Received: 22 February 2024 | Revised: 11 April 2024 | Accepted: 17 April 2024

DOI: 10.1111/cge.14537

SHORT REPORT

CLINICAL GENETICS WILEY

Pediatric acute promyelocytic leukemia and Fanconi anemia: Case report and literature review

Claire Freycon[1,2] | Edith Sepulchre[3,4] | Vincent-Philippe Lavallée[4,5] | David Mitchell[1] | Margaret L. MacMillan[6] | Catherine Vezina[1] | Catherine Goudie[1,2]

[1]Department of Pediatrics, Division of Hematology-Oncology, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

[2]Department of Child Health and Human Development, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

[3]Department of Human Genetics, GIGA Research Center – University of Liège and Centre Hospitalier Universitaire Liège, Liège, Belgium

[4]Research Center, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada

[5]Department of Pediatrics, Division of Pediatric Hematology-Oncology, Charles-Bruneau Cancer Center, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada

[6]Department of Pediatrics, Division of Blood and Marrow Transplantation & Cellular Therapy, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Claire Freycon, Department of Pediatrics, Division of Hematology-Oncology, Montreal Children's Hospital and Department of Child Health and Human Development, Research Institute of the McGill University Health Centre, McGill University Health Centre, Montreal, Quebec, Canada.
Email: claire.freycon@muhc.mcgill.ca

Funding information
Cedars Cancer Foundation/Sarah's Funds; Cancéropôle Lyon Auvergne Rhône-Alpes; Fondation Charles-Bruneau; Fonds de recherche du Québec, Grant/Award Number: 253761; Fondation ARC pour la Recherche sur le Cancer; Cole Foundation; Fondation de l'hopital pour enfants de Montreal

Abstract

Acute promyelocytic leukemia (APL) represents 5%–10% of childhood acute myeloid leukemia (AML) and is the most curable subtype of AML. Fanconi anemia (FA) is one of the most common inherited bone marrow failure syndromes caused by biallelic pathogenic variants (PV) in specific DNA-repair genes. Biallelic PVs in *FANCD1/BRCA2* (FA-D1) account for 3% of FA and are associated with early-onset leukemia and a high risk of solid tumors. We report a 4 year-old boy from non-consanguineous parents diagnosed with standard risk APL. This child had café-au-lait spots and an extra thumb remnant. Genomic sequencing revealed two PV in *FANCD1/BRCA2* confirming a diagnosis of FA-D1. Chromosomal breakage studies were compatible with FA. Each parent carried one variant and had no personal history of cancer. Morphological then molecular remissions were achieved with all-trans retinoic acid and Arsenic trioxide. This patient underwent haploidentical stem cell transplant. In addition to our patient, a literature search revealed four additional patients with APL/FA, with a total of three patients with FA-D1. This raises the possibility of an association between such rare disorders. Practical management of APL in the setting of FA-D1 is discussed with an overview of current evidence and knowledge gaps.

KEYWORDS
acute promyelocytic leukemia, cancer predisposition syndrome, cancer surveillance, Fanconi anemia, stem cell transplant

1 | INTRODUCTION

Acute promyelocytic leukemia (APL) represents 5%–10% of pediatric acute myeloid leukemia (AML).[1] It is characterized by the balanced translocation t(15;17)(q24.1;q21.2), leading to PML-RARA fusion gene.[2] Advances in therapy with the combined use of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have improved outcomes for patients with APL in the past several decades, with an average overall survival of 94% and event-free-survival of 90%.[3] A variety of cancer predisposition syndromes have been found in approximately 4% of AML,[4] including Down syndrome, Fanconi anemia, and several other bone marrow failure syndromes, without specific data for APL.

Fanconi anemia (FA) is a rare genetic disorder characterized by congenital anomalies, progressive bone marrow failure, and increased risk for malignancy, particularly myeloid malignancies as well as solid tumors such as head and neck squamous cell carcinomas (HNSCC). The diagnosis of FA is established by demonstrating increased chromosome breakage on cytogenetic testing of lymphocytes with standard concentrations of diepoxybutane (DEB) and mitomycin C, and/or with germline DNA sequencing revealing pathogenic variants (PV) in FA-related genes. Currently, PV in 23 genes are known to be associated with FA. Certain genotype–phenotype correlations are highlighted in FA, notably with FA related to biallelic variants in *BRCA2/FANCD1*[5] (FA-D1). Biallelic PV in *FANCD1/BRCA2* account for 2%–3% of all known cases of FA.[6] In this particular subtype, there is an extremely high risk for early-onset acute leukemia and solid embryonal tumors, predominantly Wilms tumor, medulloblastoma, and neuroblastoma.[7,8] The cumulative incidence of any malignancies reaches 76% to 97% in pediatric age.[7,9] This unique tumor spectrum is also seen in FA associated with biallelic PV in *FANCN/PALB2* gene.[10,11]

In this case report, we describe a child presenting with APL prior to recognition of a diagnosis of FA-D1. We also review the literature on the association between these two rare conditions and the overall clinical management strategy for this child.

2 | CASE REPORT

A four-year-old boy, from non-consanguineous healthy parents from India, presented with a recent history of muco-cutaneous bleedings and fever. The initial complete blood count revealed pancytopenia (white blood cells: 3.3×10^9/L, platelets: 8×10^9/L, hemoglobin: 60 g/L, MCV 79 fl). Hypergranular blasts with Auer rods and Faggot cells were seen on the peripheral blood and bone marrow morphology, suggesting APL. A PML-RARA rearrangement t(15;17)(q24;q21) was confirmed on cytogenetic analysis by fluorescence in situ hybridization. The patient did not have disseminated intravascular coagulation. A brain computerized tomography scan performed at diagnosis demonstrated a Chiari 1 malformation. Patient history and physical examination were notable for numerous café-au-lait macules (CALMs) and scarring from an extra thumb remnant removed surgically in the neonatal period. His weight and height were above the 99th percentile for age. The child was developmentally normal and had no clear facial dysmorphic features or other anatomical anomalies often seen in FA patients. He had no siblings. Both parents had no personal history of cancer, though certain relatives had cancer diagnoses (pedigree depicted in Figure 1).

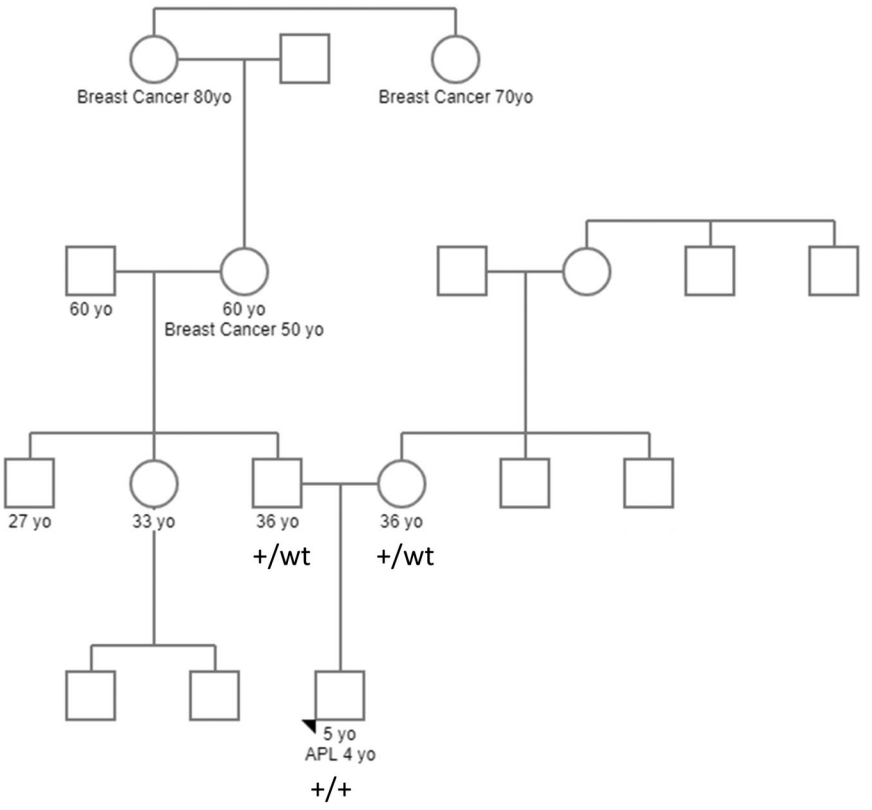

FIGURE 1 Family pedigree. APL, acute promyelocytic leukemia; wt, wild type. Arrow: proband. +/+: *BRCA2/FANCD1* compound heterozygous, +/wt: *BRCA2/FANCD1* heterozygous status.

TABLE 1 Chromosomal breakage results (cultures treated with 0.1 mcg/mL with diepoxybutane).

Percentage of aberrant cells	26
Percentage of multiaberrant cells	18
Breaks/cell	1.58
Breaks/multiaberrant cell	7.89
Percentage of cells with radial figures	12
Chromosomal fragility index	205.11

The patient received ATRA and ATO following the Children's Oncology Group protocol AAML 1331 (Standard risk). He tolerated the treatment well, without bone marrow suppression. He was in morphological remission after 1 month of induction, and in molecular remission after the end of two blocks of consolidation, which he maintained at the time of this report (17 months post diagnosis).

Paired somatic/germline DNA sequencing was available through the Quebec pediatric cancer research sequencing initiative (Signature study). Germline analyses identified two PV in *FANCD1/BRCA2* gene, c.1333dup (p.Ser445Phefs*7) in exon 10 and c.6896dup (p.Asn2299Lysfs*41) in exon 12, confirming the diagnosis of FA. These variants were confirmed clinically in the local molecular diagnostics laboratory (McGill University Health Center). Genetic analyses in both parents revealed that the c.1333dup variant was present in the father and that the c.6896dup variant was present in the mother. Chromosomal breakage analysis with DEB on lymphocytes was performed 1.5 months after the diagnosis and was compatible with a FA diagnosis, possibly reflecting the compound *BRCA2* heterozygosity (see Table 1). With this finding of FA-D1, the young boy initiated an extended cancer screening approach, which included an abdominal ultrasound and urine catecholamines every 6 months for Wilms and neuroblastoma, as well as a brain magnetic resonance imaging (MRI) annually for brain tumors.

The underlying germline condition led the oncology team to offer a hematological stem cell transplant (HSCT) in an attempt to reduce risks of disease recurrence or subsequent hematological malignancies. Given that the patient had no matched donor, he underwent an TCR alpha/beta depleted haploidentical HSCT from his mother with a conditioning regimen of anti-thymocyte globulin, Fludarabine, low dose Cyclophosphamide and total body irradiation (TBI) of 200 cGy single dose.[12] He presented an acute graft rejection with autologous recovery, possibly secondary to this attenuated conditioning. The child is clinically well 2 months post HSCT and is awaiting another haploidentical HSCT (same donor, different conditioning regimen).

3 | DISCUSSION

This case report, presenting a 4 year-old boy with APL and FA-D1, is instructive as it allows the discussion of the epidemiological aspects and the practical clinical management decisions that arise in the setting of this combination of rare disorders.

While the association of AML and FA is well known, there is no evidence in the literature to suggest a particular association between APL and FA. Through a combination of search strategies (PubMed, Google scholar, disease-specific websites), we identified four additional cases shown in Table 2.[13–15] A total of five patients (including this case report) with APL/FA (confirmed FA-D1, $n = 3$) have been reported, raising the possibility of an association between such rare disorders. Two publications did not specify the molecular subtype of FA, though one of the patients had a brother with bilateral Wilms tumors, suggesting a *FANCD1/BRCA2* or *FANCN/PALB2* genotype. Clinicians should consider the possibility of FA in patients with APL and clinical manifestations of FA such as CALMs or suspicious family histories.

Patients with FA-D1 have a distinct cancer spectrum with a strikingly high rate of solid tumors as well as hematological malignancies.[7,8] In a recent publication on 71 patients with *FANCD1/BRCA2* variants from literature review, there were 94 cancers in 66 patients, of which 33% were acute leukemia (unspecified types), 27% were brain tumors (mainly medulloblastoma), 17% were Wilms tumors and 6% were neuroblastoma (median age of diagnosis: 2, 3, 1.2, and 1 year, respectively).[11] Our patient as well as the other 2 patients with confirmed FA-D1 identified in the literature were diagnosed with APL at older ages (4–5 years) and without solid tumors, beyond the median ages at which solid tumors occur. Based on a recent cancer risk prediction scoring system in patients with FA-D1, developed by Radulovic et al,[16] our patient's genotype was consistent with a score of 1. In that study, a score of 1 was associated with 100% risk of developing a first cancer at a median age of 2.3 years and a 29% rate of multiple malignancies.

Currently, patients with standard risk APL who respond well to treatment have a good prognosis and HSCT is not typically indicated. However, the question of HSCT was raised with the knowledge of the underlying FA, given that MDS/AML are indications for prompt transplant.[17] In a previous publication on hematological malignancies in the setting of FA, post-HSCT relapse rates were reported in 50% of patients with FA-D1 (3 of 6 patients).[18] Outcome data on patients with AML and FA-D1 who did not undergo HSCT is not available in the literature.

As mentioned, a HSCT was proposed for our patient despite the good prognosis generally associated with APL and remission status due to high risk for a second hematological malignancy. It is of note that this patient has a high risk for solid embryonal malignancies, independently of a HSCT. The patient will receive a reduced intensity conditioning regimen described by Strocchio et al. ($n = 24$ patients with bone marrow failure phenotypes) prior to a haploidentical HSCT. This regimen was associated with a good engraftment rate (91.6%), a low incidence of acute and chronic graft-versus-host-disease (GvHD) (17.4% and 5.5%, respectively) and no fatal transplant related toxicities.[12] Limiting chronic GvHD is theoretically relevant given the increased risk of HNSCC in patients with FA.[19,20] However, no cases of HNSCC have been reported in patients with FA-D1.[11] Patients with FA are more sensitive to genotoxic therapies, such as radiation and alkylating agents. Nevertheless, there is no current evidence

TABLE 2 Cases with APL and FA reported in literature.

ID	Sex	Age of APL (years)	FA Gene	APL therapy	Outcome	Phenotype	Family history	References
1	M	1.7	U	Fludarabine Cytarabine ATRA No HSCT Maintenance	Relapse and died 14 months after disease progression	Features of FA and imperforate anus at birth	Death of older sibling at the age of 15 months old following surgery for bilateral Wilms tumor, he was microcephalic and born with an imperforate anus, not tested for FA	Eissa et al.[13]
2	F	5	*FANCD1/BRCA2* compound heterozygous Score 2[a]	Idarubicin Cytarabine ATRA No HSCT	Remission for more than 14 years after APL diagnosis	Short stature, primary amenorrhea, absence of spontaneous pubertal development, microcephaly, CALMs	One sister with the same variants and same phenotype, one brother died from APL at 13 years old, not tested for FA	Weinberg-Shukron et al.[14]
3	U	U	U	ATRA Idarubicin Cytarabine Mitoxantrone Etoposide Maintenance No HSCT	Remission	U	U	Kim et al.[15]
4	M	U	*FANCD1/BRCA2*	Chemotherapy HSCT	Remission	AML 2 years before APL	Brother with the same variants, no cancer, he underwent HSCT	Fanconi.org
5	M	4	*FANCD1/BRCA2* compound heterozygous Score 1[a]	ATRA ATO HSCT	Remission	CALMs, extra thumb remnant	No	Current case report

Note: This table comprises cases identified from variety of sources. Eissa et al. represents an abstract published in European Journal of Cancer in 2017. Case 4 represents a patient clearly described on the Fanconi.org website with clinical details validated by the treating transplant physician (Pediatric Blood and Marrow transplant and cellular therapy, Minneapolis).

Abbreviations: AML, acute myeloid leukemia; APL, Acute promyelocytic leukemia; ATO, Arsenic trioxide; ATRA, all-trans retinoic acid; CALMs, café-au-lait macules; FA, Fanconi anemia; HSCT, hematological stem cell transplant; U, unknown.

[a]As per Radulovic and al scoring.

confirming excessive toxicity with FA adjusted transplant conditioning in patients with FA-D1 with hematological malignancies.[18] To our knowledge, there are no reports that describe conditioning regimen and haploidentical transplant outcomes for patients with FA-D1 diagnosed with hematological malignancies, which is the current scenario for our patient. Specifically in the case of APL and FA-D1, among the 3 patients with APL (2 with confirmed FA-D1, 1 with likely FA-D1), one received a HSCT and was alive. Two patients did not receive HSCT, one of whom died of relapse and the other was alive with more than 14 years of follow-up.

The global management of patients with FA-D1 (and *FANCN/PALB2*) requires extended cancer surveillance, above what is recommended for other molecular subtypes. In the Fanconi Anemia Clinical Care Guidelines, the cancer surveillance for embryonal solid malignancies in FA-D1 is addressed without clear consensus on duration and frequency of imaging. McReynolds et al suggested surveillance protocol with abdominal ultrasound every 6 months until 10 years old, urine catecholamines every 6 months until 5 years old and brain MRI yearly until 16 years old for solid tumors. For hematological malignancies, they suggested a complete blood counts every 3–4 months and a bone marrow aspiration and biopsy yearly.[11] While the benefits of this intensive surveillance need further investigations, we initiated this screening strategy in our patient.

This case report highlights the clinical management challenges of APL within the context of FA-D1. It also reveals a series of practical knowledge and educational gaps. By increased awareness of the spectrum of clinical manifestations related to FA, earlier diagnoses of FA could be made by clinicians, thereby offering an opportunity to optimize management. This is especially true for FA-D1, where cancers occur in young children. Reporting similar cases with detailed AML phenotypes, FA genotype, management, and outcome data will increase our understanding of cancers in FA-D1. This would also contribute to the establishment of specific management guidelines and may reveal associations between rare cancer and genetic disease subtypes.

AUTHOR CONTRIBUTIONS

The draft of the manuscript was written by C.F and supervised by C.G. All authors critically reviewed, commented, and edited subsequent versions of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

C. Freycon's research was generously funded by la Fondation ARC pour la recherche sur le cancer and Cancéropôle Lyon Auvergne Rhône-Alpes. C Goudie's research is funded by the Fonds de Recherche du Quebec – Santé (253761), the Cedars Cancer Foundation/Sarah's Funds, the Fondation de l'hopital pour enfants de Montreal, and the Cole Foundation. VP Lavallée is supported by the Fonds de Recherche du Quebec – Santé and the Cole Foundation. The project was also supported by funds from the Fondation Charles Bruneau.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14537.

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.

ETHICS STATEMENT

The parents of this child provided informed consent for the publication of this case.

REFERENCES

1. Testi AM, D'Angiò M, Locatelli F, Pession A, Lo Coco F. Acute promyelocytic leukemia (APL): comparison between children and adults. *Mediterr J Hematol Infect Dis*. 2014;6(1):e2014032.
2. Rowley JD, Golomb HM, Dougherty C. 15/17 translocation, a consistent chromosomal change in acute promyelocytic leukaemia. *Lancet*. 1977;1(8010):549-550.
3. Iland HJ, Collins M, Bradstock K, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. *Lancet Haematol*. 2015;2(9):e357-e366.
4. Zhang J, Walsh MF, Wu G, et al. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med*. 2015;373(24):2336-2346.
5. Altintas B, Giri N, McReynolds LJ, Best A, Alter BP. Genotype-phenotype and outcome associations in patients with Fanconi anemia: the National Cancer Institute cohort. *Haematologica*. 2023;108(1):69-82.
6. Steinberg-Shemer O, Goldberg TA, Yacobovich J, et al. Characterization and genotype-phenotype correlation of patients with Fanconi anemia in a multi-ethnic population. *Haematologica*. 2020;105(7):1825-1834.
7. Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. *J Med Genet*. 2007;44(1):1-9.
8. Reid S, Renwick A, Seal S, et al. Biallelic BRCA2 mutations are associated with multiple malignancies in childhood including familial Wilms tumour. *J Med Genet*. 2005;42(2):147-151.
9. Dutzmann CM, Spix C, Popp I, et al. Cancer in children with Fanconi anemia and ataxia-telangiectasia-a Nationwide register-based cohort study in Germany. *J Clin Oncol*. 2022;40(1):32-39.
10. Reid S, Schindler D, Hanenberg H, et al. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nat Genet*. 2007;39(2):162-164.
11. McReynolds LJ, Biswas K, Giri N, Sharan SK, Alter BP. Genotype-cancer association in patients with Fanconi anemia due to pathogenic variants in FANCD1 (BRCA2) or FANCN (PALB2). *Cancer Genet*. 2021;258-259:101-109.
12. Strocchio L, Pagliara D, Algeri M, et al. HLA-haploidentical TCRαβ+/CD19+-depleted stem cell transplantation in children and young adults with Fanconi anemia. *Blood Adv*. 2021;5(5):1333-1339.
13. Eissa S, Moussa E, Salem S, Yassin D, Soliman S, Elhaddad AM. Clinical presentation and outcome of a child with Fanconi anemia and acute promyelocytic leukemia (APL): published abstract. *Eur J Cancer*. 2017;72(1):S147-S148. doi:10.1016/S0959-8049(17)30559-2
14. Weinberg-Shukron A, Rachmiel M, Renbaum P, et al. Essential role of BRCA2 in ovarian development and function. *N Engl J Med*. 2018;379(11):1042-1049.

15. Kim MH, Choi CS, Lee JW, et al. Outcome of childhood acute promyelocytic leukemia treated using a modified AIDA protocol. *Korean J Hematol*. 2010;45(4):236-241.
16. Radulovic I, Schündeln MM, Müller L, et al. A novel cancer risk prediction score for the natural course of FA patients with biallelic BRCA2/FANCD1 mutations. *Hum Mol Genet*. 2023;32(11):1836-1849.
17. Peffault de Latour R, Soulier J. How I treat MDS and AML in Fanconi anemia. *Blood*. 2016;127(24):2971-2979.
18. Mitchell R, Wagner JE, Hirsch B, DeFor TE, Zierhut H, MacMillan ML. Haematopoietic cell transplantation for acute leukaemia and advanced myelodysplastic syndrome in Fanconi anaemia. *Br J Haematol*. 2014;164(3):384-395.
19. Rosenberg PS, Socié G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood*. 2005;105(1):67-73.
20. Masserot C, Peffault de Latour R, Rocha V, et al. Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. *Cancer*. 2008;113(12):3315-3322.

How to cite this article: Freycon C, Sepulchre E, Lavallée V-P, et al. Pediatric acute promyelocytic leukemia and Fanconi anemia: Case report and literature review. *Clinical Genetics*. 2024;1-6. doi:10.1111/cge.14537