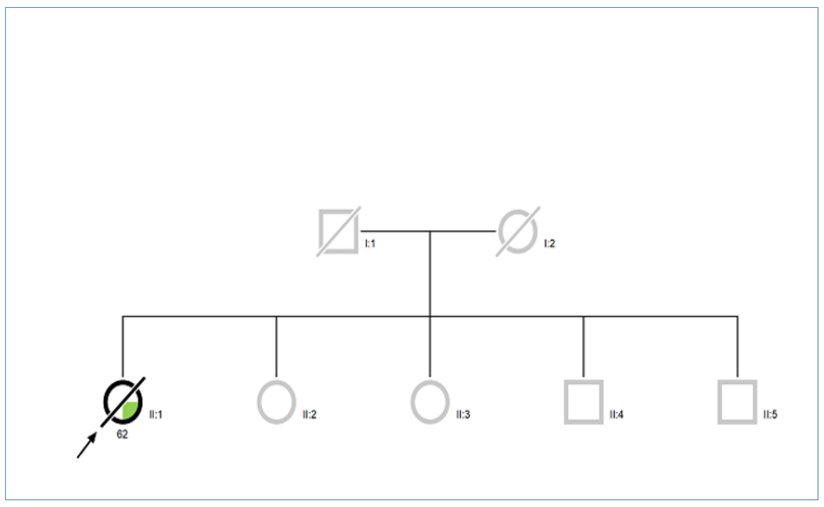
Case 1. BRCA1 T1691A variant co-segregated with a CHEK2 pathogenic variant.



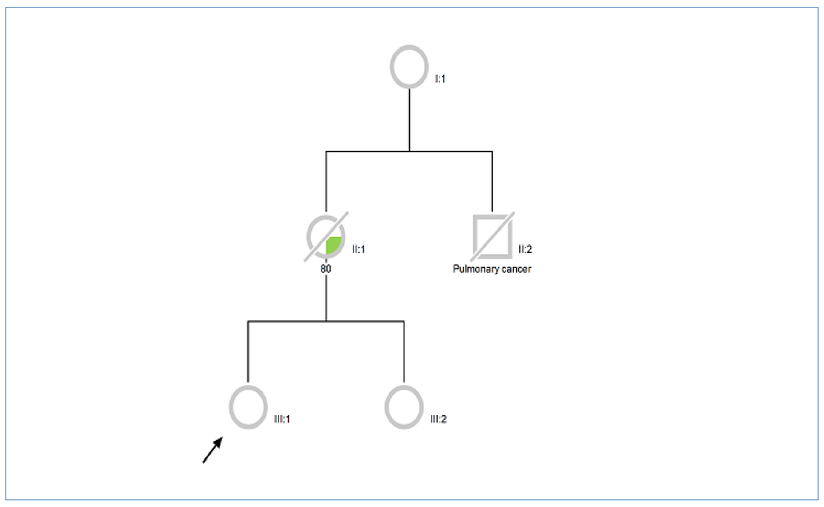
Case 2. BRCA1 T1691A variant carrier presented a second degree familial history of cancer



Case 3. BRCA1 T1691A variant co-segregated with a BRCA2 pathogenic variant.



Case 4. No familial history of cancer



Case 5. No personal history of cancer at 69 years-old.

CONCLUSION

Despite the rarity of this variant in control databases, its frequency seems to be higher than expected in our region suggesting a potential founder effect. Clinical and family history from our patients do not support a pathogenic effect of the variant, although it can not be excluded. We currently classify this variant as a variant of unknown significance. Further data are needed to classify it more precisely.

[1] Petitalot and al., Mol Cancer Res. 2019, [2] Bowman and al., Clin Cancer Res. 2020, [3] Findlay and al., Nature. 2018.