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CASE REPORT OPEN ACCESS

The Homozygous p.(Arg215Ter) Variant in *XRCC2* Is Associated With Atypical Fanconi Anemia Without Major Hematological Abnormalities in Childhood

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ABSTRACT

Fanconi Anemia (FA) is the most frequent inherited bone marrow failure syndrome. A role for the *XRCC2* gene in FA was suspected in 2012 and confirmed in 2016, but only two affected individuals have been described thus far, and no long-term follow-up is available. Here we present two young related adults born to consanguineous parents, in whom we identified the homozygous p.(Arg215Ter) variant in *XRCC2*. Both patients presented with mild intellectual disability, microcephaly, distinctive facial features, short stature, thumb abnormalities, and abnormal skin pigmentation. Unlike in FA, DEB test resulted negative in peripheral blood during childhood and no cytopenia, clonal evolution, or other hematological complications were detected until the age of 19 and 20 years, respectively. Our report suggests that the homozygous p.(Arg215Ter) variant in *XRRC2* causes a distinctive FA-like disorder, characterized by the typical physical characteristics seen in FA, but a lack of major hematological manifestations in childhood, and the presence of a more pronounced neurodevelopmental phenotype than that seen in FA.

1 | Introduction

Fanconi anemia (FA) (MIM #227650) is a group of rare disorders caused by defects in proteins involved in DNA repair and cell cycle regulation (Wiedemann 1979; Bagby and Alter 2006; Moreno et al. 2021). A main sign in FA is progressive bone marrow (BM) failure (BMF) (Dufour 2017; Soulier 2011), together with congenital malformations and a predisposition to early onset solid and hematological malignancies (Bagby and Alter 2006; Moreno et al. 2021). The median age at diagnosis of BMF is approximately 7 years (Shimamura and Alter 2010). Currently, variants in 23 genes are known to cause FA, each related to a specific FA complementation group (CG) (Hanenberg et al. 2002).

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The protein product of *XRCC2* (X-ray cross-complementing gene 2—chr. 7q36.1, OMIM # 600375) is a member of the BCDX2 complex, involved in homologous recombination (HR)-based DNA repair (Suwaki et al. 2011; Mamrak et al. 2017; Andreassen and Hanenberg 2019). The involvement of *XRCC2* in FA was first established in 2012 by Shamseldin et al. (2012) and confirmed in 2016 by Park et al. (2016), who restored cell cycle defects in Shamseldin's patient's cells transfected with wild-type *XRCC2* vehiculated by a lentivirus. The same p.(Arg215Ter) variant was later described in only one further report of a patient affected by FA (Maddirevula et al. 2019), with limited information about long-term outcome. Here we report on two affected young adults carrying this recurrent truncating variant and discuss their clinical manifestations to better delineate the phenotype of *XRCC2*-related disorder.

2 | Case Description

2.1 | Patient 1

Patient 1 is a 20-year-old male, born to consanguineous Egyptian parents, with no personal and family history of cancer (Figure 1A). The patient was born after an uneventful full-term pregnancy: birth weight, length, and OFC were below −2 SD, Apgar score 9–10. He was diagnosed at birth with atrioventricular canal, which was surgically corrected, and phimosis. He showed short stature and microcephaly (at the age of 17 years: 58.5 kg (−0.98 SD), 159 cm (−2.38 SD), and OFC 49 cm (−5 SD)). The patient had a history of global developmental delay (GDD) and borderline intellectual functioning (Intelligence Quotient (IQ): 73 at the age of 11 years). Brain MRI showed mild ventricle enlargement and cerebellar hemispheres asymmetry. Additional findings included myopia and Duane's syndrome and recurrent upper airways infections during childhood. On physical exam, the patient exhibited a sloping forehead, telecanthus, short and upslanted palpebral fissures, blepharophimosis (more marked on the right eye), epicanthus inversus, prominent nasal root, short philtrum, and micro-retrognathia. Both hands showed radial deviation with proximally placed thumbs, tapered fingers and fifth fingers brachydactyly (Figure 1B). Fetal finger pads on the right hand and ulnar deviation of the second finger on the left hand were noted. He had camptodactyly of both halluces and a large second toe on the left foot (Figure 1C,D). Skin examination identified a hypopigmented macule on the right hip and a café-au-lait spot (CALS) on the right arm (Figure 1E). No endocrinological abnormalities were detected. Previously performed karyotype, telomeric fluorescence in situ hybridization (FISH) and chromosomal microarray (CMA) were normal. Trio Exome Sequencing (ES) identified a homozygous pathogenic variant in *XRCC2* [NM_005431.2]: c.643C>T, p.(Arg215Ter). Both parents were confirmed to be heterozygous healthy carriers.

Hematological parameters upon diagnosis and at age 19 years were within the normal ranges with no evidence of BMF or solid malignancies. Chromosomal breakage susceptibility at DEB test (at concentration of 0.1 and 0.01 μg/mL) and cytofluorometric analysis of cell cycle after melphalan exposure, performed on peripheral blood (PB), resulted normal.

2.2 | Patient 2

Patient 2 is a 19-year-old girl, born to consanguineous Egyptian parents, with no personal and family history of cancer. She is the first cousin of Patient 1 (Figure 1A). She was born at term after third trimester report of severe intrauterine growth restriction (IUGR). At birth, she presented with low weight, length and head size. She was hospitalized due to microcephaly, bicuspid aortic valve, ptosis and left kidney hypofunction, vesicoureteral reflux, and anteriorly placed anus. Complete bilateral aplasia of the thumbs required several orthopedic surgeries until age 14 years. Brain MRI evidenced Arnold Chiari malformation type I and deformities of the basicranium, cervical metamers and sellar region, including neuropituitary ectopia. The latter required treatment with Growth Hormone (GH) and levothyroxine replacement therapy (Figures S1 and S2). Investigating pubertal delay, poor gonadic function with small tubular uterus and fibrotic adnexa were also found. On physical examination, she showed narrow and asymmetric palpebral fissures, hypertelorism, flat nasal root, anteverted nares and prominent columella, long philtrum, thin lips, micrognathia, and short and broad neck. She also had scoliosis, bilateral absent thumbs (Figure 1F), a single palmar crease bilaterally, and brachydactyly of all toes (Figure 1G). Skin examination identified multiple CALS. Previously performed karyotype, telomeric FISH and CMA were normal. Trio ES—performed at the age of 17 years, independently from that of her cousin—identified the same homozygous pathogenic variant in *XRCC2* [NM_005431.2]: c.643C>T, p.(Arg215Ter). Her parents were healthy carriers of the variant. Hematological workup performed after the diagnosis did not identify any relevant abnormalities in PB and in BM, except for mild dyshematopoiesis. Karyotype on BM blood was normal (46,XX). FISH for chromosomal abnormalities associated with hematological malignancies [e.g., 17p13.1 (TP53), 5q, 7q, and 20q] and trisomy 8 resulted negative in all analyzed nuclei. DEB test and cell cycle analysis after exposure to melphalan, performed on PB, resulted normal at diagnosis. At the age of 19 years, a follow-up DEB test showed cellular alterations above the normal range on two (0.1 and 0.001 μg/mL) of the three (0.1, 0.01 and 0.001 μg/mL) DEB concentrations tested on PB and a high rate of cellular abnormalities for all tested DEB concentrations (up to 100% altered cells for 0.1 μg/mL) on skin-derived fibroblasts (never tested before). The clinical manifestations of Patient 1 and 2 and of the previously reported affected individuals are summarized in Table 1. The details of the DEB tests are shown in Table S1.

3 | Discussion

XRCC2 is involved in HR repair of DNA damage, but little is known about its role in disease. Of the ≈600 *XRCC2* single nucleotide variants deposited in publicly available database (https://www.ncbi.nlm.nih.gov/clinvar, https://databases.lovd.nl/shared/genes/XRCC2, accessed on 16 June 2025), the majority are of unknown clinical significance. Some have been suspected to confer breast cancer predisposition in heterozygotes (Alter and Best 2020), and a homozygous missense variant has been associated with spermatogenic failure in men (OMIM #619145) and premature ovarian failure in women (OMIM #619146), with no conclusive evidence

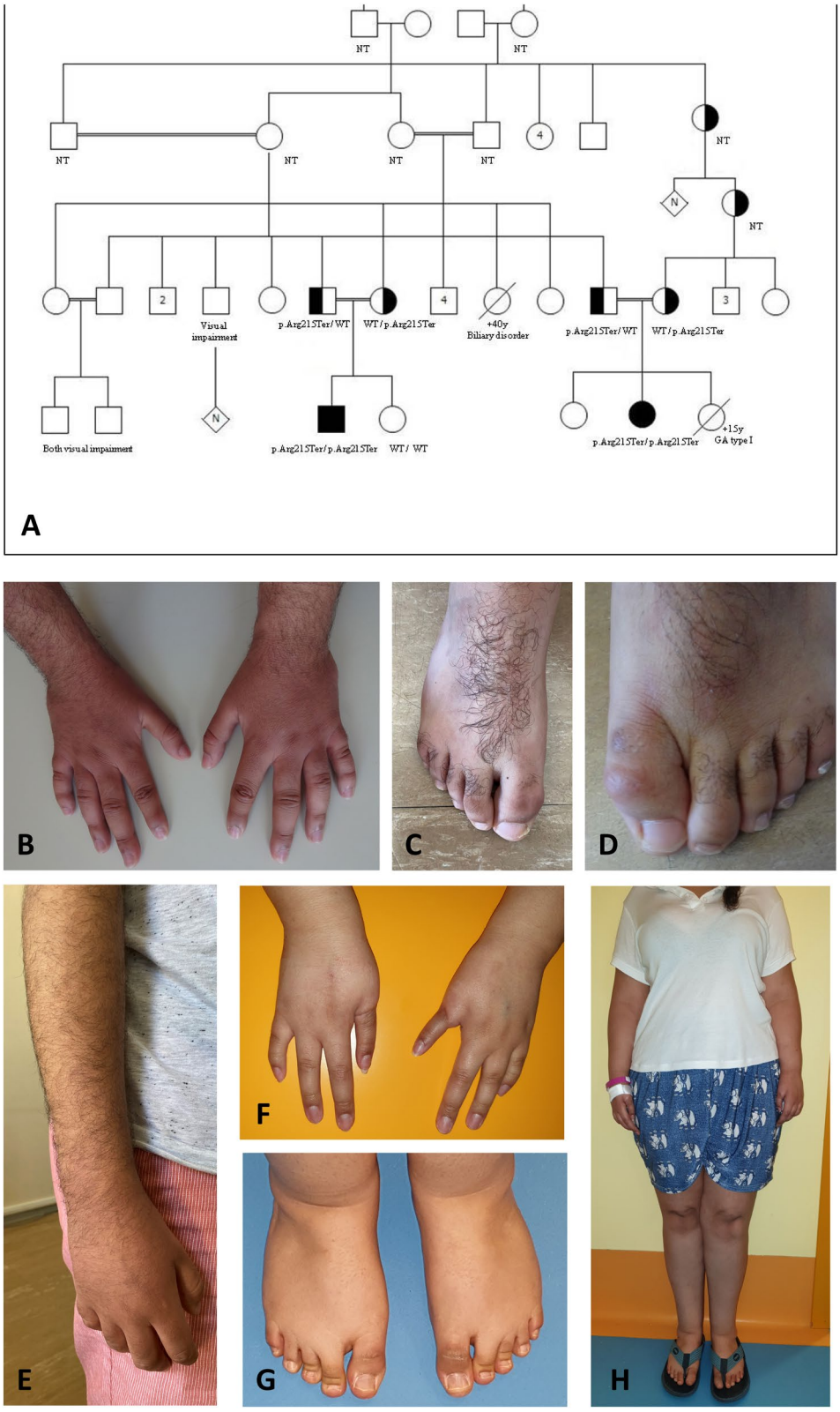

FIGURE 1 | A. Pedigree. Black square: Affected male (Patient 1); black circle: Affected female (Patient 2); half-blackened squares and circles: Unaffected heterozygous healthy carriers. Abbreviations: WT: Wild type; NT: Not tested. Lower panel: Photographs of the patients. Hands (B), feet (C, D), arm (E) of Patient 1; hands (F), feet (G) and body (H) of Patient 2.

(Yang et al. 2018). Only two reports have suggested a role of biallelic *XRCC2* truncating variants in FA (Park et al. 2016; Maddirevula et al. 2019). Both children harbored the p.(Arg215Ter) variant, of which no homozygotes are reported in healthy populations (GnomAD v4.1, accessed on 23 June 2025). They showed growth delay, microcephaly, cardiac and urinary anomalies, bilaterally hypoplastic/absent thumbs, and abnormal DEB test.

TABLE 1 | Clinical characteristics of patients with the homozygous p.(Arg215Ter) variant in *XRCC2*.

	Shamseldin et al. (2012); Park et al. (2016)	Maddirevula et al. (2019)	Present patient 1	Present patient 2
Sex	M	F	M	F
Age	7 years	3 years	20 years	19 years
IUGR/SGA	Yes	Yes	Yes	Yes
Short stature	Yes (severe)	Yes (−3 SDS)	Yes (−2.3 SDS)	Yes (−2.3 SDS)
Microcephaly	Yes	Yes, progressive (−2 SDS)	Yes (−5 SDS)	Yes (−4 SDS)
DD/ID	NA	No	Yes (BIF: IQ 73)	Yes
Facial features	NA	Epicanthal folds, short neck	Sloping forehead, telecanthus, short and upslanted palpebral fissures, blepharophimosis, epicanthus inversus, prominent nasal root, short philtrum, micro-retrognathia	Microphtalmia, hypertelorism, flat nasal root, anteverted nares and prominent columella, long philtrum, thin lips, micrognathia, short and broad neck
Upper limbs anomalies	Bilat. absent 1st metacarpal and scaphoid bones, absent/ hypoplastic radii	Bilat. hypoplastic thumbs, absent flexor pollicis brevis	Bilat. proximally placed thumbs	Bilat. aplasia of thumbs
Brain MRI anomalies	NA	No	Ventricles'enlargement, cerebellar asymmetry	ACM type I, deformities of basicranium, cervical metamers and sellar region
Cutaneous manifestations	NA	Multiple CALS	One hypopigmented macule, one CALS	Multiple CALS
Ocular anomalies	NA	Strabismus	Myopia, divergent strabismus and exoforia	NA
Cardiac malformations	PDA	NA	AVC	Bicuspid aortic valve
Urogenital malformations	Ectopic left kidney	NA	Phimosis	Ectopic and hypofunctioning left kidney, VUR, small tubular uterus and fibrotic adnexa
Hematological anomalies	No	Pancytopenia	No	No
Other skeletal anomalies	No	Bilat. acetabular dysplasia	No	No

(Continues)

TABLE 1 | (Continued)

	Shamseldin et al. (2012); Park et al. (2016)	Maddirevula et al. (2019)	Present patient 1	Present patient 2
Other	Congenital left facial nerve palsy	No	No	Anteriorly placed anus
Chromosomal breakage test	Abnormal (marked increase in the frequency of dsDNA breaks)	Abnormal (breakage 100%)	Normal on PB	Normal on PB at diagnosis. Abnormal on FB at 19 years (breakage up to 100%)

Abbreviations: ACM: Arnold Chiari malformation; AVC: atrioventricular canal defect; BIF: borderline intellectual functioning; Bilat.: bilateral; CALS: café au lait spots; DD: developmental delay; F: female; FB: fibroblasts; ID: intellectual disability; IQ, Intelligence Quotient; IUGR: intrauterine growth restriction; M: male; NA: not available; OFC: occipito-frontal circumference; PB: peripheral blood; PDA: patent ductus arteriosus; SDS: standard deviations; SGA: small for gestational age; VUR: vesicoureteral reflux.

To the best of our knowledge, this is the first independent report of two affected adult patients with the same homozygous pathogenic variant and an overlapping phenotype. After contacting the authors of the original studies, we hypothesize that the p.(Arg215Ter) may be a founder variant in the middle eastern population, but further studies are needed to prove it (raw data of Patient 1 are available in File S1). The present patients are also the oldest individuals diagnosed with FA group U reported thus far with a relatively long-term follow-up from birth to adulthood. Although the physical characteristics of all described patients are highly suggestive of a defect in a gene involved in DNA breaks repair, the long-term follow-up of the patients described here argues against the association of *XRCC2* pathogenic variants with hematological signs in childhood. In the most common FA CG (A, C, and G), BMF occurs in the first decades of life (median age 7 years; >90% of patients by 40 years of age) (Shimamura and Alter 2010) and can be the key for FA diagnosis in mildly affected patients. BMF exhibits a wide variability, ranging from mild cytopenia to aplastic anemia or even myelodysplastic syndromes and acute myelogenous leukemia (Moreno et al. 2021). Despite its name, the first hematological sign of FA is usually thrombocytopenia, frequently associated with leukopenia (mostly neutropenia), later evolving into pancytopenia. None of the present patients has so far exhibited any of the hematological abnormalities, including an additional adult male with the recurrent p.(Arg215Ter) variant who was reported in a male infertility cohort and also had short stature and hypoplastic kidneys (Alhathal et al. 2020). However, no additional data were available for the patient described by Alhathal and colleagues as Fanconi Anemia was out of the scope of the paper.

XRCC2 is a paralog (and enhancer) of *RAD51* (OMIM # 179617), the key player of the HR cascade (Tambini et al. 2010; Bonilla et al. 2020). *RAD51* expression seems to be positively related to cancer development, creating a unique biological paradox (Matos-Rodrigues et al. 2021). Truncating variants in *XRCC2*—such as the p.(Arg215Ter) identified here—would downregulate RAD51 response to DNA damage (Tambini et al. 2010), suggesting the reason for the lack of an early hematological phenotype in homozygous patients and the negative history of breast cancer in the heterozygotes, in line with more recent observations (Dufour and Pierri 2022; Fiesco-Roa et al. 2019). Nevertheless, although the hematological assessment in the two patients reported here was normal until adulthood and no major alterations were found at DEB test on PB, breakages were seen when tested on Patient 2's fibroblasts at age 19 years. These results further highlight the high phenotypic variability of the FA-spectrum, including atypical clinical presentations. A regular hematological follow-up is warranted for the described patients, and routine radiological studies, cancer screening, hormonal replacement therapy, and other medical exams or therapies should be customized based on specific risk–benefit ratio.

Although a natural history study on a higher number of affected individuals is needed to confirm our hypothesis, our data suggest that the homozygous p.(Arg215Ter) variant in *XRCC2* causes a distinctive FA-like disorder, characterized by the typical physical features observed in FA, lack of major hematological manifestations in childhood, and a more pronounced neurodevelopmental phenotype, which is uncommon in FA and may be due to the involvement of *XRCC2* in neural development (Deans et al. 2000).

Intriguingly, a recent work has reviewed *RAD51*-related FA phenotypes (Altintas et al. 2025), highlighting the atypical presentation observed in this specific subtype of FA (FANCR), which appears quite similar to FANCU. In fact, FANCR patients exhibit features of the VACTERL (Vertebral anomalies, Anal atresia, Cardiac anomalies, Tracheoesophageal fistula, Esophageal/duodenal atresia, and Renal and Limb anomalies) or PHENOS (abnormal Pigmentation, small Head, small Eyes, central Nervous system anomalies, Otological anomalies, short Stature) associations and often display developmental delay.

Similarly to what we observed in the patients reported here, also in *RAD51* patients, as well as in FANCO and FANCS cases, no hematologic anomalies or bone marrow failure have been reported, counting these diseases in the "FA-like" end of Fanconi spectrum (Bogliolo and Surrallés 2015).

In keeping with these observations, the phenotype of patients with *XRCC2*-related disorder may resemble that of several other conditions related to the cell cycle and control of DNA replication, as previously recognized for another FA gene, *BRCA2* (Shaheen et al. 2014). Short stature with microcephaly and a distinctive facial appearance, skeletal anomalies, and developmental delay may be suggestive of the "microcephalic primordial dwarfisms" (MPDs) spectrum, which includes microcephalic osteodysplastic primordial dwarfism (MOPD, OMIM #210710), Meier Gorlin syndrome (MGS, OMIM #224690), Seckel syndrome (SS), microcephaly-micromelia syndrome (MMS; OMIM #251230), and microcephaly, short stature, and limb abnormalities (MISSLA; OMIM #617604). These syndromes are caused by pathogenic variants in genes involved in DNA replication/cell cycle regulation, and it has been recently proposed to group them under the label of "cell cycle-opathies." This group would include the broad spectrum of conditions characterized by primary microcephaly, short stature, and skeletal findings caused by mutations in genes responsible for regulating cell replication processes (Karaca et al. 2019). The present report further strengthens the affinity between cell cycle-opathies and FA.

In conclusion, the report of four individuals (two here and two in the literature) with a highly specific and consistent phenotype confirms that the homozygous variant p.(Arg215Ter) in *XRCC2* causes a recognizable phenotype. It also highlights the clinical heterogeneity of the FA spectrum and warrants in-depth phenotyping of individuals with specific variants of the FA pathway.

Author Contributions

S.C., G.B.M., F.F., and A.P.: writing of the manuscript. **C.B., G.B.M., M.G.P., S.G., G.C.P., M.N.S., F.G., A.A., F.F., and A.P.:** clinical evaluation of the patients. **M.I. and P.C.:** genetic analyses. **F.F. and P.A.:** conceptualization and supervision. All authors review and approval of the manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

Patients and families gave their consent to the review of medical records and to photographs and their publication, and the study was conducted in accordance with the principles stated in the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Patient's height curve (Cacciari table (28)), showing regular growth, though at lower percentiles, during growth hormone (GH) replacement therapy. The patient has now reached definitive height (149 cm, −2.3 SDS). Since GH replacement has had a very good clinical response, the fact the patient remained in the lower part of the curve could be due to other genetic and clinical issues connected to FA. **Figure S2:** Patient's weight and BMI curve (Cacciari table (28)), showing progressive weight gain, with BMI highlighting severe obesity. This trend is often observed in FA patients, but in this case lock-down during the COVID-19 pandemic era could also have affected the patient's diet and physical activity (29). **Table S1:** Detailed results of the Diepoxibutane (DEB) tests. **File S1:** VCF file of selected haplotype, chromosome 7, Patient 1.