The Application of Clinical Genetics

Dovepress

open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

A New de novo *BRCA1* Mutation in a Young Breast Cancer Patient: A Case Report

Amina Scherz[1], Susanna Stoll[2], Benno Rothlisberger[3], Manuela Rabaglio[1]

[1]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Department of Medical Oncology, University Hospital and Stadtspital Triemli, Zurich, Switzerland; [3]GENETICA AG, Zurich, Switzerland

Correspondence: Manuela Rabaglio, Email manuela.rabaglio@insel.ch

Background: *BRCA1* and *BRCA2* genes represent the most investigated breast and ovarian cancer predisposition genes. Ten cases of pathogenic de novo *BRCA1* variations and six cases of pathogenic de novo *BRCA2* variation have been reported at present. Here, we report a new case of a de novo *BRCA1* gene mutation.

Case Presentation: A 30-year-old woman with no health issues and no family history for hereditary breast and ovarian cancer was diagnosed with a hormone receptor positive/HER2 negative invasive breast cancer. Genetic testing revealed a pathogenic variant in *BRCA1* (c.4065_4068delTCAA) which was not found in her parents or sister.

Conclusion: We report a new case of de novo *BRCA1* mutation, confirmed by repeated germline testing of the index patient and her parents. The published *BRCA1/2* de novo mutation rate is low. This is probably due – in part – to the strict testing criteria.

Keywords: BRCA1 gene, breast cancer, de novo mutation, early onset, case report

Background

Hereditary cancer results from mutations in specific genes, such as those involved in regulating cell growth and DNA repair. Some of these mutations are inherited from one parent.[1] De novo mutations are genetic alterations arising for the first time in a germ cell (ie, ovum or sperm) or in the fertilized egg itself during early embryogenesis. The majority of hereditary breast and ovarian cancer cases are due to pathogenic or likely pathogenic variants in the *BRCA1/2* genes.[2] Pathogenic germline variants in the *BRCA1* or *BRCA2* gene lead to an increased lifetime risk of breast, ovarian and further less frequently present cancers in women and an increased lifetime risk of breast, prostate and other tumors in men.

BRCA1 and *BRCA2* genes were discovered in 1994 and 1995, respectively,[3,4] and represent the most investigated breast and ovarian cancer predisposition genes. In recent years, numerous mutations have been described in these genes, of which very few cases involved de novo *BRCA1/2* alterations. In fact, only ten cases of de novo *BRCA1* mutations and six cases of de novo *BRCA2* mutations have been reported at present.[5–15] The *BRCA1/2* de novo mutation rate was previously estimated to be 0.3% (0.1–0.7%). In a French study population of 12805 patients diagnosed with breast and/or ovarian cancer, 1527 were found to be BRCA1/2 mutated (12%), of whom three *BRCA1* mutations and one *BRCA2* mutation were de novo.[6] This is in contrast with other genes, ie, *TP53, NF1* and *RB1*.

We report a new case of a de novo *BRCA1* gene mutation in a woman with an early onset breast cancer without a relevant family history.

Case Presentation

A 30-year-old woman with no health issues so far was diagnosed with a hormone receptor positive/HER2 negative invasive breast cancer. Her family history was not suggestive of a hereditary cancer syndrome (Figure 1). Only a cousin of her father had been diagnosed with a breast cancer at the age of 55 years. She underwent a neoadjuvant chemotherapy, followed by bilateral mastectomy and salpingo-ovarectomy. Regarding the early onset of her cancer, genetic testing was

Received: 24 January 2023
Accepted: 13 April 2023
Published: 11 May 2023

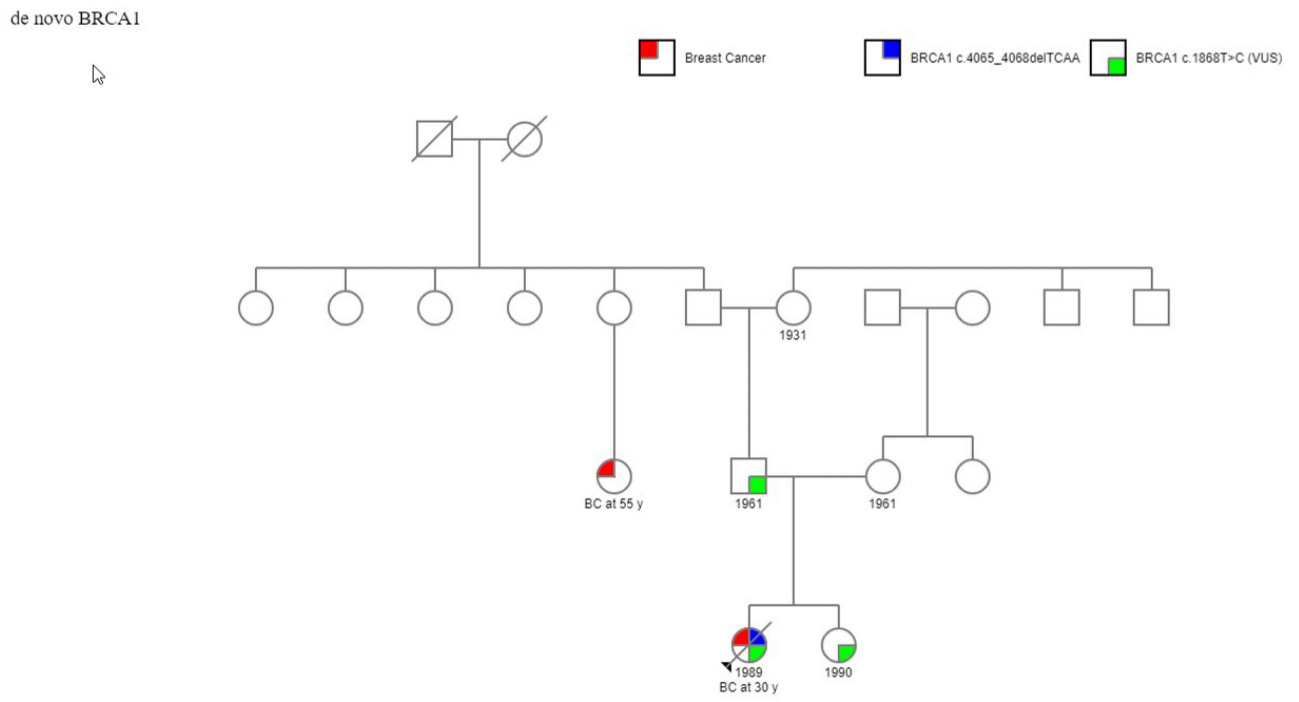

Figure 1 Family pedigree chart for case.

offered to the patient. It revealed a pathogenic variant (c.4065_4068delTCAA) and a variant of unknown significance (VUS) in the *BRCA1* gene. Her healthy sister and her father were tested thereafter and both were found to be carriers of the VUS – but not the pathogenic variant – in the *BRCA1* gene. In her mother neither the pathogenic *BRCA1* mutation (c.4065_4068delTCAA) nor the described *BRCA1* VUS was detected. The findings were confirmed by an analysis of additional blood samples taken from each parent and the patient. In the absence of a germline mutation in both parents, we assume a de novo origin of the mutation during parenteral germ cell gametogenesis. A non-paternity event could be excluded by the detection of the VUS in the *BRCA1* gene, which was first reported in the patient and later in her father and sister. We concluded that our patient must be a carrier of a de novo *BRCA1* mutation.

Materials and Methods

DNA extraction from blood leucocytes was done followed by PCR amplification and DNA sequencing (Cancer Panel V2, Illumina, MiSeq-Tec (Illumina), Alignment: NextGene V2.4.1.1 (Softgenetics)). A pathogenic mutation (NM_007294.3:c.4065_4068delTCAA/p.(Asn1355Lysfs*10)) and a VUS (NM_007294.3:c.1868T>C)/p.Leu623Pro) were found in the *BRCA1* gene. The detected pathogenic variant was already reported by Friedman et al.[16] Recently, it has been also described by Rashid et al as founder mutation in breast cancer patients from Pakistan.[17]

This pathogenic variant NM_007294.3:c.4065_4068delTCAA/p.(Asn1355Lysfs*10) results in a frameshift of the reading frame and, presumably, a premature stop codon. Thus, this deletion leads to a shortened protein and/or degradation of the transcript by NMD (nonsense mediated mRNA decay).

PCR amplification and Sanger sequencing were performed in the healthy sister and parents.

Results and Discussion

Our patient with a pathogenic *BRCA1* variant is a Swiss citizen without a migration background. Neither the mother nor the father or sister are carriers of the pathogenic *BRCA* mutation, providing additional evidence for the de novo occurrence of this variant.

A search in PubMed (Search Terms: BRCA/germline/mutation/de novo) yielded 13 publications reporting 16 de novo *BRCA1/2* mutations.[6–15,18–20,21] The largest published clinical trial – from Golmard et al – detected – on

Table 1 *BRCA1* and *BRCA2* de Novo Mutations Reported in the Literature and in This Case Report Updated and Revised from L Golmard et al 2015

Gene	Mutation	Clinical Features (Age at Diagnosis)	Family History	Population
BRCA1	c.3769_3770delGA	BC (<40)	None	Australia[7]
BRCA1	c.5332+1G>A	Bilateral IDBC (38, 43)	Maternal aunt, BC (54)	UK[8]
BRCA1	Exons 1–12 deletion	IDBC (30)	None	China[9]
BRCA1	Gene deletion	Bilateral BC (28, 37)	None	Spain[10]
BRCA1	c.3494_3495delTT	BC (52), OC (53)	None	Belgium[11]
BRCA1	Mosaic exon 16 deletion	Bilateral BC (39, 47)	Paternal cousin, BC (30)	UK[12]
BRCA1	c.5468–2 A>G	OC (39)	Two paternal aunts, BC (57, 75)	France[6]
BRCA1	c.2296_2297delAG	BC (31)	None	France[6]
BRCA1	Mosaic exons 1–13 deletion	IDBC (41)	Two sisters, BC (62, 63) Paternal grandmother, BC (75)	France[6]
BRCA1	c.5095C>T	IDBC (32)	None	Italy[22]
BRCA1	**c.4065_4068delTCAA**	**IDBC (30)**	**Paternal aunt, BC (55)**	**Case in this report**
BRCA2	c.2808_2811del	Multifocal BC (39)	Paternal cousin, BC (54)	Netherlands[13]
BRCA2	c.7260insA	Bilateral IDBC (35)	None	USA[14]
BRCA2	c.8754+1G>A	IDBC (40)	Mother, BC (59)	Denmark[15]
BRCA2	c.5301insA	IDBC (35)	Paternal grandmother, BC (42)	USA[18]
BRCA2	c.51dupA	Bilateral IDBC (27, 37)	None	Spain[19]
BRCA2	c.6082_6086delGAAGA	Bilateral BC (40, 48)	Daughter, BC (31)	France[6]

Abbreviations: BC, breast cancer; IDBC, invasive ductal breast carcinoma; OC, ovarian cancer.

a series of 12805 consecutive unrelated patients diagnosed with breast and/or ovarian cancer who met the inclusion criteria for *BRCA1/2* gene analysis according to French guidelines – a *BRCA1* or *BRCA2* variation in 1527 (12%) patients. A total of 801 (6.3%) *BRCA1* and 726 (5.7%) *BRCA2* mutation carriers were identified. In this study, de novo status was found for three *BRCA1* mutations and one *BRCA2* mutation, resulting in de novo mutation rates of 0.4% and 0.1% for *BRCA1* and *BRCA2* genes, respectively, and an overall *BRCA1/2* de novo mutation rate of 0.3%.

de novo mutations are generally identified in sporadic cases in most genetic diseases. However, in the 2015 study by Golmard et al, cases with a family history of breast cancer significantly outnumbered, while in the other published cases, half were found to have a family history of breast cancer (Table 1). The authors attribute this observation to the high incidence of breast cancer in the normal population, bias for family cancer cases due to the strong impact of family history as a criterion for *BRCA1/2* genetic testing, and genetic heterogeneity in breast cancer.

Conclusion

We report a new case of de novo *BRCA1* mutation, confirmed by repeated germline testing of the index patient and her parents. The published *BRCA1/2* de novo mutation rate is low. This is probably due – in part – to the strict testing criteria, which are not uniform internationally and the restrictions regarding the cost coverage by the insurance companies. Most described de novo BRCA1/2 variations were found in patients with early-stage breast cancer and without a family history

of the disease. Genetic testing of breast cancer patients based on their young age or family history does not allow detection of all *BRCA1/2* carriers who may benefit from preventive interventions. In our opinion, we should focus on identifying as many carriers of a pathogenic *BRCA* variant as possible. Genetic testing based on selection criteria mainly considering family history, age of onset and tumor characteristics may underestimate the prevalence of de novo mutations. By detecting a larger number of de novo mutations, more patients could benefit from preventive interventions and tailored treatments. Genetic testing for a pathogenic variant in offspring of a carrier of a de novo variant is useful in identifying individuals at high risk for malignancies.

Abbreviations

BRCA1, BReast Cancer Gene 1; *BRCA2*, BReast Cancer Gene 2; *NF1*, Neurofibromatosis Gene 1; *RB1*, Retinoblastoma Gene 1; *TP53*, Tumor Protein P53 Gene; VUS, Variant of unclear significance; PCR, Polymerase chain reaction; DNA, Deoxyribonucleic acid; HER2, Human epidermal growth factor receptor 2.

Data Sharing Statement

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Patient/Proband gave informed consent to tests as well as to use data/material for further anonymous use according to local and national guidelines.

Consent for Publication

Patient/Proband gave informed consent to tests as well as to use data/material for further anonymous use including publication according to local and national guidelines. Institutional approval was given (KEK – Kantonale Ethikkommission für die Forschung am Menschen, Bern, Switzerland).

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work".

Funding

No funding was received for this case report.

Disclosure

The authors declare no conflicts of interest.

References

1. Lynch HT, Watson P, Conway TA, Lynch JF. Clinical/genetic features in hereditary breast cancer. *Breast Cancer Res Treat*. 1990;15:63–71. doi:10.1007/BF01810778
2. Smith P, McGuffog L, Easton DF, et al. A genome wide linkage search for breast cancer susceptibility genes. *Genes Chromosomes Cancer*. 2006;45 (7):646–655. doi:10.1002/gcc.20330
3. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*. 1994;266:66–71. doi:10.1126/science.7545954
4. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995;378:789–792. doi:10.1038/378789a0
5. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105:812–822. doi:10.1093/jnci/djt095
6. Golmard L, Delnatte C, Laugé A, et al. Breast and ovarian cancer predisposition due to de novo BRCA1 and BRCA2 mutations. *Oncogene*. 2016;35 (10):1324–1327. doi:10.1038/onc.2015.181

7. Tesoriero A, Andersen C, Southey M, et al. De novo BRCA1 mutation in a patient with breast cancer and an inherited BRCA2 mutation. *Am J Hum Genet*. 1999;65:567–569. doi:10.1086/302503
8. Edwards E, Yearwood C, Sillibourne J, Baralle D, Eccles D. Identification of a de novo BRCA1 mutation in a woman with early onset bilateral breast cancer. *Fam Cancer*. 2009;8:479–482. doi:10.1007/s10689-009-9270-8
9. Kwong A, Ng EK, Tang EY, et al. A novel de novo BRCA1 mutation in a Chinese woman with early onset breast cancer. *Fam Cancer*. 2011;10:233–237. doi:10.1007/s10689-011-9429-y
10. Garcia-Casado Z, Romero I, Fernandez-Serra A, et al. A de novo complete BRCA1 gene deletion identified in a Spanish woman with early bilateral breast cancer. *BMC Med Genet*. 2011;12:134. doi:10.1186/1471-2350-12-134
11. De Leeneer K, Coene I, Crombez B, et al. Prevalence of BRCA1/2 mutations in sporadic breast/ovarian cancer patients and identification of a novel de novo BRCA1 mutation in a patient diagnosed with late onset breast and ovarian cancer: implications for genetic testing. *Breast Cancer Res Treat*. 2012;132:87–95. doi:10.1007/s10549-011-1544-9
12. Delon I, Taylor A, Molenda A, et al. A germline mosaic BRCA1 exon deletion in a woman with bilateral basal-like breast cancer. *Clin Genet*. 2013;84:297–299. doi:10.1111/cge.12057
13. Van der Luijt RB, van Zon PH, Jansen RP, van der Sijs-Bos CJ, Wárlám-Rodenhuis CC, Ausems MG. De novo recurrent germline mutation of the BRCA2 gene in a patient with early onset breast cancer. *J Med Genet*. 2001;38:102–105. doi:10.1136/jmg.38.2.102
14. Robson M, Scheuer L, Nafa K, Ellis N, Offit K. Unique de novo mutation of BRCA2 in a woman with early onset breast cancer. *J Med Genet*. 2002;39:126–128. doi:10.1136/jmg.39.2.126
15. Hansen TV, Bisgaard ML, Jønson L, et al. Novel de novo BRCA2 mutation in a patient with a family history of breast cancer. *BMC Med Genet*. 2008;9:58. doi:10.1186/1471-2350-9-58
16. Friedman L, Ostermeyer E, Szabo C, et al. Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families. *Nat Genet*. 1994;8:399–404. doi:10.1038/ng1294-399
17. Rashid M, Muhammad N, Naeemi H, et al. Chasing the origin of 23 recurrent BRCA1 mutations in Pakistani breast and ovarian cancer patients. *Int J Cancer*. 2022;151:402–411. doi:10.1002/ijc.34016
18. Marshall M, Solomon S, Lawrence Wickerham D. Case report: de novo BRCA2 gene mutation in a 35-year-old woman with breast cancer. *Clin Genet*. 2009;76:427–430. doi:10.1111/j.1399-0004.2009.01246.x
19. Diez O, Gutiérrez-Enríquez S, Mediano C, et al. A novel de novo BRCA2 mutation of paternal origin identified in a Spanish woman with early onset bilateral breast cancer. *Breast Cancer Res Treat*. 2010;121:221–225. doi:10.1007/s10549-009-0494-y
20. Bonaïti B, Alarcon F, Andrieu N, et al. A new scoring system in cancer genetics: application to criteria for BRCA1 and BRCA2 mutation screening. *J Med Genet*. 2014;51:114–121. doi:10.1136/jmedgenet-2013-101674
21. Van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. *Clin Genet*. 2014;85:318–327. doi:10.1111/cge.12187
22. Antonucci I, Provenzano M, Sorino L, Rodrigues M, Palka G, Stuppia L. A new case of "de novo" BRCA1 mutation in a patient with early-onset breast cancer. *Clin Case Report*. 2017;5(3):238–240. doi:10.1002/ccr3.718