Letter to the Editor
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The First Case of Acute Myeloid Leukemia With Underlying Fanconi Anemia due to *FANCF* Variants in Korea

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Dear Editor,

The current WHO classification of tumors of hematopoietic and lymphoid tissues includes a disease entity of myeloid neoplasms with germline predisposition associated with inherited bone marrow failure syndromes (BMFS), including Fanconi anemia (FA) [1]. We report a Korean girl diagnosed as having AML associated with FA. The Institutional Review Board of Samsung Medical Center (SMC, Seoul, Korea) approved this report and granted a waiver of informed consent (2021-11-060-001).

A 5-year-old girl was admitted to SMC for pallor and easy bruising. Complete blood cell counts revealed white blood cells (WBCs), 3.25×10^9/L (absolute neutrophil count 0.65×10^9/L); Hb, 71.0 g/L; and platelets, 39.0×10^9/L. Peripheral blood smear and bone marrow (BM) analyses revealed pancytopenia and hypercellular marrow with increased myeloblasts (30%) occasionally harboring Auer rods (Fig. 1). Chromosome analysis revealed a normal female karyotype 46,XX [20]. Next-generation sequencing (NGS) panel testing for somatic mutations in AML revealed *NPM1* c.863_864insTCTG (p.Trp288Cysfs*12). *FLT3* internal tandem duplication was negative. The patient was diagnosed as having AML with mutated *NPM1*. Follow-up WBC counts after induction therapy remained persistently low ($<0.50\times10^9$/L). The prolonged pancytopenia led to the suspicion of underlying BMFS and prompted us to perform NGS panel testing for BMFS that includes 22 genes with written consent from the parents. We detected two heterozygous variants in *FANCF* (NM_022725.3): c.2T>C and c.167del (Fig. 2B). No other significant variants were detected in the 22 BMFS genes screened. Chromosomal breakage analysis revealed significant genomic instability, compatible with FA (Fig. 2C). Her diagnosis was modified to AML with germline predisposition associated with FA. The chemotherapy regimen was switched to reduced-intensity FLAG combination therapy (fludarabine, cytarabine, and granulocyte colony-stimulating factor); allogeneic hematopoietic stem cell transplantation (HSCT) was performed. BM analysis 1 year after HLA-matched sibling donor HSCT revealed 80% cellularity without residual leukemic cells. She is currently on regular follow-up as an outpatient.

FA is the most common genetic cause of BMFS, and there are at least 22 FA-associated genes [2]. *FANCA, FANCC,* and *FANCG* are the most frequent culprits, responsible for ~90% of cases. FA attributed to *FANCF* variants accounts for 2% of cases. FANCF complexes with FANCA, FANCC, and FANCG in the nucleus and serves to maintain genomic integrity [3]. The main mode of inheritance in FA is autosomal recessive, which is the case in *FANCF*. Based on limited data in FA due to *FANCF*

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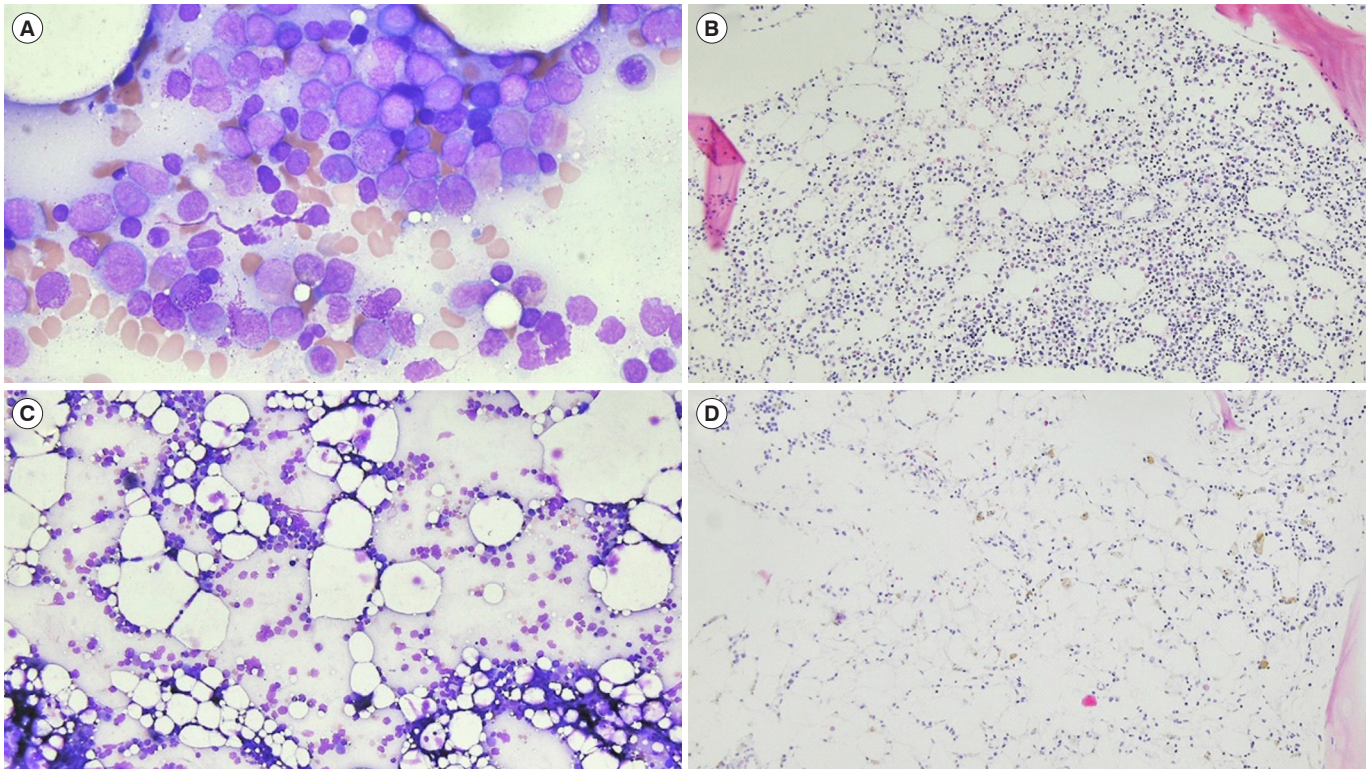

Fig. 1. BM aspirate smear (A, Wright–Giemsa stain, ×400) and biopsy section (B, H&E stain, ×100) at the initial diagnosis of AML. Follow-up BM aspirate smear (C, Wright–Giemsa, ×100) and biopsy section after chemotherapy (D, H&E stain, ×100) showing decreased cellularity.
Abbreviations: BM, bone marrow; H&E, hematoxylin and eosin; AML, acute myeloid leukemia.

variants, small deletions causing frameshift are the most common; genotype–phenotype correlations have revealed that recurrent c.484_485del of *FANCF* is associated with a more severe phenotype [4-6]. Our patient harbored two *FANCF* variants. c.2T>C was absent in large population databases, such as gnomAD v2.1.1 (https://gnomad.broadinstitute.org), and has been reported as a variant predicted to disrupt translation initiation [5,7]. c.167del is a novel variant with an allele frequency of 0.01% in the East Asian population (2/18,336 in gnomAD) and was predicted to be deleterious, resulting in premature termination due to frameshift (p.Thr56Argfs*25). The two variants were present in *trans*, as neither of the variants appeared in the same read (Fig. 2A). According to the American College of Medical Genetics guidelines, both variants were classified as likely pathogenic variants [8].

Clinically, cytopenia in FA most commonly manifests with significant thrombocytopenia, red blood cell macrocytosis, and increased fetal Hb. We speculate that in our patient, the initial cytopenic phase was intervened by AML development. Growth deficiency is present in up to 70% of FA patients, while other physical abnormalities may be subtle or absent [2]. Our patient was of a height around the third percentile and weight below the 25th percentile, without definite physical abnormalities. This observation was in line with the clinical findings in a previously reported patient who was compound heterozygous for c.2T>C and a small deletion [5].

Diagnosing underlying BMFS is important in myeloid neoplasms to identify those who can benefit from tailored treatments, such as reduced-intensity chemotherapy and HSCT, as well as to determine the eligibility of related stem cell donors [1]. While longitudinal follow-up studies on chemotherapy regimens are limited, a recent retrospective study of the European Society for Blood and Marrow Transplantation group reported that the achievement of complete remission prior to HSCT has a survival benefit in FA patients with myeloid neoplasms [9].

To our knowledge, this is the first Korean report of AML with underlying FA due to *FANCF* variants. Our study underscores that the precedent BMFS can be masked in pediatric patients with myeloid neoplasm due to subtle physical abnormalities; therefore, routine workup for BMFS by comprehensive NGS panel testing to cover rare culprits such as *FANCF* is required.

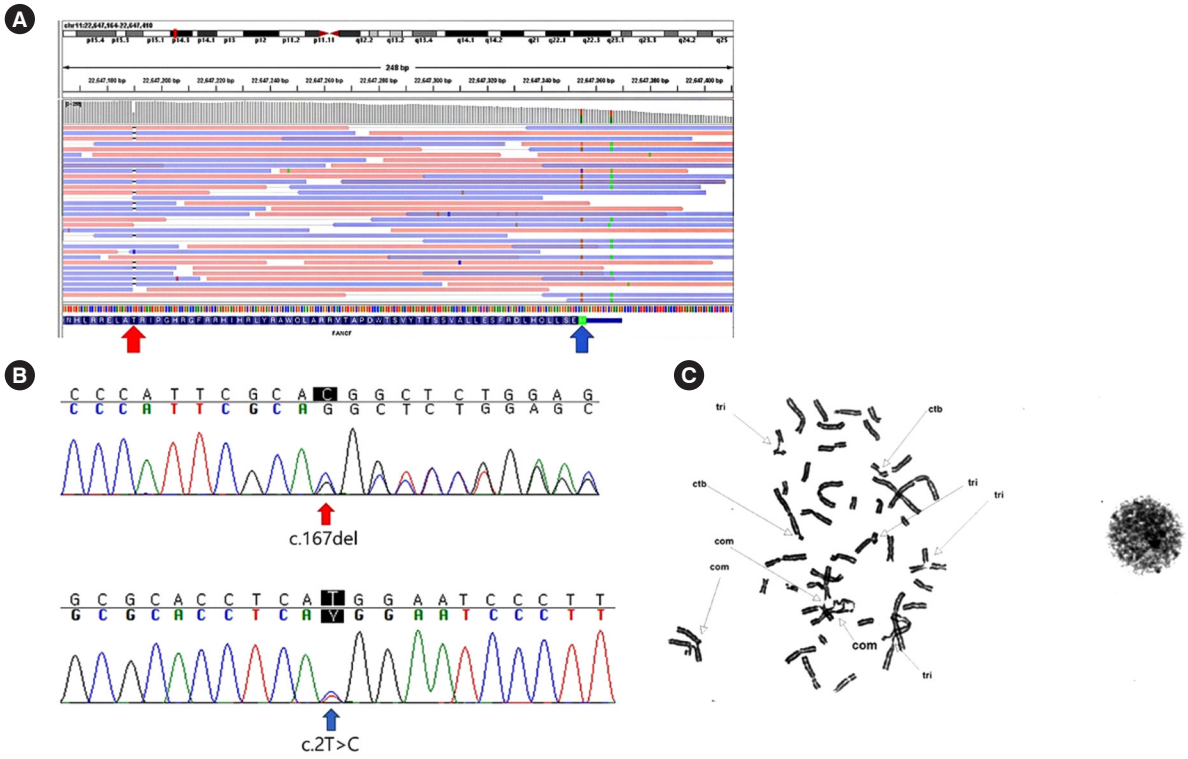

Fig. 2. NGS (A) and Sanger (B) sequencing chromatograms showing heterozygous *FANCF* variants c.167del (red arrow) and c.2T>C (blue arrow). (C) Chromosomal breakage analysis with mitomycin C showing increased breaks per cell and triradial formations.
Abbreviations: NGS, next-generation sequencing; tri, triradial; ctb, chromatid break; com, complex.

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AUTHOR CONTRIBUTIONS

All authors participated in manuscript writing and review. The submission of the final manuscript was approved by all authors.

CONFLICTS OF INTEREST

None declared

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