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CLINICAL REPORT

FANCC Dutch founder mutation in a Mennonite family from Tamaulipas, México

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Abstract

Background: Fanconi anemia (FA) (OMIM #227650) is a rare hereditary disease characterized by genomic instability. The clinical phenotype involves malformations, bone marrow failure, and cancer predisposition. Genetic heterogeneity is a remarkable feature of FA; at least 22 *FANC* genes are known to cooperate in a unique FA/BRCA repair pathway. A common rule on the mutations found in these genes is allelic heterogeneity, except for mutations known to have arisen from a founder effect like the *FANCC* c.67delG in the Dutch Mennonite Community. Here, we present an 11-year-old male patient, member of the Mennonite Community of Tamaulipas México, with a clinical and cytogenetic diagnosis of FA.

Method: Chromosome fragility test was performed in all siblings. Genomic DNA was obtained from peripheral blood samples. Sanger sequencing was used to identify the *FANCC* c.67delG mutation (NC_000009.11(NM_000136.2):c.67delG p.(Asp23IlefsTer23)) and its accompanying haplotype.

Results: The *FANCC* c.67delG mutation in 13 members of his family confirmed a FA diagnosis in two of his siblings and identified heterozygous carriers. Haplotype analysis supports that in this family, FA is caused by the founder mutation that initially appeared in Mennonite Dutch and followed this population's migrations through Canada and further to Mexico.

Conclusion: The identification of the *FANCC* c.67delG mutation in this family not only allows proper genetic counseling, but it also grants the possibility to raise awareness of FA risk among the Mennonite community living in Mexico.

KEYWORDS

FANCC, *FANCC* c.67delG, fanconi anemia, Mennonite

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1 | INTRODUCTION

Fanconi anemia (FA) (OMIM #227650) is a rare hereditary disease characterized by genomic instability. The clinical phenotype involves diverse congenital malformations, bone marrow failure, and a high risk of cancer, mainly leukemia and solid tumors.

Genetic heterogeneity is a remarkable feature of FA; at least 22 *FANC* genes are known to cooperate in a unique FA/BRCA pathway that regulates the response to genotoxic agents and participates in maintaining genome integrity (Knies et al., 2017; Rodríguez & D´Andrea, 2017).

A vast number of different mutations have been documented in these genes, making allelic heterogeneity the rule. Nevertheless, specific mutations with a founder effect have been found, particularly in genetically isolated populations. Such is the case for the *FANCA* c.295C>T mutation in Spanish Gypsies (Callén et al., 2005), the *FANCC* c.711+4A>T in Ashkenazi Jews (Whitney, Jakobs, Kaback, Moses, & Grompe, 1994), and the *FANCC* c.67delG found in people of Dutch ancestry and Canadian Mennonites (de Vries et al., 2012).

Mennonites originated in 16th-century Europe, they belong to the Anabaptist movement that believes in separation of Church and State, adult baptism and pacifism. In order to maintain their traditional life style, this group has resorted to successive migrations. Their journey had several stops around Europe before heading to Manitoba in Canada at the end of the 19th-century (Smith, 2005). At the beginning of the 20th century, a group of traditional old colonist Mennonites from the Manitoba settlement arrived to Mexico, where around 100,000 Mennonites currently live. They were initially established in the Northern state of Chihuahua and further expanded their settlements to the neighboring states of Durango and Tamaulipas and more recently to the southern states of Campeche and Quintana Roo (Bixler-Márquez, 1988). Their successful effort to preserve their traditions has also led to genetic isolation (Allen & Redekop, 1987), resulting in a high rate of recessive monogenic diseases (Orton, Innes, Chudley, & Bech-Hansen, 2008).

There are only a few papers evaluating the genotypes of individuals from the Mexican Mennonite community. Alanis-Bañuelos (2007) analyzed the *CYP2D6* genotype of 21 members of the Mennonite community residing in the state of Durango. The allelic frequencies they report correspond to those found in Caucasian populations (Alanis-Bañuelos et al., 2007). In addition, in an extended Mennonite kindred from Durango, Cruz-Aguilar recently described a nonsense *ALMS1* mutation responsible for Alström syndrome (Cruz-Aguilar, Galaviz-Hernandez, Hiebert-Froese, Sosa-Macias, & Zenteno, 2017), an autosomal recessive disease that has also been described by Orton in a Mennonite patient from a settlement in Northern British Columbia (Orton et al., 2008).

The purpose of this study is to report the FA genotype found in a Mexican Mennonite community recapitulating the migration history of this group; in addition, we use several somatic phenotype scoring systems to describe the genotype–phenotype correlation of the FA patients with the homozygous *FANCC* c.67delG mutation.

2 | PATIENT

The proband is an 11-year-old male patient, member of the Mennonite Community of Tamaulipas, Mexico. He was born after an uneventful pregnancy, with adequate somatometry at birth. He is said to have had anemia at the age of 2 years, and was referred to our clinic at the age of 11 years after an infectious episode that revealed pancytopenia. His blood counts showed: Hb: 8.8 g/dl, MCV: 102.5 fl, ANC: 900/μl, platelets: 63,000/μl. This prompted a bone marrow biopsy that showed 10%–15% cellularity, indicating bone marrow failure. Physical examination showed height and weight in the 10–25 percentile with an adequate cephalic perimeter, eyes were normally set and showed upward palpebral fissures and a left epicanthal fold. Upon inspection, facial skin hyperpigmentation was noticeable and two 3 × 1 cm hyperpigmented café-au-lait spots were found in the back of his torso as well as a 4 × 1.5 cm hypochromic spot in the lumbar area. Upper extremities showed no radial alterations, with normal appearing thumbs and bilaterally palpable thenar muscles. Pubertal clinical data were not yet present. FA was corroborated by cytogenetic analysis through a DEB test. Upon the FA diagnosis, congenital malformations were intentionally sought: cardiac, renal, and ear malformations were not found by imaging studies, spine X-rays revealed a wedged T12 vertebrae (HP:0011940). Central nervous system imaging and ophthalmologic evaluation were not performed because the patient did not present clinical data warranting this kind of evaluation.

3 | MATERIALS AND METHODS

3.1 | Editorial policies and ethical considerations

The Institutional Ethics and Research Committees of the Instituto Nacional de Pediatría approved this study. After obtaining written informed consent, blood samples were obtained from the index patient, his siblings, and parents.

3.2 | Chromosome fragility test

DEB test was performed in all siblings. Two-paired lymphocyte cultures per each blood sample were grown in RPMI medium (Gibco, BRL, Grand Island, NY) and supplemented

with phytohemagglutinin (Gibco, BRL, Grand Island, NY). Half of the cultures were treated with 0.1 μg/ml diepoxybutane (DEB) (Sigma, St Louis, MO) from the start of incubation to induce DNA damage, the other half were used for analysis of spontaneous chromosomal breakage. All cultures were incubated for 72 hr at 37°C in a 5% CO_2 incubator and harvested. Metaphase spreads were prepared using standard protocols (Esmer et al., 2004). A normal non-FA peripheral blood sample and a FA lymphoblastic cell line were simultaneously processed to be, respectively, used as negative and positive controls for chromosome fragility. Chromosomal aberrations including breaks, fragments, dicentrics, rings, and radial figures were scored, and the frequency of aberrations per cell was calculated.

3.3 | Genotyping

Genomic DNA was obtained from peripheral blood samples using the Gentra Puregene Kit (QIAGEN, Venlo, Limburg, NL) it was then quantified using a NanodropTM spectrophotometer (Nanodrop Technologies, Wilmington, DE) and DNA integrity was verified by standard agarose gel electrophoresis.

PCR of each amplicon was performed from 100 ng of DNA template using purposely designed primers targeting exon 1 of *FANCC* (OMIM #613899, NM_000136.2) in the proband and his siblings, and neighboring SNPs rs1016013 and rs2277182, that have shown a CC/GG genotype in alleles from Mennonite descent irrespective of the presence of the *FANCC* (NC_000009.11(NM_000136.2):c.67delG p.(Asp23IlefsTer23)) mutation, in the proband and his parents. Primer sequences are described in Table S1 in the supplemental information; PCR products were purified with QIAquick kit (QIAGEN, Venlo, Limburg, NL) according to manufacturer instructions. Purified amplicons were bidirectionally sequenced using the Big Dye Terminator sequencing Kit, and resolved on an Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA). The electropherograms were analyzed with Chromas V2.5.1 software (www.technelysium.com.au) and target sequences were compared to the corresponding reference sequences from GenBank (https://www.ncbi.nlm.nih.gov). Alleles were described according to current nomenclature guidelines (http://www.hgvs.org/mutnomen/).

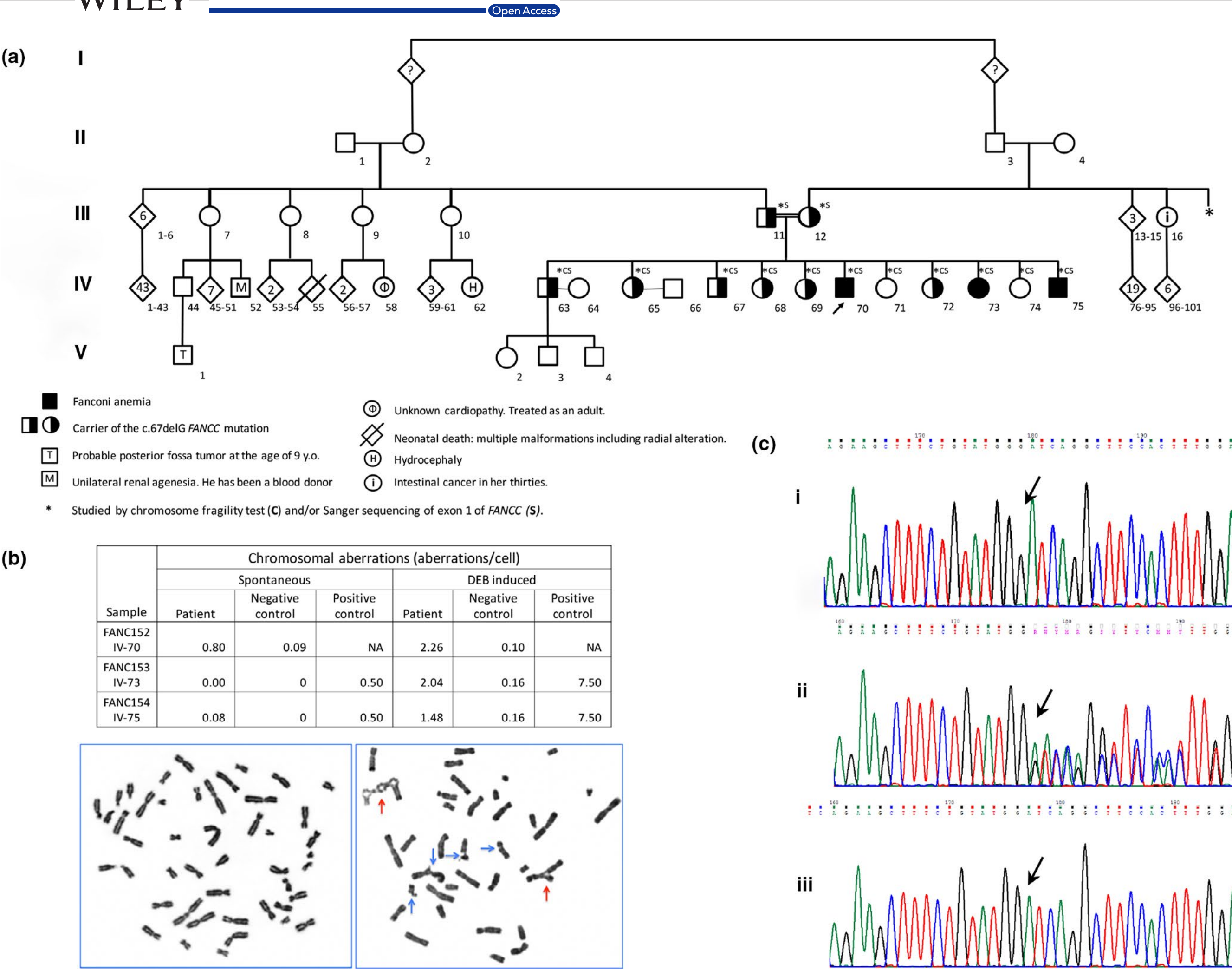
3.4 | Genotype–phenotype correlation

In order to attempt genotype–phenotype correlation, the somatic phenotypes of our patients and other published cases with the same mutation were described using different scoring systems that have previously been used in FA patients: (a) The simplified severity score (SSS) which is calculated by assigning a positive score of +1 to the presence of eight clinical manifestations (growth retardation, birthmarks, kidney, and urinary malformations, microphthalmia, low platelets, thumb, and radius abnormalities) and a negative score of −1 to the presence of two features (learning disabilities and other skeletal alterations) (Auerbach, Rogatko, & Schroeder-Kurth, 1989); (b) The Congenital ABnormalities Score (CABS) that considers the presence of the following set of variables: developmental delay, cardiopulmonary abnormality, abnormal kidney, abnormal hearing or deafness, abnormal head, and stature below the 10th percentile (Rosenberg, Huang, & Alter, 2004); (c) The VACTERL-H acronym: Vertebral, Anal, Cardiac, Traqueo-Esophagic, Renal, Limbs, Hydrocephaly (Alter & Rosenberg, 2013); and (d) The PHENOS acronym: Pigmentation, Small Head (microcephaly), Small Eyes (microphthalmia), Neurology (central nervous system anomaly), Otology, Short stature (Alter & Giri, 2016).

4 | RESULTS

Upon inquiry, the parents refer that they were both born in one of the original Mennonite settlements of Chihuahua, they are aware that at least one of the members of generation I, depicted in the family tree, arrived to Mexico in the 1920's migration. They also refer that they know they have common ancestors, although they could only refer which branches of the family tree connect them but were unable to pinpoint the exact tie (Figure 1a). The DEB test confirmed a FA diagnosis in the proband and revealed it in two of his siblings (Figure 1b). Both of these newly detected cases have height and weight in the 25–50 percentile, they have no renal or radial malformations and have not developed overt clinical hematological manifestations of the disease. However, peripheral blood cell counts from case IV-73, who is currently 5 years old, showed leukopenia of 3,000/μl, neutropenia of 1,110/μl, thrombocytopenia of 105,000/μl, and macrocytosis with normal hemoglobin levels of 12 g/dl. Blood cell counts from case IV-75, currently 2 years 9 months old, are in normal range (Leukocytes 7,300/μl, ANC: 4,599/μl, platelets: 225,000/μl, Hb: 11.8 g/dl). Unfortunately, no spine X-rays could be performed in any of the young affected siblings.

Sequence analysis confirmed the FA diagnosis in all three siblings with a positive DEB cytogenetic diagnosis (IV-70, IV-73, and IV-75) revealing *FANCC* c.[67delG];[67delG] genotypes (NC_000009.11(NM_000136.2):c.67delG p.(Asp23IlefsTer23)). Moreover, both parents and six siblings are heterozygous carriers of the mutation and harbor the *FANCC* c.[67delG];[=] genotype. The two remaining siblings did not carry this mutation (Figure 1c.). The distribution of genotypes in the studied individuals from generation IV is consistent with an unaltered Hardy–Weinberg equilibrium ($\chi^2 = 0.11$, one degree of freedom). The haplotype analysis,



Sample	Chromosomal aberrations (aberrations/cell)					
	Spontaneous			DEB induced		
	Patient	Negative control	Positive control	Patient	Negative control	Positive control
FANC152 IV-70	0.80	0.09	NA	2.26	0.10	NA
FANC153 IV-73	0.00	0	0.50	2.04	0.16	7.50
FANC154 IV-75	0.08	0	0.50	1.48	0.16	7.50

FIGURE 1 Cytogenetic and Molecular diagnosis in the family. (a) Family pedigree (b) DEB test results of the three affected individuals. Each time a patient is tested, a healthy individual's sample and cells from an FA-derived lymphoblastic cell line are analyzed in parallel as negative and positive controls for the test (historic values of the DEB test from our laboratory are: mean spontaneous aberrations/cell frequency for FA patients 0.28, for negative controls 0.03; mean DEB-induced aberrations/cell frequency for FA patients 2.54 and for negative controls 0.07). Left panel: Chromosomes from untreated FA cells. Right panel: Chromosomes from DEB-treated FA cells. Chromatid breaks are indicated with blue arrows and red arrows point radial figures. NA, data not available. (c) Sanger electropherograms: the arrows indicate the c.67 position, (i) wild-type *FANCC* [=];[=] genotype, (ii) heterozygous *FANCC* c.[67delG];[=] genotype and homozygous *FANCC* c.[67delG];[67delG] genotype. HGVS nomenclature (NC_000009.11(NM_000136.2):c.67delG p.(Asp23IlefsTer23))

which only contemplated the rs1016013 and the rs2277182 alleles that are, respectively, located 0.6 and 0.9 Mb upstream from the *FANCC* c.67delG mutation, showed that the proband and both his parents are homozygous for the alleles "C" and "G" (data not shown), evidencing that both the mutated allele as well as the wild type one are accompanied by these two SNPs.

Table 1 shows the clinical data of the three patients described here as well as other patients with the c.[67delG];[67delG] genotype available in the literature, according to published description systems. The SSS is available for all referred patients; most of them have scores of zero or one and none has a score larger than three. The other description systems could only be applied to the patients for whom raw clinical information was available; the CABS, and the VACTERL-H and PHENOS acronyms could only be retrieved in two patients other than the ones presented here. All patients had CABS of 0, except for a patient that had a score of 2. None of the patients had a concurrent diagnosis of VACTERL-H association, which requires at least three characteristics from the acronym, and neither of them presented four or more PHENOS features, which is what has been described as a FA signal in patients with a VACTERL-H diagnosis.

5 | DISCUSSION

Belonging to the Mennonite community as well as the particular migratory history of this family anticipated the finding of the *FANCC* c.67delG mutation. This genotype has also been found in FA patients of Dutch descent who do not

TABLE 1 Phenotype in patients with homozygous *FANCC* c.67delG mutation[a]

	FANCC Genotype	Simplified severity score[a,b]	CABS[b,c]	VACTERL-H[c,d]	PHENOS[d,e]	Reference
VU001	c.[67delG];[67delG]	Mild FA (1)	ND	ND	ND	Yamashita et al. (1996)
VU002	c.[67delG];[67delG]	Mild FA (2)	ND	ND	ND	
VU158	c.[67delG];[67delG]	Mild FA (1)	ND	ND	ND	
VU166	c.[67delG];[67delG]	Mild FA (1)	ND	ND	ND	
PD25	c.[67delG];[67delG]	Mild FA (2)	ND	ND	ND	
Older sib of VU1454	c.[67delG];[67delG]	Mild FA (3)	2	C	PS	de Vries et al. (2012)
VU1454	c.[67delG];[67delG]	Mild FA (1)	0	None	P	
FANC152 (IV-70)	c.[67delG];[67delG]	Mild FA (1)	0	V	P	This study
FANC153 (IV-73)	c.[67delG];[67delG]	Mild FA (1)	0	None (No vertebral X rays)	None	
FANC154 (IV-75)	c.[67delG];[67delG]	Mild FA (0)	0	None (No vertebral X rays)	None	

Note: ND: No Data, the authors do not describe raw clinical data for each patient.
[a]Nomenclature *FANCC* mutation according to HGVS: (NC_000009.11(NM_000136.2):c.67delG p.(Asp23IlefsTer23))
[b]Simplified severity score according to Auerbach et al. (1989). A score of 3 or less is considered a mild phenotype (Verlander et al., 1994; Yamashita et al., 1996).
[c]CABS number of abnormalities in the set of developmental delay, cardiopulmonary abnormality, abnormal kidney, abnormal hearing or deafness, abnormal head, and stature below the 10th percentile (Rosenberg et al., 2004).
[d]VACTERL-H: Vertebral, Anal, Cardiac, Traqueo-Esophagic, Renal, Limbs, Hydrocephaly (Alter &Rosenberg, 2013).
[e]PHENOS: Pigmentation, Small Head (microcephaly), Small Eyes (microphthalmia), Neurology (central nervous system anomaly), Otology, Short stature (Alter & Giri, 2016).

belong to the Mennonite community (De Vries et al., 2012), as well as in populations where a founder effect is not clear (Faivre et al., 2000). The historical link between the Mexican and the Canadian Mennonites is further substantiated by the fact that this family carries the haplotype composed by rs1016013/CC and rs2277182/GG in both the disease and the healthy alleles, like it was shown in the Manitoba Mennonite kindred de Vries described (de Vries et al., 2012).

Various systems have been used to describe the somatic phenotype of FA patients. The SSS was originally developed to distinguish FA patients who have a DEB-positive test from patients with other aplastic anemias. (Auberbach et al., 1989). A value of less than three is interpreted as a mild phenotype (Verlander et al., 1994; Yamashita et al., 1996). The three FA patients reported here show scores of one or less which is in agreement with what has been found in other patients with the same genotype.

In FA patients, the adjusted numeric CABS score is correlated with the risk to develop bone marrow failure (BMF): each unit increase of the score represents a 1.23-fold increase in the risk without taking into account the genotype. All the patients from our family have favorable CABS of 0 and no radial alteration, which does not modify the BMF risk. The cumulative incidence of BMF for patients with this phenotype according to Rosenberg is 6% by age 5 years and 18% by age 10 (Rosenberg et al., 2004). Bone marrow transplantation was performed in the proband (IV-70) at the age of 11 years, the donor was HLA compatible sibling IV-72, the patient is currently 28 months posttransplant with a stable chimera, his sister (IV-73) showed bicytopenia by age 5, and his young affected brother (IV-75) is yet to show hematologic symptoms. Regarding the patients described by de Vries, there is no hematologic information available for VU1454 who also had CABS 0, but the older sib who had a score of 2 meaning a 1.5-fold ($1.23^2 = 1.5$) increase risk of BMF, died from bone marrow transplantation complications by the age of six. None of these *FANCC* c.67delG patients show more than 2 abnormalities contemplated in the CABS, which is below the mean of 3.3 abnormalities found in the cohort of patients described by Rosenberg et al., (2004).

The combination of the acronyms VACTERL-H and PHENOS encompass most of the physical abnormalities that can be found in FA patients, and include all the physical features considered by both SSS and CABS. In thoroughly studied FA patients, VACTERL-H association was found in up to 33%, and the FA signal composed by four PHENOS features was present in all of them, meanwhile in FA patients who do not have VACTERL-H, PHENOS features are less frequent (Alter & Giri, 2016). Patients with mutations in *FANCC* are not overrepresented among patients with VACTERL-H (Alter &Rosenberg, 2013). None of the patients shown in Table 1 have a concurrent diagnosis of VACTERL-H association, and they barely present any PHENOS feature.

In published cases, this mutation has been associated with a mild phenotype where, despite variability, the main clinical

feature is hematological. Patients with the *FANCC* c.[67delG];[67delG] genotype have been found to present later age of onset and a milder course of hematologic symptoms when compared to other FA patients irrespective of their genotype. They have also been found to have lower numbers of somatic abnormalities and early cancer onset has not been reported (de Vries et al., 2012; Faivre et al., 2000; Yamashita et al., 1996). The clinical presentation of the patients from this family is in agreement with this, as evidenced by the scoring systems used, showing a mild somatic phenotype. Although the main purpose of these systems was other than simply describing the phenotype of FA patients, they are useful to systematically describe and classify the somatic phenotypic variability of FA.

The finding of this mutation in the Mennonite community of Tamaulipas has raised awareness on the possibility of undiagnosed FA patients with mild phenotypes living in the Mexican Mennonite community. Given the inbred genetic background of this community the clinical study of Mennonite FA patients could be an opportunity to study possible genotype–phenotype correlations in a setting with a fairly controlled genetic background.

The identification of the *FANCC* c.67delG mutation in this family is central to guide the selection of the BMT donors, assuring the election of a non-FA family member. Moreover, it allows proper genetic counseling as well as raising awareness of FA risk among the Mennonite community living in Mexico, for whom the carrier frequency of this mutation is unknown. Moreover, direct genotyping of the *FANCC* c.67delG mutation can be offered to patients with suspected FA and to individuals interested in making informed reproductive decisions.

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CONFLICT OF INTEREST

The authors certify that they do not have any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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