Case report: *de novo BRCA1* pathogenic variant in a woman with breast cancer at age 33

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Introduction

BRCA1 and *BRCA2* are tumour suppressor genes that aid in non-homologous DNA repair. Germline pathogenic variants (PVs) in these genes cause hereditary breast and ovarian cancer syndrome (HBOC). *De novo* PVs in *BRCA1* and *BRCA2* are rare. We present a woman with a *de novo BRCA1* PV diagnosed with breast cancer (BC) at age 33 (Figure 1). Neither of her parents carried this familial variant and parental inheritance testing was done to rule-out a non-paternity event. A *de novo* PV is the most plausible explanation for this case.

Methods

- Patient files, pedigree, and paternity test results were obtained, reviewed and analyzed.
- Available literature on *de novo BRCA1/2* PV cases were reviewed.
- A retrospective chart review was conducted to summarize the frequency and type of *de novo BRCA1/2* PVs reported in literature.

Results

Case presentation

- We present a 33 year old woman with right invasive ductal carcinoma of the breast, confirmed by an ultrasound guided biopsy.
- Lumpectomy and sentinel lymph node biopsy was completed, showing a 1.8cm mass.
- ER (estrogen receptor), PR (progesterone receptor), and HER2 (human epidermal growth factor receptor 2) negative.
- Genetic testing was completed by PCR (polymerase chain reaction) /automated bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA) of genomic DNA from a blood sample.
- An ACMG category 2 likely pathogenic variant in exon 18 of *BRCA1*, c.5144G>A was identified.

Parental inheritance testing

- Mother and father tested negative for the germline pathogenic variant.
- Brother tested negative.
- Sister has not yet been tested.
- Repeat site-specific testing of both parent's blood samples confirmed absence of the *BRCA1* c.5144G>A PV.
- Microsatellite analysis and PCR amplification concluded that the result of parental inheritance was consistent with the family relationship indicated on the pedigree below.

***BRCA1/2* PV case review**

- To date, twelve *BRCA1* (including the present) and six *BRCA2 de novo* PVs have been published
- Most PVs have been identified in patients diagnosed with BC before the age of 40.

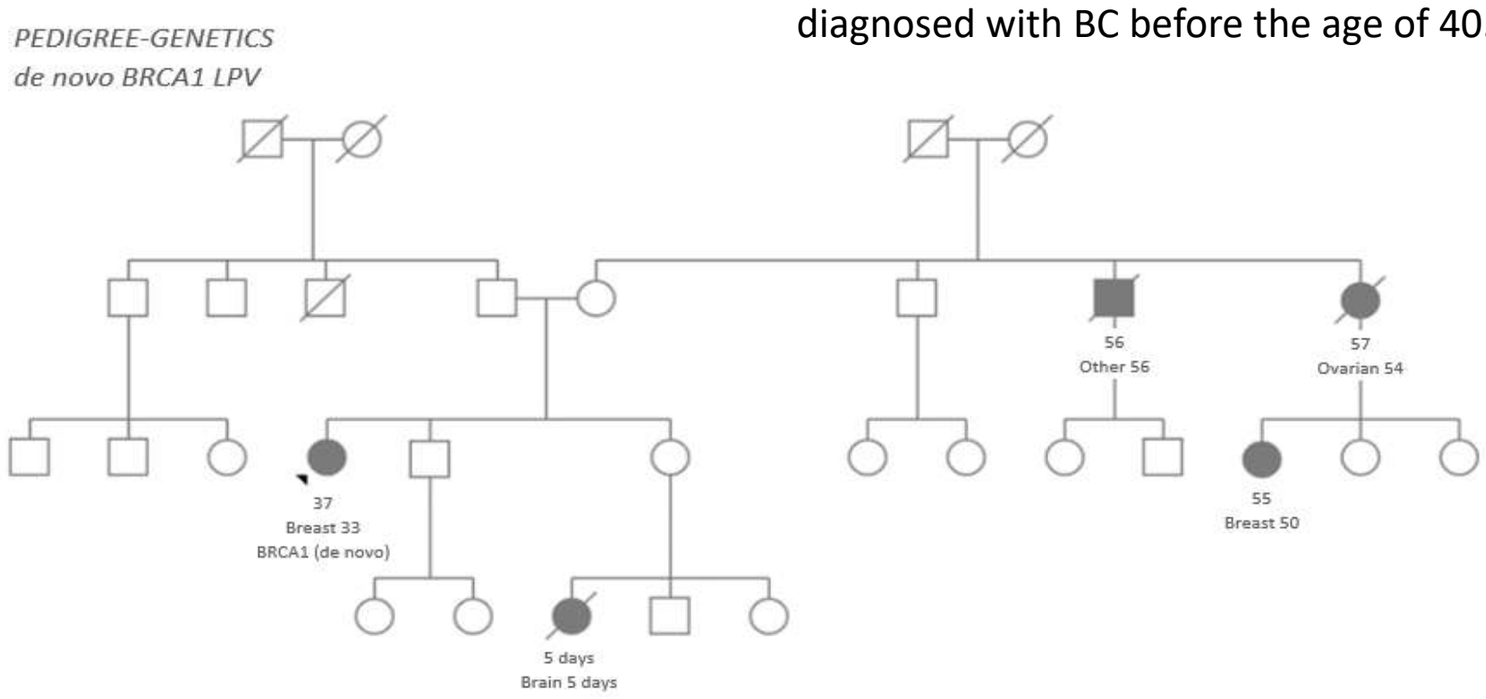

Figure 1. Pedigree of patient carrying the *de novo* LPV in the *BRCA1* gene. An arrow indicates the proband. Type of cancer and age at diagnosis are indicated below.

Discussion and Conclusion

- *De novo* PV is the most plausible explanation for this case of a *BRCA1* c.5144G>A LPV next to a germline mosaicism.
- The event of non-paternity would be highly unlikely as parental inheritance testing was conducted and results sustained the paternity and maternity with high probability.
- To date, twelve cases of *de novo BRCA1* PVs (including the present case), and six cases of *de novo BRCA2* PVs have been reported, most identified in patients diagnosed before the age of 40.
- Cases of *BRCA1* and *BRCA2* PVs are of significant clinical value in breast and ovarian cancer prevention and management.
- Knowledge of the rate of *de novo* PVs would provide additional information to practicing geneticists and to aid in pedigree assessment for the HBOC syndrome in families, as well as identification and referral of probands with a HBOC-phenotype that lack in family history.

Selected References

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We thank the generous support of Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Joey and Mary Furfari Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund, and Ofelia Cancer Research Fund.