




CASE REPORT

Dual BRCA1 and BRCA2 pathogenic variants in an adolescent with syndromic intellectual disability

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Abstract

Pathogenic variants in the *BRCA1* and *BRCA2* genes are associated with increased risk for breast and ovarian cancers. Concurrent mutations in both genes in the same individual are rare but pose specific challenges when identified, usually through multigene panel testing or infrequently from a genome-wide analysis, such as whole-exome sequencing (WES). We present a 15-year-old female patient with syndromic intellectual disability whose exome reanalysis identified secondary findings of pathogenic *BRCA1* and *BRCA2* variants, both inherited paternally. We discuss the significant challenges posed by this finding in genetic counseling and cancer risk management of an adolescent with nonverbal intellectual disability, as well as the impact on their family. This rare case highlights the potential increased diagnostic yield of whole exome sequencing reanalysis and the consequences of secondary medically actionable results in a pediatric patient.

KEYWORDS

early detection of cancer, gynecology medical genetics, incidental findings, intellectual disability, pediatrics, prevention & Control, whole-exome sequencing

1 | INTRODUCTION

Germline pathogenic variants in breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*) are associated with hereditary breast and ovarian cancer syndrome (HBOC). Mutations in these genes significantly increase the risk for female and male breast cancers, ovarian cancer, and to a lesser extent, prostate cancer, pancreatic cancer, and melanoma (the cancer risk varies based on the gene affected).^{1,2} Given these risks (along with poor prognosis in the event of a cancer diagnosis), cancer risk management is a priority in individuals with identified pathogenic variants.³ Breast cancer screening in women with *BRCA1/2* pathogenic variants relies on annual clinical breast examination, mammography, and breast MRI starting at

30 years of age. Bilateral prophylactic mastectomy is offered as an option to patients, as it decreases breast cancer incidence by 90% or more in patients with a *BRCA1/2* mutation.¹ Unfortunately, no screening test or algorithm has been shown to reduce mortality with ovarian cancer; serial transvaginal ultrasound and serum cancer antigen 125 (CA-125) have been proposed.² In the absence of an effective screening program, the option of bilateral salpingo-oophorectomy offers the greatest risk reduction against developing ovarian cancer in women at high risk: The procedure has been shown to reduce the lifetime risk of ovarian cancer by about 80%.⁴

The co-presence of mutations in both *BRCA1* and *BRCA2* genes (double heterozygous [DH]) is a rare event. Patients with DH mutations should be managed similar

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to *BRCA1* mutation carriers rather than *BRCA2* mutation carriers due to factors such as lower age of diagnosis of breast and ovarian cancer with *BRCA1* mutations.⁵ However, the available literature on patients presenting with DH mutations is sparse, and all pertains to adult cases.

We present a 15-year-old female patient with drug-resistant epilepsy, nonverbal intellectual disability whose initial genetic workup was nondiagnostic. The family consented to whole-exome sequencing (WES), including medically actionable secondary findings. The first exome analysis identified a secondary finding of a paternally inherited pathogenic *BRCA2* variant. Exome reanalysis two years later showed biallelic variants of uncertain significance in a candidate gene as a potential explanation to her neurodevelopmental issues, *NHL repeat-containing 2* (*NHLRC2*), and a novel secondary finding, a pathogenic *BRCA1* variant, also paternal in origin.

This rare case highlights the management and approach to medically actionable secondary findings of WES in pediatric and adolescent patients. Furthermore, it expands on the implication of the commonality of WES's incidental findings and if reanalysis of exome sequencing years down the line increases diagnostic yield.

2 | CASE PRESENTATION

The patient is the second child of healthy nonconsanguineous parents of mixed Belgian, Hungarian, English, and Scottish descent. The patient was born at 37.5 weeks by induction due to maternal migraines following an uncomplicated pregnancy. She had some mild respiratory distress at birth which quickly improved. Her birthweight was 3.03 kg (54th percentile). As an infant, she had feeding difficulties with ineffective latching but gained weight appropriately with bottle feeding. There is a history of torticollis at 4 months of age.

She met motor milestones until 9 months of age, after which time significant motor delays were observed. She walked at the age of 18 months with a crouched stance. Currently, at 16 years of age, she can walk independently for short distances, with an unusual gait and a kyphotic stance; she requires constant supervision. Her fine motor skills never progressed beyond childhood and are limited. She had a few words which she then lost, and she remains nonverbal. As an infant, she had startle behaviors, which were spasm-like; however, the electroencephalograms (EEGs) did not suggest infantile spasms. At the age of 6, she began to have absence episodes and partial and generalized tonic-clonic seizures, which have continued since. Her epilepsy has been classified as treatment resistant, due to failure of several antiepileptic agents and she is

currently controlled with a vagal nerve stimulator. The patient was also diagnosed with celiac disease at 7 years of age due to persistent diarrhea leading to hyponatremia and hospitalizations, and clinical response to a gluten-free diet (no biopsy performed).

Genetic testing between 4 and 10 years of age was normal, including chromosomal microarray analysis, Angelman, Rett syndrome testing, comprehensive epilepsy panel, and mitochondrial DNA testing. Subsequently, a clinical trio WES was arranged which did not identify causative variants in genes to explain the patient's presentation; however, a paternal secondary finding of a pathogenic variant in the *BRCA2* gene (c.475+1G>T) was identified. Follow-up counseling was provided to the father who was 41 years old at the time of those results. Prostate cancer screening was initiated with annual serum prostate-specific antigen (PSA) along with a referral to urology for that ongoing surveillance.

Three years later, exome data reanalysis was offered to the patient's family to help provide a genetic diagnosis, given the rapid accrual of knowledge in genomic medicine with new genes available for analysis. The exome reanalysis identified biallelic variants (one on each copy) in a candidate gene *NHLRC2*. One of the variants was reported as pathogenic (c.1750delC) and was inherited from her mother. The other variant was reported as a variant of uncertain significance (c.2074G>T) and was inherited from her father. The reanalysis of the exome sequencing confirmed the previously identified *BRCA2* pathogenic variant and found a new pathogenic variant in the *BRCA1* gene (c.5096G>A), which was again inherited from the patient's father. This c.5096G>A *BRCA1* variant was initially classified as a variant of uncertain significance.⁶ However, in 2018, an analysis of a large cohort of 129 families, using several analytical approaches, confirmed that the c.5096G>A *BRCA1* variant is associated with intermediate cancer risks (compared with the average *BRCA1* truncating variant) and thus was identified in our proband's WES reanalysis. Interestingly, this variant was found to have a lower associated cancer risk (20% for risk for breast cancer and 6% for ovarian cancer by age 70 for a female) than typical *BRCA1* pathogenic variants.⁶

On family history, paternal grandmother had breast cancer in her 40s. Maternal grandmother had colon cancer at age 64. There is no family history of other malignancy. The patient's mother has migraines. Her father and paternal grandmother have Crohn's disease. There are no individuals with seizures, intellectual disability, or other neurological issues in the family.

Given the patient's severe intellectual disability and complete dependence for activities of daily living, there is no prospect of independent life or starting a family. Her family therefore wondered about earlier than typical

prophylactic surgical interventions. Gynecology consult was undertaken to review the genetics and other clinical challenges. This initially focused on the patient's functionality, menstrual and hygiene challenges with her developmental delay, with further discussions to focus on response to therapeutic options in the patient and family context.⁷ One of the significant challenges with decision-making for the family will be morbidity and life expectancy with respect to surgery versus more conservative or medical options.

The risks and potential complications of these invasive surgeries, such as pain, infection, and more importantly long-term effects including premature menopause, increased risks of osteoporosis, and cardiovascular disease ultimately affecting the quality of life, outweigh the minimal difference in cancer prevention.^{11,12} Counseling on earlier interventions by referral to a gynecologist has been critical in managing the family's expectations focusing on balancing current needs of the patients versus future expectations. The family have therefore agreed to forego any prophylactic surgical interventions until later in life with proper counseling.

3 | DISCUSSION

Reanalysis of WES can increase the molecular diagnostic yield up to 10%–20% due to factors such as newly discovered disease genes and upgraded variant classifications of disease genes.^{8,9} Reanalysis of the patient's WES identified biallelic variants in a candidate gene *NHLRC2*. Variants in this gene have only been reported in association with a severe condition characterized by fibrosis, neurodegeneration, and cerebral angiomas (FINCA).¹⁰ Although WES reanalysis has not yet resulted in a confirmed diagnosis or change in the patient's neurological management, it has provided an additional yet unrelated risk factor and revealed a potential candidate gene that could be researched further. Thus, exome reanalysis, one of the first steps in undiagnosed rare genetic diseases, can change clinical management due to new findings and ultimately benefit patients and their families. A caveat to consider is that reanalysis can increase the probability of incidental/secondary results; therefore, careful pre-test counseling remains essential.

In the present case, the secondary findings of the *BRCA1* and *BRCA2* pathogenic variants have important implications for the patient and their immediate family members. For the proband, regular and lifetime surveillance with imaging could pose a challenge due to her intellectual disability; thus, risk-reductive interventions, such as prophylactic bilateral mastectomy and salpingo-oophorectomy, could offer the best protection against

developing cancer. Historical data demonstrate that DH individuals had an approximately 10-year earlier onset of first cancer compared to single heterozygous females.⁵

Currently, the treatment plan focuses on the patient's quality of life, specifically managing the hormonal impact on her seizures. Focusing on menstrual history, the patient has regular menstrual cycles, however, at times experiences vomiting, which has led to increases in seizure activity compared to perimenstrual baseline. Notably, combined hormonal contraceptive use is well established as a risk reduction method (estimated 40%–50%) for ovarian cancer, including *BRCA1/2* carriers.² There is no associated risk increase or reduction in breast cancer in *BRCA1/2* carriers using combined hormonal contraceptives.² Thus, the patient was initially trialed on a combined hormonal contraceptive and later progestin-only pills, but due to side effects such as agitation and breast growth, the contraceptives were discontinued. As a result, a monthly leuporelin injection, a gonadotropin-releasing hormone (GnRH) analogue, is being trialed. Additionally, the patient's mother is currently charting her behaviors, mood, and seizures around her menses to determine whether this is a viable option.

The secondary findings also prompted the cascade testing of at-risk relatives who may have the familial pathogenic variant and require increased surveillance and early interventions. Several family members are currently pursuing genetic counseling and *BRCA1* and *BRCA2* variant testing to determine their carrier status.

4 | CONCLUSION

Our case features the unique challenges posed by the finding of multiple hereditary cancer susceptibility mutations in a pediatric patient with syndromic intellectual disability. This rare case highlights both the potential increased diagnostic yield of WES reanalysis and the unforeseen consequences of secondary medically actionable results, specifically in pediatric and adolescent patients. These consequences also extend to at-risk relatives who could require further testing and possible increased surveillance and early interventions. Thus, proper counseling, referral to appropriate specialists and evidence-based management, with the acknowledgement that hereditary cancer screening and management guidelines typically change in time based on new information, are essential for physicians, patients, and their families in these rare circumstances.

AUTHOR CONTRIBUTIONS

Arash Algouneh served as a first and submitting author who drafted original manuscript. Michelle Caudle

(Co-author) consented the family and did revisions to the original manuscript draft. Tugce Balci (Co-author) did revisions to the second manuscript draft (Genetics data). Andrea Andrade (Co-author) did revisions to the second manuscript draft (Neurology Data). Debbie Penava (Co-author) did revisions to the second manuscript draft (Gynecology Data). Maha Saleh involved in supervising and corresponding author, consented the family, revised original and final drafts as well as addressed comments from reviewers.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.




ETHICAL APPROVAL

The local Institutional Review Board deemed the study exempt from review.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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