

De Novo *BRCA1* Pathogenic Variant in a Woman with Breast Cancer at Age 33: A Case Report

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Abstract

BRCA1 and *BRCA2* are tumor suppressor genes that aid in non-homologous DNA repair. Germline pathogenic variants in these genes cause hereditary breast and ovarian cancer syndrome (HBOC). *De novo* pathogenic variants (PVs) in *BRCA1* and *BRCA2* are rare. In the literature, to date, twelve *BRCA1* (including the present) and six *BRCA2 de novo* PVs have been published. We present a woman of Scottish and English descent, with a *de novo BRCA1* likely pathogenic variant (LPV) diagnosed with triple negative breast cancer at age 33. The patient was referred for genetic counseling. Neither of her parents carried this familial variant and parental inheritance testing was done to rule-out a non-paternity or non-maternity event. A *de novo* LPV is the most plausible explanation for this case. Knowing whether there is a *BRCA1* or *BRCA2* PV is of significant clinical value in breast and ovarian cancer prevention and management. Knowledge of the rate of *de novo* PVs provides additional information to practicing geneticists and genetic counselors to aid in pedigree assessment for the HBOC in families.

Keywords: *BRCA1*; *De novo*; Mutation; Breast cancer; Pathogenic variant

Abbreviations: BC: Breast Cancer; HBOC: Hereditary Breast and Ovarian Cancer; MLPA: Multiplex Ligation-Dependent Probe Amplification; BBC: Bilateral Breast Cancer; OC: Ovarian Cancer; PV: Pathogenic Variant; LPV: Likely Pathogenic Variant; ACMG: American College of Medical Genetics; SIFT: Scale Invariant Feature Transform

Introduction

Up to 10% of breast cancers are thought to be hereditary in etiology and despite multi-gene panel testing, pathogenic variants (PVs) in *BRCA1* and *BRCA2* are still the leading cause of hereditary breast and ovarian cancer syndrome (HBOC). HBOC is characterized by a family history of breast cancer, ovarian cancer, male breast cancer, and to a lesser extent, prostate cancer, pancreatic cancer and melanoma [1,2]. *BRCA1* and *BRCA2* have been tested for over 20 years yet there are very few reported cases of *de novo* PVs in the literature. To the best of our knowledge, 11 cases of *de novo BRCA1* PVs and six cases of *de novo BRCA2* PVs have been reported (Table 1). This study presents a case of a *de novo BRCA1* likely pathogenic variant (LPV) in a 33-year-old woman with triple negative breast cancer.

Case Report

A 33-year-old woman with right invasive ductal carcinoma of the breast was referred for genetic counseling due to her personal and family history of early-onset breast cancer. This patient initially palpated a lump in the right breast and went on to have a mammogram followed by an ultrasound guided biopsy confirming invasive ductal carcinoma. She then completed lumpectomy and sentinel lymph node biopsy which showed a 1.8 cm mass, ER, PR and HER2-negative.

The patient is of Scottish and English descent and has a significant maternal family history of cancer. Her maternal aunt was diagnosed with stage 4 ovarian papillary serous cystadenocarcinoma at the age of 54 and died at age 57. Her maternal cousin was diagnosed with right invasive ductal carcinoma of the breast at age of 50. The patient does not have any known paternal cancer history. Neither her brother nor sister, ages 45 and 43, were diagnosed with cancer.

Genetic testing was completed by PCR/automated bidirectional Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of genomic DNA extracted from a blood sample. An ACMG category 2 likely pathogenic variant (LPV) in exon 18 of *BRCA1* was identified in this patient, c.5144G>A (BIC 5263G>A). This variant results in the substitution of asparagine for the serine at position 1715. In silico analysis by SIFT and POLYPHEN-2 predict this variant to be not tolerated and possibly damaging, respectively. Several functional studies demonstrate this variant is deleterious [3-5] and this variant has also shown to segregate with disease in an extended family [6].

Results

Genetic counseling was then offered to each of the patient's parents. The mother and father tested negative for the *BRCA1* c.5144G>A likely pathogenic variant. A second blood sample was acquired and repeat site-specific predictive testing confirmed both parents tested negative [7-10]. The patient's brother also tested negative whereas the sister has not yet had predictive testing. This finding suggests a *de novo* likely pathogenic variant (Figure 1).

In order to rule out a non-paternity event microsatellite analysis was completed using multiple markers on chromosomes 13, 18, 21, X and Y. PCR amplification of three variable regions followed by capillary electrophoresis allowed comparison of the sizes of the amplified alleles. Nine polymorphic markers were used which showed alleles from both parents for the chromosomes listed above [11-15]. The result

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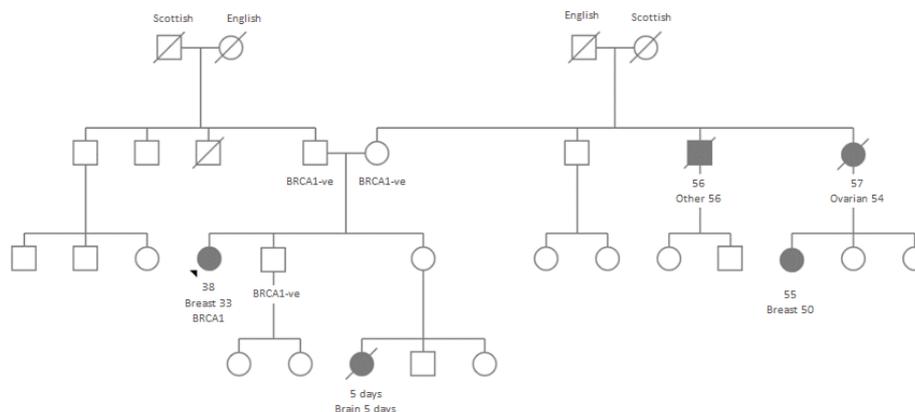


Figure 1: Pedigree of patient carrying the *de novo* likely pathogenic variant in the *BRCA1* gene. An arrow indicates the proband, Type of cancer and age at diagnosis are indicated below, BRCA1-ve indicates family members who have tested negative for the familial BRCA1 LPV.

Genes	(Likely) Pathogenic Variants	Cancer type (age of diagnosis)	Breast/ovarian cancer in family history	References
<i>BRCA1</i>	c.3769_3770delGA	BC (<40)	None	Tesoriero et al. [19]
<i>BRCA1</i>	c.5332+G>A, in intron21	BC (38)	Maternal Aunt BC (<54)	Edwards et al. [7]
<i>BRCA1</i>	Exons 1-12 deletion	BC (30)	None	Kwong et al. [8]
<i>BRCA1</i>	Deletion	BC (28, 37)	None	Garcia-Casado et al. [9]
<i>BRCA1</i>	c.3494_3495delTT	BC (52), OC (53)	None	De-Leeneer et al. [10]
<i>BRCA1</i>	g.146232_149957del	BC (39)	Paternal cousin BC (30)	Delon et al. [11]
<i>BRCA1</i>	c.5468A>G	OC (39)	Two paternal aunts, BC (57, 75)	Golmard et al. [1]
<i>BRCA1</i>	c.2296_2297delAG	BC (31)	None	Golmard et al. [1]
<i>BRCA1</i>	Exons 1-13 deletion	BC (41)	Two sisters BC (62, 63) Paternal grandmother BC (75)	Golmard et al. [1]
<i>BRCA1</i>	Exons 4-6 deletion	BBC (29, 33)	None	Musani et al. [12]
<i>BRCA1</i>	c.5095C>T	BC (32)	None	Antonucci et al. [13]
<i>BRCA1</i>	c.5144G>A	BC (33)	Maternal aunt OC (54)	Tam et al. [1] (this report)
<i>BRCA2</i>	Exon 14, 7260insA	BC (35)	None	Robson et al. [14]
<i>BRCA2</i>	3034del4	BC (39)	Paternal cousin BC (54)	Van der Luijt et al. [15]
<i>BRCA2</i>	c.8754+1G>A	BC (40)	Mother, BC (59)	Hansen et al. [16]
<i>BRCA2</i>	c.5301insA	BC (35)	Paternal grandmother BC (42)	Marshall et al. [17]
<i>BRCA2</i>	c.51dupA	BBC (27, 37)	None	Diez et al. [18]
<i>BRCA2</i>	c.6082_6086delGAAGA	BC (40, 48)	Daughter BC (31)	Golmard et al. [1]

Table 1: Summary of *BRCA1* and *BRCA2* gene PV cases.

was consistent with the family relationship indicated on the pedigree submitted, effectively ruling out a non-paternity event.

Discussion

The LPV *BRCA1* c.5144G>A was found in a patient with early onset triple negative breast cancer and was not found in her biological parents. Her brother also tested negative and her sister has not yet undergone testing. Laboratory error, although plausible is highly unlikely as repeat testing was conducted on separate samples submitted by the patient and her parents. The event of non-paternity would be highly unlikely as parental inheritance testing was conducted, and results sustained the stated paternity and maternity with high probability [16,17].

The most likely explanation for this finding is that the *BRCA1* LPV identified in the proband is *de-novo*. Low-level mosaicism of the *BRCA1* LPV in the patient is another plausible explanation in this scenario. One approach to rule out mosaicism is through punch biopsy, fibroblast culture and DNA extraction however this was declined by the proband. DNA extraction from hair follicles have been reported in the

literature however this process has not been validated by the molecular lab used in this case report [18,19].

To the best of our knowledge, twelve cases of *de novo BRCA1* PVs (including the present case), and six cases of *de novo BRCA2* PVs have been reported (Table 1). Most PVs have been identified in patients diagnosed with breast cancer before the age of 40.

Conclusion

De novo PVs in *BRCA1* and *BRCA2* genes are rare. This case presents a *de novo* LPV in the *BRCA1* gene in a woman with triple negative, early onset breast cancer. Neither parent carries the familial *BRCA1* variant. Paternity testing was done to show true paternity and maternity. Plausible explanations include a *de novo* variant or mosaicism. A further understanding in the frequency and recognition of *de novo BRCA1* and *BRCA2* PVs could be of significant value in pedigree assessment, referral and identification in probands with *BRCA1* and *BRCA2* PVs.

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