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Fanconi Anemia: Challenges in Diagnosis and Management—A Case Series Report

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ABSTRACT

Fanconi anemia (FA) is a rare inherited disorder characterized by congenital abnormalities, progressive bone marrow failure, and a predisposition to malignancies. Detecting FA can be challenging, as it involves identifying increased chromosomal sensitivity to DNA cross-linking agents and detecting causative genetic variants via genome sequencing. We report two cases of siblings with FA, both confirmed to have the FANCD2 variant through whole-exome sequencing (WES). The first patient presented with epistaxis, petechiae, ecchymosis, and lower limb edema. The second patient exhibited epistaxis, diabetes, developmental delay, and physical abnormalities. Interestingly, both patients had negative results on the initial chromosomal breakage test with mitomycin C, a commonly used diagnostic tool for FA. However, further investigation with WES revealed the presence of the FANCD2 variant, confirming the FA diagnosis. This case report highlights the challenges in diagnosing FA, particularly when initial screening tests yield negative results. Molecular genetic testing, such as WES, can provide a definitive diagnosis and guide appropriate management strategies. Early and accurate diagnosis is crucial for improving outcomes in individuals with this potentially fatal illness, as promising advancements in treatments such as hematopoietic stem cell transplantation and gene therapy offer hope for addressing FA.

JEL Classification: Hematology

1 | Introduction

Fanconi anemia (FA) is a rare heterogenous genetic disorder that is the result of autosomal recessive inheritance, although it can also be inherited rarely through the X-linked recessive model [1]. The global occurrence of FA is estimated to be 1 in every 160,000–360,000 individuals, with a carrier frequency of 0.3%. However, it is known to be more common in communities where there are consanguineous marriages such as Ashkenazi Jews, South African blacks, Turks, Saudi Arabians, and Iranians [2, 3]. The clinical manifestations of FA are diverse and can include pancytopenia, hyperpigmentation, skeletal abnormalities, small stature, low birth weight, radial ray affection, vertebral anomalies, microcephaly, deafness, congenital heart defects, kidney malformations, genitourinary abnormalities, and supernumerary thumbs [4, 5]. While hematological abnormalities are the characteristic feature of FA, bone marrow failure (BMF) is usually the first sign of FA. Approximately 80% of people with FA develop progressive BMF between the ages of 8 and 10, and 23% of patients may later develop various types of cancer [6]. Patients frequently present with low platelet counts (thrombocytopenia $\geq 30 \times 10^9$/L) which can often be managed with conservative therapy for several years.

The genetic basis of FA is complex, with variants identified in 22 distinct FA genes, which include FANCA, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T, U, V, and W [7]. Over 80% of these genetic

Summary

- This case series highlights the diagnostic challenges of Fanconi anemia when initial chromosomal breakage tests yield negative results.
- Whole-exome sequencing is essential in confirming the diagnosis, particularly for cases with genetic mosaicism, emphasizing the importance of molecular genetic testing in suspected Fanconi anemia cases.

changes occur in the FANCA, FANCG, and FANCC genes, while other variants are less common [8]. Most variants in the FANC genes are inherited recessively, except for FANCB (X-linked) and FANCR (dominant) [8]. To understand how these variants lead to the clinical manifestations of FA, it is crucial to assess the role of FA proteins in DNA repair processes. The proteins encoded by FA genes function to fix the interstrand cross-links (ICL) that usually occur during DNA replication and transcription, using a pathway called the Fanconi pathway [9–11]. ICL is a covalent linkage between two strands of the double helix and is considered one of the most dangerous types of DNA damage [12]. The absence or malfunction of any FANC protein can significantly impair DNA repair or impact DNA replication, leading to chromosomal breakage, genetic instability, premature aging, aplastic anemia, and ultimately, cancer [13–15].

FA core proteins (consisting of FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM, and FANCT) work in coordination with other DNA repair systems such as nucleotide-excision repair, translation synthesis, and homologous recombination (HR) [16–18]. These core proteins also interact with cell cycle checkpoint response mediators and DNA damage response proteins, including ataxia telangiectasia mutated (ATM) and Nijmegen breakage syndrome 1 (NBS1). Additionally, they interact with DNA-repair response protein FANCR/RAD51 and multiple breast cancer–associated proteins such as FANCS/BRCA1 and FANCD1/BRCA2, collectively forming what is known as the FA/BRCA pathway.

The complex pathophysiology of FA presents unique challenges in diagnosis, requiring a combination of clinical, cytogenetic, and molecular approaches. The diagnosis of FA is established through the identification of hypersensitivity to clastogenic DNA cross-linking agents such as mitomycin C (MMC) and diepoxybutane (DEB) [19]. However, some individuals with FA may receive false-negative results on chromosome breakage tests due to hematopoietic reversion or mosaicism [20, 21]. This means that these patients may have two different populations of blood cells. One population is susceptible to DNA-damaging agents such as MMC or DEB, which is in line with an FA diagnosis, while the other group is resistant to these DNA-damaging agents [22]. In such cases, additional diagnostic methods, such as flow cytometry to detect MMC sensitivity in skin fibroblasts, can accurately identify these cases [20, 21].

Molecular analysis is necessary for a definitive diagnosis, prognosis assessment, and genetic counseling. Various molecular screening techniques, including polymerase chain reaction (PCR)-direct sequencing, multiplex ligation-dependent probe amplification (MLPA), and progression to next-generation sequencing (NGS) through whole-exome sequencing (WES) or targeted exome sequencing (targeted-seq), could be utilized to identify specific genetic variants in these patients [23, 24].

Given the complex etiology of FA and its potentially severe outcomes, effective management of the disease requires a multifaceted treatment approach. Regarding the treatment, different therapeutic approaches such as the administration of androgen and hematopoietic growth factors, as well as hematopoietic stem cell transplantation (HSCT), are currently employed for treating FA [25]. From a clinical perspective, with the increased availability of donors and enhanced conditioning regimens, HSCT has become a standard treatment option for the blood-related symptoms of FA [26, 27]. Currently, research into novel therapies, including gene therapy and targeted molecular approaches, is ongoing.

This case series report focuses on two brothers diagnosed with Fanconi's anemia. Despite negative results from the MMC chromosomal breakage test, genetic testing confirmed that both brothers had FANCD2 and FA variants. These cases highlight the challenges in diagnosing FA and underscore the importance of comprehensive genetic testing in suspected cases.

2 | Method and Case Presentation

2.1 | Patient 1

2.1.1 | Consent

The patient's parent provided written informed consent for the publication of their medical information in this case report.

2.1.2 | Family History

An 8-year-old boy from Afghanistan, residing in *Varamin*, *Tehran* suburb, was born on March 22, 2015. He is the seventh child of consanguineous parents (first-degree cousins). His older brother died at age 11 due to FA, and his older sister had a history of glioblastoma. Another sibling has a liver tumor and physical abnormalities.

2.1.3 | Clinical Presentation

The patient was admitted to the hospital hematology ward presenting with epistaxis, petechiae, ecchymosis, and lower limb edema. He exhibited physical abnormalities including microcephaly, shorter limbs, and a shorter thumb. Over the preceding 4 years, the patient experienced recurrent episodes of nose and mouth bleeding, bruising, petechiae, and purpura.

2.1.4 | Laboratory Findings

Complete blood count (CBC) revealed leukopenia, anemia, and thrombocytopenia with macrocytic anemia. Bone marrow

aspiration showed hypocellularity without fibrosis or blasts. Detailed laboratory results are presented in Table 1.

2.1.5 | Treatment and Outcome

The patient received supportive platelets and packed cell transfusions. Despite being a potential candidate for BMT, no HLA-matched donor was found among his siblings. On May 27, 2023, the patient was admitted to *Aliasghar Hospital* with severe hematemesis and epistaxis. Despite treatment efforts, the patient died of his condition before a suitable donor could be found for BMT.

2.2 | Patient 2

2.2.1 | Family History

This 12-year-old boy is the older brother of Patient 1 and the fifth child in the family.

2.2.2 | Clinical Presentation

The patient had been under medical supervision since age six due to epistaxis and low hemoglobin. He presented with multiple clinical manifestations including diabetes (type unspecified), petechiae and ecchymosis in various organs, syndromic facies, microcephaly, developmental delay, mild intellectual disability, and speech impairment. Notably, the patient's right thumb was absent, and the left thumb was deformed. Abdominal examination revealed no abnormalities in the kidney, liver, or spleen.

2.2.3 | Laboratory Findings

CBC revealed leukopenia and thrombocytopenia. Peripheral blood smear showed macrocytes, and bone marrow aspiration demonstrated hypocellularity without fibrosis or blasts. Table 1 provides a detailed summary of the laboratory findings for both patients.

2.2.4 | Outcome

The patient died at home from a cardiac event on April 12, 2023, before reaching the hospital.

3 | Results

This study utilized a comprehensive diagnostic approach for FA, including chromosomal breakage analysis, and WES. These methods were utilized to overcome the challenges in diagnosing FA, particularly in cases where routine tests may yield inconclusive results.

3.1 | DNA Extraction for Molecular Genetic Testing

Following the acquisition of informed consent, 2 mL of EDTA blood samples were collected from the patients. Genomic DNA was isolated from white blood cells using the SinaPure DNA(EX6001) kit.

3.2 | Chromosomal Breakage Analysis with MMC

The primary step in genetic testing for FA encompasses analyzing cross-linking agents like MMC or DEB. An increased number of chromosomal gaps and breaks, as well as distinct radial formations, are observed in individuals with FA diagnosis [28].

In the present study, approximately 3–4 mL of peripheral blood samples were obtained from each patient in a heparinized tube. We obtained chromosomal spreads by initiating a 72-h culture of peripheral blood cells using phytohemagglutination. Our study analyzed a total of 280 metaphase spreads. Twenty spreads were from routine culture, while 160 spreads were from cultures treated with two different concentrations of MMC. Additionally, we obtained 100 spreads from a normal control group within the same age range. The chromosomal breakage analysis revealed that neither patient reached the threshold for a positive test, which is typically considered as breakage exceeding 10 times that of the control. Patient 1 showed an average of 0.04 breaks per metaphase, which is within the normal range. Patient 2 exhibited a slightly higher rate of 0.06 breaks per metaphase, including one radial rearrangement. While this result for Patient 2 does not meet the criteria for a positive test, it is higher than that observed in normal individuals, suggesting a borderline result. The information is summarized in Table 2.

Despite the inconclusive results from the chromosomal breakage analysis, the clinical presentation of both patients strongly suggested a diagnosis of FA. Considering the limitations of chromosomal breakage testing, particularly in cases of somatic mosaicism or certain FA subtypes, further genetic investigation was warranted. Therefore, WES was employed as a more comprehensive genetic testing approach.

3.3 | Whole-Exome Sequencing

WES utilizes NGS technology to detect variations in the coding sections, or exons, of established genes. This method has been

TABLE 1 | Summary of laboratory findings for Patients 1 and 2.

	WBC ($\times 10^3$/mm^3)	RBC (mL/mm^3)	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pgm)	MCHC (g/dL)	RDW (%)	Platelet ($\times 10^3$/mm^3)
Patient 1	2.8	1.01	3.4	11.4	112.9	33.7	29.8	15.5	<10
Patient 2	2.5	1.22	4.1	13.6	111.5	33.6	30.1	15.4	15

TABLE 2 | Chromosomal breakage analysis results.

Subject	Total metaphases	Cells with breaks	Total breaks	Radial rearrangements	Breaks per metaphase
Patient 1	100	3	4	0	0.04
Patient 2	100	6	6	1	0.06
Normal control	100	1	1	0	0.01

- Cultures were treated with MMC.
- A breakage rate exceeding 10 times the control is considered clinically significant for FA diagnosis.

shown to identify over 95% of exons, including numerous single nucleotide polymorphisms (SNPs) that contribute to disease susceptibility [29]. Moreover, WES can detect variations in the coding regions of genes, including those not typically included in targeted FA panels [30]. The reduced cost of sequencing and improved computational capabilities have made WES an increasingly valuable tool in clinical genetic testing platforms, enhancing the ability to diagnose rare genetic diseases such as FA [31].

In this study, WES was performed on DNA samples from both patients. Following data acquisition, specialized software was used for analysis. Analysis of the sequencing data revealed a homozygous frameshift variant c.7480C>T (p.Arg2494Ter) in the FANCD1 gene in both patients, confirming the diagnosis of FA.

4 | Discussion

The cases presented here illustrate the complexities and challenges in diagnosing and managing FA, a rare genetic condition characterized by bone marrow failure, chromosome breakage, and an increased risk of cancer. Despite negative results from the chromosomal breakage test (MMC), which is a commonly used diagnostic tool for FA, both patients were ultimately confirmed to have the FANCD2 variant through WES.

Notably, to the best of our knowledge, this study represents the first reported cases where patients with confirmed FANCD2 variants and FA demonstrated negative results on the chromosomal breakage test using MMC. This unexpected result underscores the complexity of FA diagnosis and the potential limitations of standard diagnostic tests in certain genetic variants of the disease.

The FANCD2 gene is one of the 22 genes associated with FA, and variants in this gene account for a significant proportion of FA cases [8]. Eight of the FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM) and other components assemble in a nuclear complex known as the FA "core complex." This complex is essential for the monoubiquitination of FANCD2 at amino acid residue K561 [32, 33]. Monoubiquitination occurs in response to DNA damage and during the S phase of the cell cycle [33]. The monoubiquitinated form of FANCD2 (FANCD2-L) is directed to nuclear foci containing proteins such as BRCA1, BRCA2, and RAD51, which are involved in DNA-damage signaling and recombinational repair [34–36]. The specific role of FANCD2 is not fully understood, but FANCD2-deficient DT40 cells exhibit deficiencies in homologous recombination-mediated DNA double-strand break repair, translation synthesis, and gene conversion [37, 38]. Therefore, the FANCD2 protein plays a crucial role in maintaining genome stability and repairing ICLs in DNA [38, 39]. Defects in this pathway can lead to chromosomal instability, impaired DNA repair, and an increased risk of malignancies, as is considered frequent in FA patients [15]. The FA phenotype caused by a lack of FANCD2 is relatively severe [40]. Unlike other FA genes, splicing variants are the primary type of variant in FANCD2 [41]. Understanding the complex role of FANCD2 is crucial for interpreting the clinical and diagnostic findings in our patients.

With this understanding of FANCD2's critical role in DNA repair and genomic stability, we can better interpret the unexpected diagnostic results in our cases. The negative results from the chromosomal breakage test in these cases highlight the importance of considering molecular genetic testing, even when initial screening tests are negative. While the chromosomal breakage test is a valuable diagnostic tool, it is not completely reliable or accurate, and false-negative results can occur due to factors such as somatic mosaicism or hematopoietic reversion [19, 21, 42]. In such cases, molecular genetic testing can provide a definitive diagnosis and guide appropriate management and genetic counseling.

The clinical manifestations of FA can vary widely, even among patients with the same genetic variant, as illustrated by the differences between the two brothers in this report. Patient no.1 presented with more severe hematological abnormalities, including epistaxis, petechiae, ecchymosis, and lower limb edema, while Patient no.2 exhibited additional features such as diabetes, developmental delay, and physical abnormalities. This variability underscores the importance of comprehensive clinical evaluation and management tailored to the individual patient's needs.

Interestingly, the diagnosis of high-grade glioblastoma in the 9-year-old sister raises important considerations relevant to the FA cases described. While the sister herself was not reported to have FA, the occurrence of such an aggressive malignancy at a young age within the same family suggests a potential shared genetic predisposition or underlying genomic instability that may have contributed to the development of these different conditions.

The occurrence of both FA and early-onset glioblastoma within the same family underscores the complex interplay of genetic factors in this consanguineous background. The consanguineous marriage between the parents, who are first-degree cousins, increases the risk of inheriting autosomal recessive disorders like FA, as well as other potential genetic

predispositions [43]. The presence of multiple affected children in the family, including the two brothers with FA and the sister with glioblastoma, suggests a shared genetic factor or variant that may have contributed to the development of these distinct but related conditions.

Unfortunately, both patients died due to the complications of their disease before receiving definitive treatment, such as HSCT or gene therapy, which are emerging as promising treatment options for FA patients [25, 27]. Early diagnosis and timely intervention are crucial in improving outcomes for these patients.

While the precise connection between FA and glioblastoma is not well established, this case series highlights the potential for rare and severe manifestations within families with underlying genetic defects in DNA repair pathways. Further investigation into the genetic profiles of these individuals may shed light on the specific mechanisms linking FA and brain tumors, as well as the influence of consanguinity on the manifestation of such conditions.

5 | Conclusion

In conclusion, diagnosing and managing FA present significant challenges due to the disorder's genetic heterogeneity and variable clinical presentation. Our case series of two brothers with FA, confirmed through WES despite negative chromosomal breakage tests, highlights the importance of comprehensive genetic testing. Negative results from initial screening tests should not prevent further investigation, as molecular genetic testing may be necessary to confirm a diagnosis. Early diagnosis and appropriate management, including consideration of emerging treatments such as HSCT and gene therapy, are essential for improving outcomes in patients with this life-threatening condition.

Author Contributions

Aziz Eghbali: conceptualization. **Seyed Mehrab Safdari:** methodology, writing – original draft, writing – review and editing. **Maedeh Yousefi Roozbahani:** investigation, writing – original draft. **Khatereh Tavajohi:** methodology. **Soudabeh Hosseini:** conceptualization, investigation, methodology.

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During the preparation of this work, the author(s) used Open AI in order to improve the article's English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Ethics Statement

Our study was approved by an ethics committee of Aliasghar Children's Hospital and Iran University of Medical Sciences.

Consent

The patient's parent provided written consent for the publication of this report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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