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SHORT REPORT

Biallelic variants in *BRCA1* gene cause a recognisable phenotype within chromosomal instability syndromes reframed as *BRCA1* deficiency

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ABSTRACT

Pathogenic variants in *BRCA1* gene in heterozygous state are known to be associated with breast-ovarian cancer susceptibility; however, biallelic variants cause a phenotype recognised as Fanconi anaemia complementation group S. Due to its rarity, medical management and preventive screening measures are insufficiently understood. Here, we present nine individuals (one new and eight previously presented) with biallelic variants in *BRCA1* gene, to delineate clinical features in comparison with other chromosomal instability syndromes and understand the patients' health risk. Features seen in these 9 individuals (7 females/2 males) include prenatal and postnatal growth failure (9/9), microcephaly (9/9), hypo/hyperpigmented lesions (9/9), facial dysmorphism (9/9), mild developmental delay (8/9) and early-onset solid tumours (5/9). None presented bone marrow failure or immunodeficiency. Individuals with biallelic variants in *BRCA1* also showed chromosomal instability by mitomycin and diepoxybutane test. The phenotype caused by biallelic *BRCA1* variants is best framed between Fanconi anaemia and Nijmegen syndrome, yet distinct due to lack of bone marrow failure and immunodeficiency. We hypothesise that disease class should be reframed and medical management in people with biallelic variants in *BRCA1* should emphasise on detection of solid tumour development and avoiding exposure to ionising radiation.

INTRODUCTION

Heterozygous pathogenic variants in *BRCA1* gene (MIM 113705) are known to associate with breast-ovarian cancer susceptibility (MIM 604370),¹ while biallelic variants cause a phenotype characterised by short stature, microcephaly, neurodevelopmental delay, dysmorphic features, skin pigmentation lesions and chromosomal fragility, recognised as Fanconi anaemia complementation group S (MIM 617883).^{2–6} Due to its rarity, medical management and preventive screening measures are insufficiently understood, especially in males. Biallelic *BRCA1* have been associated with Fanconi anaemia phenotype due to multiple congenital anomalies and increased sensitivity to ionising radiation. However, bone marrow failure, a hallmark characteristic of Fanconi anaemia, was not reported in people with biallelic variants in *BRCA1* gene.⁵ People with

biallelic *BRCA1* variants have an increased risk for early-onset solid tumours, while solid tumour development is observed in less than 2% of patients with mutations in canonical Fanconi anaemia genes.⁷ Other chromosomal breakage syndromes that cause short stature and microcephaly, as well as increased cancer risk, include ataxia telangiectasia, Bloom syndrome and Nijmegen syndrome. Nevertheless, the syndromes differ in presentation and cancer type predisposition. Understanding the natural history of the disease, possible complications and long-term survival is equally important for creating appropriate medical recommendations. Therefore, we aim to present nine individuals (one new and eight previously presented) with biallelic variants in *BRCA1* gene, to delineate clinical features and understand disease presentation and health risk in these patients, in comparison with other chromosomal instability syndromes.

SUBJECTS AND METHODS

Clinical, laboratory and genetic assessments were performed in Romanian Regional Centers of Medical Genetics Timis and Dolj, part of European Reference Network ERN ITHACA.

High-density SNP array was performed using the Infinium OmniExpress-24 BeadChip array (Illumina, San Diego, USA), as described elsewhere.⁸ *Next-generation sequencing and Sanger sequencing* were performed in Timisoara using TruSightOne 4813 genes kit and MiSeq machine (Illumina, San Diego, USA) according to manufacturer's protocols. Bioinformatics analysis was described elsewhere.⁹ Single-nucleotide variants were confirmed by Sanger sequencing, together with familial segregation analysis, using ABI3730 DNA Analyzer (Applied Biosystems, CA, USA) with BigDye Terminator v1.1 Cycle Sequencing Kit. *Chromosomal breakage study with diepoxybutane (DEB) and mitomycin (MMC)* was tested in heparinised peripheral blood from the patient and a healthy control, using standard protocols.¹⁰ A score (breaks/cell) superior to 0.8 in DEB culture was considered positive for diagnosis. Cells with more than 10 breaks were considered positive in MMC culture.

RESULTS

A male newborn presented with intrauterine growth restriction, microcephaly, hypotelorism, epicanthal

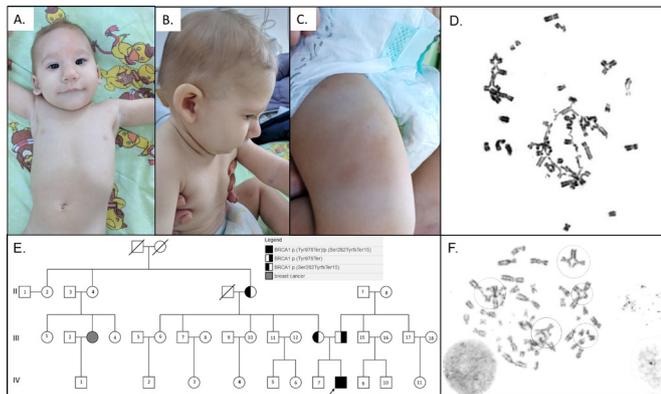


Figure 1 Phenotype and family tree. (A) Image of the proband's face. (B) Proband's right profile. (C) Right anterior thigh showing hypopigmented spots in the proband. (E) Family tree. (D) Proband's cells showing chromosomal breakage induced by mitomycin C test and (F) dyepoxibutane test.

folds, convergent strabismus, bulbous nose, wide-set nipples, micropenis, bilateral cryptorchidism, clinodactyly, hypochromic spots and café-au-lait spots on the thorax and anterior thighs (figure 1A, B, C). He was born from non-consanguineous, healthy parents, at 37 weeks of gestation, with birth weight 1810 g (<-3.71 SD), birth length 46 cm (<-2.05 SD) and cranial perimeter 28 cm (<-5.09 SD). Blood count was normal at birth. Seckel syndrome and craniosynostosis were suspected. Cranial CT at age 2 weeks showed open cranial sutures and normal brain structure.

At age 6 months, he was 57 cm in length (-4.97 SD) and 33 cm in head circumference (-8.47 SD), while at age 2 years, height was 70 cm (-5.30 SD) and head circumference was 36 cm (-8.80 SD). He was able to sit at age 7 months and started walking at age 1 year and 7 months. At 2 years, he spoke three words and was hyperkinetic. Family tree, presented in figure 1E, showed a cousin of the proband's mother with breast cancer at age 35 years.

Other disorders were considered in the differential diagnosis, as follows: short stature and microcephaly syndromes, skeletal dysplasias, growth hormone deficiency, chromosome instability conditions (Fanconi anaemia, Nijmegen breakage syndrome (NBS), Bloom syndrome, ataxia telangiectasia), NBS-like disorder, RAD50 deficiency and Seckel syndrome.

The family was evaluated by a geneticist at age 1 month. Karyotype was 46,XY without any rearrangements. The molecular karyotype (SNP array) did not show pathogenic copy number gain or loss, $\text{arr}(1-22)\times 2,(\text{X},\text{Y})\times 1$. The next-generation sequencing (NGS) TruSightOne panel showed two pathogenic variants in *BRCA1* gene: one pathogenic stopgain variant (GRCh37) NM_007300.3:c.2933dupA, NP_009231.2:p.(Tyr978Ter), rs878853292 paternal and a pathogenic frameshift deletion NM_007300.3:c.843_846delCTCA, NP_009231.2:p.(Ser282Tyrfs*15), rs80357919 maternal. The variants were confirmed by Sanger sequencing in the patient and additionally established they are in trans position, as parental origin could be elucidated. Chromosomal breakage study with DEB showed 1.67 breakage/cell (figure 1F), while MMC-treated cells presented more than 10 breaks/cell in 80% versus 20% in healthy control's cells (figure 1D). The patient's phenotype is presented in table 1, alongside eight other patients presented in literature.²⁻⁶

Blood count and other blood work were in the normal range, including liver, renal, bone, glucose and lipid metabolism.

Immunoglobulin levels were normal. Luteinising hormone was 8.26 (normal 0.1–0.4 mIU/mL) and follicle-stimulating hormone was 22.25 (normal 0.2–2.8 mIU/mL). Testosterone was 0.07 mg/mL; however, at 6 months, boys normally show very low testosterone levels. Anti-Müllerian hormone (AMH) at 6 months was 83.89 pmol/L and considered low (25th centile for age 287.97 pmol/L¹¹), thus suggesting hypergonadotropic hypogonadism.¹² Insulin-like growth factor 1 was 19.3 ng/mL (median value for age 89.3 ng/mL¹³), in connection to the patient's growth failure. Abdominal ultrasound was unremarkable. Testes were shown in the inguinal canal bilaterally. Cardiological evaluation at 6 months revealed persistent ductus arteriosus with a left to right shunt, spontaneously closed by age 1 year.

DISCUSSION

Phenotypic description of *BRCA1* deficiency

We report a male infant of Romanian descent carrying two pathogenic variants in trans, in the *BRCA1* gene. The NM_007300.3:c.2933dupA of paternal origin in our patient creates a premature translational stop signal (p.Tyr978*) in the *BRCA1* gene (ClinVar ID:236270). Loss-of-function variants in *BRCA1* are known to be pathogenic.¹¹ The pathogenic frameshift deletion c.843_846delCTCA (ClinVar ID:17683), of maternal origin, creates a premature translational stop signal (p.Ser282Tyrfs*15) that is expected to result in absent or disrupted protein product. This variant has been described in the literature (also as 962del4) in several individuals with breast and/or ovarian cancer from Romania,¹⁴ Europe and outside Europe.^{15 16}

Until now, eight individuals have been reported with biallelic *BRCA1* pathogenic variants.²⁻⁶ A summarisation of the features identified in our patient and in those previously reported is presented in table 1; however, a detailed description of the phenotype or medical history was not available for all. The majority (7/9) were females and were diagnosed using whole exome sequencing or NGS panels of genes, mainly due to the presence of malignancy (5/9). Only one other male patient was identified through familial screening for *BRCA1* variants identified in his sister after she presented neuroblastoma at the age of 2 years.⁶ Despite relatively high carrier frequencies in populations, biallelic variants in *BRCA1* have rarely been reported, presumably because most combinations of deleterious *BRCA1* variants would result in embryonic lethality.⁵

Four of the nine patients reported presented solid tumours as follows: breast carcinoma in 2/7 females, ovarian cancer in 1/7 females and neuroblastoma in 1/9 individuals. One patient presented T-cell acute lymphoblastic leukaemia. However, age at follow-up ranged from 2 to 31 years, while the majority of individuals (6/9) were under 16 years when reported. All individuals presented family history with various cancer types, most commonly involving the breast, ovaries and uterus. A longer follow-up period is needed to understand the natural history of disease and tumour onset.

Most individuals (6/8 with available information) were born small for gestational age, while other two individuals had borderline suboptimal birth weight (2790 g/2900 g). All individuals (8/8) presented congenital and postnatal progressive microcephaly (ranging from -8 to -2 SD for age and gender), failure to thrive and short stature (range -6 to -2 SD). Most individuals had mild learning disability (8/9). The only patient with normal intelligence was reported by Keupp *et al.*⁴ However, in the 30-year-old female, one of the *BRCA1* variants (p.Arg1699Gln) was hypomorphic and estimated to confer intermediate cancer risk.⁴ In this individual, the chromosomal breakage percentage/

Table 1 Characteristic features of people with biallelic BRCA1 pathogenic variants

Phenotype	Summary n=9 individuals	Domchek et al Dec 2012 ²	Sawyer et al Dec 2013 ⁵	Freire et al Nov 2017 ³	Seo et al A.I.1 Apr 2018 ⁶	Seo et al A.I.4 Apr 2018 ⁶	Seo et al B.II.2 Apr 2018 ⁶	Seo et al B.II.4 Apr 2018 ⁶	Keupp et al Jun 2019 ⁴	Present case 2020
Genotype	5/9 homozygous	Compound heterozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Compound heterozygous
BRCA1 transcript	Various	c.2457delC/ c.5207T>C in trans	c.594_597del/ c.5095C>T in trans	c.2709T>A	c.1115G>A	c.1115G>A	c.1292T>G	c.1292T>G	c.181T>G/c.5096G>A in trans	c.2933dupA/ c.843_846del(CCA in trans
BRCA1 protein product	Various	p.(Asp821Ilefs*25)/p. (Val1736Ala)	p.(Ser198Argfs*35)/p.(Arg1699Trp)	p.(Gly903*)	p.(Trp372Ter)	p.(Trp372Ter)	p.(Leu431Ter)	p.(Leu431Ter)	p.(Cys61Gly)/p.(Arg1699Gln)	p.(Tyr978Ter)/p. (Ser282TyrfsTer15)
Genetic test for diagnosis	Panel or WES	NA	WES	WES	Panel 241 genes	Panel 241 genes	WES	WES	Panel 30 genes TruRisk	Panel 4813 genes TruSightOne
Gender	2/9 male	Female	Female	Female	Female	Female	Female	Female	Female	Male
Karyotype	Normal 9/9	46,XX	46,XX	46,XX	46,XX	46,XX	46,XX	46,XX	46,XX	46,XY
Age at follow-up (years)	2–31	28	25	3.7	5	8	7	31	31	2
Growth failure prenatal	8/9 yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Weight for gestational age, birth weight (g) and SD	6/8 term	NA	SGA, term, 1990g	SGA, term, 1630 g, length 39.5 cm (-5.5 SD)	SGA, 33 weeks, 1470 g	AGA, 38 weeks, 2790 g	SGA, term, 1600 g	AGA, 2900 g	NA	SGA 37 weeks, 1810 g, length 45 cm (-2.5 SD)
Growth failure postnatal height SD	9/9 yes moderate to severe	Adult height 150 cm (-2.1 SD)	Adult height 135 cm (-4.35)	At 2.5 years, height 68 cm (-6.1 SD)	At 5 years, height 92 cm (-3.6 SD)	Failure to thrive	Height <3rd percentile	Height <3rd percentile	Adult height 150 cm (-2.1 SD)	At 2 years, height 70 cm (-5.3 SD)
Microcephaly	9/9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Head circumference percentile	8/8 Disproportional microcephaly	NA	At birth 27 cm (-5.8 SD), adult HC 48.5 cm (-4.5 SD)	At birth 25 cm (-7.7 SD)	At 5 years, HC 39 cm (-7.6 SD)	NA	NA	NA	Adult 52 cm (-2.5 SD)	28 cm at birth (-5 SD) 36 cm at 2 years (-8.1 SD)
Developmental delay IQ	8/9 mild	Yes, delayed speech at age 4 years	Yes IQ=NA	Yes IQ=NA	Yes IQ=NA	Yes, mild IQ=NA	Yes (IQ: 50–69)	Yes (IQ: 62)	No	Yes mild
Eye anomaly	Microphthalmia, blepharophimosis	NA	Blepharophimosis	Long eyelashes	Microphthalmia	Microphthalmia	Microphthalmia	Microphthalmia	NA	Microphthalmia
Ear anomaly	5/8 yes	NA	Yes	Yes	No	Cupped ears	No	No	Yes, low set	Cupped ears
Palpebral slanting	5/7 upslanting	NA	Upslanting	Upslanting	Upslanting	Upslanting	No	No	NA	Upslanting
Epicanthus	3/7 yes	NA	Yes	No	No	Yes	No	No	NA	Yes
Strabismus	2/9 yes	No	Yes	No	No	No	No	No	No	Yes
Bulbous nose	3/8 yes	Yes, small alae nasi	No	Yes	No	No	No	No	No	Yes
Forehead	Bitemporal narrowing	Anterior hairline low	Bitemporal narrowing	Bitemporal narrowing	NA	NA	NA	NA	NA	Bitemporal narrowing
Coarse facial features	2/4 yes	Yes	No	Yes (possibly due to ethnicity)	NA	NA	NA	NA	No	no
Inferior segment face	5/9 micrognathia	Macrognathia	Narrow palate, dental malocclusion	Micrognathia	Micrognathia	Micrognathia	NA	NA	Triangular face	Micrognathia
Skin pigment lesions	8/9 yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypopigmentated spots	6/8 yes	NA	Yes	No	Yes	Yes	Yes	No	No	Yes
Hyperpigmentated spots	8/8 yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limb defect	6/8 yes	No	Campodactyly, 2–3 toe syndactyly	Climodactyly	Small oedematous palms, soles	Small palms	Hypoplastic thumb	No	No	Climodactyly
Hearing loss	2/8 yes	NA	Yes	No	No	No	No	No	Yes (right side)	No
Other	Undescended testes, joint laxity, heart defect, gastrointestinal and skeletal involvement	NA	Sparse hair, high-pitched voice, duodenal stenosis, joint laxity, delayed bone age	Atrial septal defect	Optic nerve hypoplasia, bilateral hip dysplasia	Right first rib hypoplasia, left 11 ribs, short neck	Right undescended testis, adrenal insufficiency	Heart defect (ASD and VSD), growth hormone deficiency	Coeliac disease and congenital hip dislocation (left side)	Wide-set nipples, micropenis, bilateral undescended testis, persistent ductus arteriosus
Reported deceased	2/9 deceased at the time of presentation	Yes, 6 months after diagnosis of ovarian cancer	No	No	Yes at 5 years	No	No	No	No	No

Continued

Table 1 Continued

Phenotype	Summary n=9 individuals	Domchek et al/Dec 2012 ²	Sawyer et al/Dec 2013 ⁵	Freire et al/Nov 2017 ³	Seo et al/A.I.1 Apr 2018 ⁶	Seo et al/A.II.4 Apr 2018 ⁶	Seo et al/B.II.2 Apr 2018 ⁶	Seo et al/B.II.4 Apr 2018 ⁶	Keupp et al/Jun 2019 ⁴	Present case 2020
Chromosomal breakage spontaneous	6/6 no, various types of reporting results	NA	0% vs 0% in control	0.12 vs 1.0 in control	13.3% vs 6.6% in control	NA	6% vs 0 in control	2% vs 0 in control	NA	No
Chromosomal breakage induced 0.2 µg/mL DEB	7/8 yes, various types of reporting results	NA	30% vs 0% in control	1.9 vs 1.0 in control	70% vs 7%	32% vs 8% in control	1.44 vs 1.0 in control	2.14 vs 1.0 in control	6% of cells; 0.12 breaks/cell within the normal range	1.67 vs 1.0 in control
Chromosomal breakage induced MMC	3/3 yes	NA	Increased radial chromosomes vs control	NA	NA	92% vs 34% in control	NA	NA	NA	80% vs 20% in control
Malignancy yes/no	5/9 at the time of diagnosis	Yes	Yes	No	Yes	No	No	Yes	Yes	No
Cancer type	Breast, ovarian cancer, ALL, neuroblastoma	Ovarian cancer	Ductal breast carcinoma	-	T-cell acute lymphoblastic leukaemia	-	-	Neuroblastoma	invasive-ductal breast carcinoma	-
Age of cancer (years)	2–30	28	23	-	5	-	-	2	30	-
Other	Unclear sensitivity to chemotherapy	Hypersensitivity to chemotherapy Carboplatin	No hypersensitivity to chemotherapy	-	-	-	-	-	Hematotoxicity due to chemotherapy	-
Bone marrow failure	9/9 no	No	No	No	No	No	No	No	No	No
Cancer family history	Burden of breast, ovarian, uterine, urological, lung, intestinal, prostate cancer	Breast, ovarian and peritoneal cancer in 1st and 3rd degree relatives	Ovarian in 1st and 2nd degree relatives, lung, endometrial, skin 2nd and 3rd degree relatives	Breast cancer	Intestinal and urological cancer, 2nd and 3rd degree relatives	Intestinal and urological cancer, 2nd and 3rd degree relatives	Uterine, oesophageal, and lung cancer, 2nd and 3rd degree relatives	Uterine, oesophageal and lung cancer, 2nd and 3rd degree relatives	Prostate cancer, breast cancer in 3rd degree relatives	Breast cancer in 3rd degree relatives

SD calculated using WHO standards and reference.

AGA, appropriate for gestational age; ALL, acute lymphoblastic leukaemia; ASD, atrial septal defect; DEB, diepoxybutane; MMC, mitomycin C; n, number; NA, not available; SGA, small for gestational age; VSD, ventricular septal defect; WES, whole exome sequencing.

cell remained in normal range, suggesting a genotype–phenotype correlation.⁴ The patients reported by Keupp *et al*⁴ and Domchek *et al*,² both with hypomorphic variants, presented the mildest phenotype out of the nine individuals reviewed, also showing the least affected growth and head circumference, nonetheless presented breast/ovarian cancer around the age of 30 years.

The individuals with biallelic *BRCA1* variants had similar dysmorphic features: narrow forehead (3/4), upslanting palpebral fissures (5/7), microphtalmia/blepharophimosis (6/8), epicanthus (3/8), ear anomaly (5/8), micrognathia (5/9), coarse facial features (2/4), bulbous nose (3/8) and strabismus (2/9). All patients presented skin pigment lesions, 8/8 had hypopigmented spots (café-au-lait) and 6/8 additionally presented hypopigmented spots. Other features were hearing loss (2/8), various limb defects (6/8) including clinodactyly, small hands, hypoplastic thumbs and toe syndactyly, joint laxity (including hip dislocation 2/9), heart defect (including atrial and ventricular septal defect, and persistent ductus arteriosus), gastrointestinal malformation (duodenal stenosis), delayed bone age and growth hormone deficiency. Both boys presented undescended testes (2/2), while micropenis and low AMH was observed in one, suggesting that hypogonadism might be a constant feature in males. Cultured lymphocytes or fibroblasts from the individuals with biallelic variants in *BRCA1* displayed induced chromosome instability (using DEB and/or MMC). No sign of immunodeficiency or recurrent infections was reported. None of the patients showed bone marrow failure, differentiating the *BRCA1* deficiency from classic Fanconi anaemia and Nijmegen phenotypes.

Phenotypic overlap between *BRCA1* deficiency and chromosomal instability syndromes

All those affected by chromosome breakage disorders have a greatly increased likelihood of developing cancer and of having prenatal and postnatal growth failure, hypo/hyperpigmented skin lesions, dysmorphic features and gonadal dysfunction.¹⁷ Except for ataxia telangiectasia, the other disorders present various VACTER-L anomalies.¹⁷ Most individuals with Fanconi anaemia present bone marrow failure.⁷ In those with ataxia telangiectasia, progressive neurodegeneration is the most prominent feature, usually without microcephaly or intellectual disability. In those with NBS, Bloom syndrome and ataxia telangiectasia, immunodeficiency is usually present. The risk of cancer development at virtually any site and of any type separates Bloom syndrome from the other chromosome instability syndromes.¹⁷ In this framework, the phenotype caused by biallelic *BRCA1* variants is best mounted between Fanconi anaemia and Nijmegen syndrome, yet distinct from them due to lack of bone marrow failure and immunodeficiency. With a better understanding of molecular cause of disease, phenotypes become more refined and disease classifications need to be adjusted.

Medical management for patients with *BRCA1* deficiency

Similarly to other genes involved in the DNA double-strand break repair pathway, the *BRCA1* gene function disruption causes delayed DNA damage recognition, disturbed cell-cycle checkpoint, incomplete DNA repair and increased genomic instability, ultimately triggering increased cancer risk for patients.¹⁸ Therefore, patients within this group of disorders require multidisciplinary management and long-term follow-up. Of great importance are preventive measures to avoid radiation, and production of reactive oxygen species stimulated by pollutants (heavy metals, tobacco, smoke, drugs or chemotherapeutic drugs that frequently induce DNA damage). X-rays and CT

scans should be avoided, instead use MRI and ultrasound, where possible. Actively searching for malignancy, with emphasis on early-onset solid tumours, is essential. Nonetheless, screening for immunodeficiency and bone marrow deficiency is reasonable. Growth failure may be the most important initial concern of the family. However, overfeeding should be avoided and growth hormone supplementation should only be administered to children with proven growth hormone deficiency, as there is a possible increase in cancer predisposition.¹⁹ Even though there are no growth curves for this group of disorders, a final height between 135 and 150 cm was seen in girls presented here. Cryptorchidism should be surgically corrected and pubertal development should be carefully monitored. Other family members carrying heterozygous pathogenic variant in *BRCA1* gene should undergo screening for breast, ovarian, uterine and prostate cancer.

CONCLUSION

This analysis of nine individuals shows that biallelic *BRCA1* variants cause a rare syndrome with prenatal and postnatal growth failure, hyper/hypopigmented spots, progressive microcephaly, mild learning disability, induced chromosomal breakage and high susceptibility for solid tumours, without immunodeficiency or bone marrow failure, differentiating the *BRCA1* deficiency from classic Nijmegen syndrome and Fanconi anaemia typical phenotype. Cancer type encountered in patients were breast carcinoma, ovarian cancer, neuroblastoma and acute lymphoblastic leukaemia.

Patients within this group of disorders require multidisciplinary management and long-term follow-up that includes preventive measures. Further research is required to guide the clinical management of *BRCA1* deficiency.

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Contributors AC-E collected patient's data and summarised clinical and genetic findings. AC-E, NA, CP, AM, A-LR, RP and MI participated in genetic studies, genetic analyses, bioinformatics and data interpretation. AC-E, SA and MP followed the patient. AC-E drafted the manuscript. All coauthors critically reviewed the manuscript and approved the final submitted version.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

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