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# Current insights into inherited bone marrow failure syndromes

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Inherited bone marrow failure syndrome (IBMFS) encompasses a heterogeneous and complex group of genetic disorders characterized by physical malformations, insufficient blood cell production, and increased risk of malignancies. They often have substantial phenotype overlap, and therefore, genotyping is often a critical means of establishing a diagnosis. Current advances in the field of IBMFSs have identified multiple genes associated with IBMFSs and their pathways: genes involved in ribosome biogenesis, such as those associated with Diamond-Blackfan anemia and Shwachman-Diamond syndrome; genes involved in telomere maintenance, such as dyskeratosis congenita genes; genes encoding neutrophil elastase or neutrophil adhesion and mobility associated with severe congenital neutropenia; and genes involved in DNA recombination repair, such as those associated with Fanconi anemia. Early and adequate genetic diagnosis is required for proper management and follow-up in clinical practice. Recent advances using new molecular technologies, including next generation sequencing (NGS), have helped identify new candidate genes associated with the development of bone marrow failure. Targeted NGS using panels of large numbers of genes is rapidly gaining potential for use as a cost-effective diagnostic tool for the identification of mutations in newly diagnosed patients. In this review, we have described recent insights into IBMFS and how they are advancing our understanding of the disease's pathophysiology; we have also discussed the possible implications they will have in clinical practice for Korean patients.

**Key words:** Bone marrow failure syndromes, Fanconi anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, Severe congenital neutropenia

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## Introduction

Inherited bone marrow failure syndrome (IBMFS) encompasses a heterogeneous and complex group of genetic disorders characterized by physical malformations and insufficient blood cell production. Bone marrow failure (BMF) manifests symptoms similar to aplastic anemia, mono- or bicytopenias, depending on the affected cell lineage. IBMFS includes disorders like Fanconi anemia (FA), dyskeratosis congenita (DC), Diamond-Blackfan anemia (DBA), severe congenital neutropenia (SCN), Shwachman-Diamond syndrome (SBDS), and thrombocytopenia with absent radii. Various features of each of these disorders are summarized in Table 1. There is often substantial phenotypic overlap between these disorders, making genotyping a critical means for establishing a diagnosis. Mutations in many different genes have been associated with the development of BMF; these findings have enhanced our understanding of normal hematopoiesis and its disruption in IBMFs patients.

The genetic etiology of IBMFS includes germline mutations in several key biological

**Table 1.** Inherited bone marrow failure syndrome

| Disorder | Inheritance | Major characteristic feature | Hematology/oncology | Specific diagnostic test |
|---|---|---|---|---|
| Fanconi anemia | AR, XR | Skin hyperpigmentation with café-au-lait spots, short stature, microcephaly, abnormal thumbs/radii including hypoplastic, bifid, rudimentary, thenar hypoplasia, renal anomaly | Macrocytosis, anemia, thrombocytopenia, neutropenia, hypocellular marrow | Chromosome breakage test |
| Diamond-Blackfan anemia | AD, AR | Prenatal growth retardation, short stature, craniofacial malformation, cleft lip and/or palate, malformed thumbs | Macrocytosis, anemia with reticulocytopenia, erythroid hypoplasia in marrow | Erythrocyte adenosine deaminase, HbF |
| Shwachman-Diamond syndrome | AR | Short stature, exocrine pancreatic insufficiency, chronic dyspepsia, skeletal abnormalities | Macrocytosis, neutropenia, myeloid hypoplasia in marrow | Serum trypsinogen, pancreatic isoamylase, fecal elastase, pancreatic imaging, HbF |
| Severe congenital neutropenia | AD, AR, XR | Life-threatening infections in infancy | Neutropenia, maturation arrest of myeloid precursors at promyelocyte stage | None |

AR, autosomal recessive; XR, X-linked recessive; AD, autosomal dominant; HbF, fetal hemoglobin.

processes, such as DNA repair, telomere biology, and ribosomal biogenesis, which underlie FA, DC, and DBA, respectively. Additionally, as these disorders are associated with developmental abnormalities and an increased risk of cancer, early and adequate genetic diagnosis is required for proper management and follow-up. Furthermore, the heritable nature of these conditions and the anticipated risk for other family members and future generations underscore the value of this information for genetic counseling. Recent advances using new technologies such as next generation sequencing (NGS) have identified new candidate genes associated with the development of BMF.

In this review, we have described recent insights into IBMFS and shown how they are advancing our understanding of disease pathophysiology; we have also discussed their possible implications in clinical practice for Korean patients.

## Fanconi anemia

Fanconi anemia (FA, MIM #227650) is a complex disease that can affect many systems in the body. FA is characterized by congenital abnormalities, progressive development of BMF, and an increased susceptibility to malignancy, including myelodysplastic syndrome (MDS), leukemia (especially acute myeloid leukemia [AML]) and solid tumors (particularly squamous cell carcinoma). Affected individuals often (but not always) present with physical abnormalities, including short stature, Fanconi facies and microphthalmia, thumb and radius deformities, skin pigmentation such as café-au-lait spots, and cardiac, renal, genitourinary, and/or other malformations[1]. Approximately 30% of patients with FA have no overt somatic abnormalities[2]. The majority of patients present symptoms toward the end of their first decade of life. However, increasingly, patients are being diagnosed in adulthood and many patients diagnosed in childhood are surviving into adulthood[3]. Increased
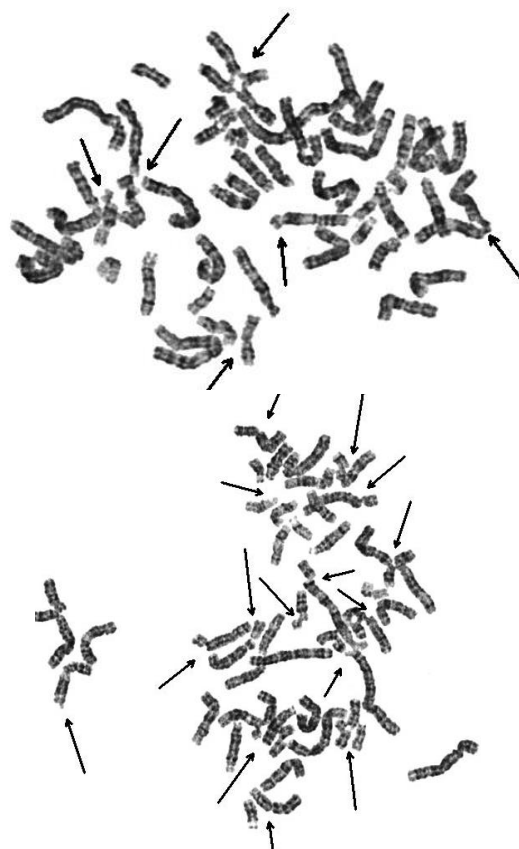


**Fig. 1.** Karyotype with induction of chromosome breakage by using mitomycin C, in patients diagnosed with Fanconi anemia (arrows: chromosomes with breaks, fusions, and radials).

fetal hemoglobin, serum alpha-fetoprotein, and macrocytosis are commonly observed in FA, but their absence does not rule out the possibility of the disease. A precise diagnosis can be made on the basis of a careful family-history survey, physical examination, and a positive chromosomal breakage

test in the majority of cases. Cells from FA patients display a high frequency of spontaneous chromosomal breakage and hypersensitivity to DNA cross-linking agents such as mitomycin C and diepoxybutane[4]. Chromosomal instability, especially upon exposure to an alkylating agent, is present in affected patients and is the basis for a diagnostic test (Fig. 1). However, inconclusive chromosome breakage results caused by somatic mosaicism may complicate the diagnosis of FA. If the test is negative in peripheral blood lymphocytes and yet the clinical setting is highly suspicious, skin fibroblasts must be assessed[5,6].

FA is a genetically heterogeneous disease. With the exception

**Table 2.** Genes associated with inherited bone marrow failure syndromes

| Disorder | Inheritance | Gene | Location | Proportion |
|---|---|---|---|---|
| FA | AR | FANCA | 16q24.3 | 60%–70% |
| | | FANCC | 9q22.3 | ~14% |
| | | FANCD1/BRCA2 | 13q12.3 | ~3% |
| | | FANCD2 | 3p25.3 | ~3% |
| | | FANCE | 6p21.3 | ~3% |
| | | FANCF | 11p15 | ~2% |
| | | FANCG/XRCC9 | 9p13 | ~10% |
| | | FANCI | 15q26.1 | ~1% |
| | | FANCJ | 17q22.3 | ~2% |
| | | FANCL | 2p16.1 | ~0.2% |
| | | FANCM | 14q21.3 | ~0.2% |
| | | FANCN | 16p12.1 | ~0.7% |
| | | FANCO | 17q22 | ~0.2% |
| | | FANCP | 16p13.3 | ~0.2% |
| | | FANCQ | 16p13.12 | Rare |
| | XR | FANCB | Xp22.31 | ~2% |
| DBA | AD | RPS19 | 19q13.2 | ~25% |
| | | RPL5 | 1p22.1 | ~6.6% |
| | | RPS17 | 15q25.2 | ~1% |
| | | RPS24 | 10q22–q23 | ~2% |
| | | RPL35A | 3q29-qter | ~3% |
| | | RPL11 | 1p36.1–p35 | ~4.8% |
| | | RPS26 | 12q13.2 | ~2.6% |
| | | RPS7 | 2p25.3 | ~1% |
| | | RPS10 | 6p21.31 | ~6.4% |
| SDS | AR | SBDS | 7q11 | >90% |
| SCN | AD | ELA2/ELANE | 19p13.3 | 50%–60% |
| | | GFI1 | 1p22 | ~1% |
| | | CSF3R | 1p35–34.3 | |
| | AR | HAX1 | 1q21.3 | 10%–15% |
| | | G6PC3 | 17q21.31 | |

FA, Fanconi anemia; DBA, Diamond-Blackfan anemia; SDS, Shwachman-Diamond syndrome; SCN, severe congenital neutropenia; AR, autosomal recessive; XR, X-linked recessive; AD, autosomal dominant.

of X-linked recessive FA-B, FA-associated genes are inherited in an autosomal recessive pattern. At least 16 genes exist that are responsible for the known FA complementation groups (Table 2)[7,8]. All FA products function in a common DNA repair signaling pathway that closely cooperates with other DNA repair proteins for resolving interstrand cross-links during replication[9]. FA-A, B, C, E, F, G, L, and M associate in a nuclear core complex, which is required for FANCD2 activation via monoubiquitination during the S phase and in response to DNA damage[10]. Germline mutations in any of the FA genes result in markedly reduced or abolished protein function and deficient DNA repair. Among them, FANCA (60%–70%), FANCC (up to 14%), and FANCG (up to 10%) mutations accounted for more than 90% of FA in a Western population[11]. Concerning Asian populations, genetic abnormalities in FA have been studied in a Japanese population. FANCA and FANCG mutations have been detected in 70%–80% and 10%–22%, respectively, of Japanese FA patients[12]. Recently, investigation of genetic abnormalities revealed that mutations in FANCA and FANCG are common in Korean FA patients (46% and 54%, respectively)[13,14]. A recent report also identified four common founder mutations, including two FANCA mutations (c.2546delC and c.3720_3724delAAACA) and two FANCG mutations (c.307+1G>C and c.1066C>T), which had previously been shown to be common in an East Asian FA population[13]. Based on results from previous research on Korean and Japanese patients, our suggestion is a mutation screening workflow for East Asian FA patients (Fig. 2).

Whole exome sequencing (WES) has accelerated the identification of mutations in rare cases of FA without a known genetic etiology. Targeted NGS has the potential to be used as a cost-effective diagnostic tool for the identification of FA-associated mutations in newly diagnosed patients. A study that sequenced germline DNA of 11 patients with known FA mutations on a custom NGS sequencing panel of eight FA genes (FANCA, FANCB, FANCC, FANCD1, FANCE, FANCG, FANCI, and FANCM) indicated the importance of NGS in uncovering somatic mosaicism by comparing different tissue types[15]. The combination of custom array comparative genomic hybridization (aCGH) to detect deletions and duplications of FA genes, WES to evaluate mutations, and RNA-Seq to evaluate gene expression changes resulting from these mutations proved to be an efficient means for the characterization of both the complementation group and the germline mutations[16].

The most frequent malignancy in FA is AML, but solid tumors can develop at a very young age in patients[17]. A review of cases of FA reported in the literature showed that 9% of patients developed leukemia and 7% developed MDS, 5% had solid tumors, and 3% had liver tumors. The risk of developing solid tumors, particularly of the head and neck, skin, esophagus, and gynecologic areas also increases[18]. AML with complex
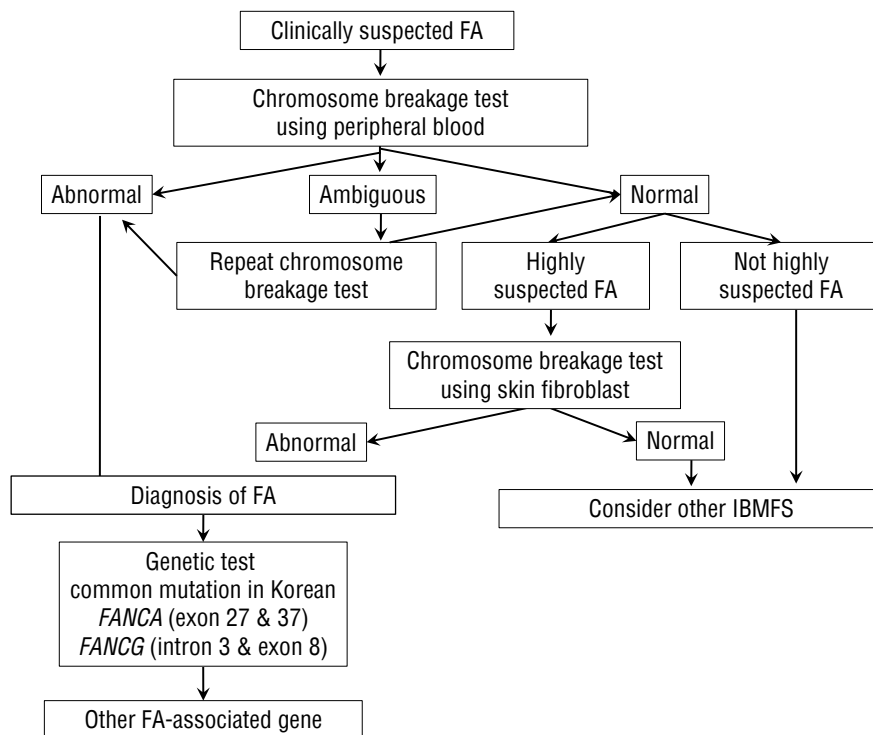
Fig. 2. Diagnostic algorithm for Fanconi anemia (FA). IBMFS, inherited bone marrow failure syndrome.
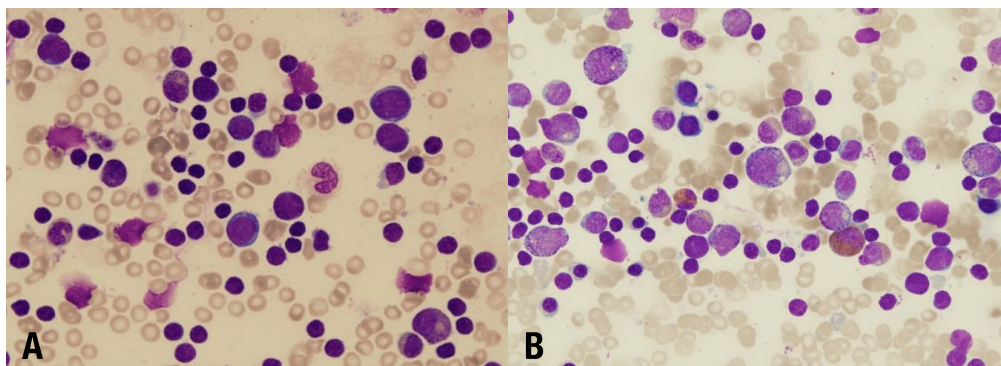


Fig. 3. Bone marrow in Diamond-Blackfan anemia, revealing a severe lack of erythroid precursors (A: Wright's stain, ×400) and severe congenital neutropenia, showing increased promyelocytes and a marked absence of mature granulocytes (B: Wright's stain, ×400).

hypodiploidy and loss of heterozygosity of 17p and congenital pigmented dermofibrosarcoma protuberans were reported in Korean FA patients[19,20]. Long-term follow-up of 12 FA patients helped track the development of AML during follow-up in two patients[21]. In addition, with the development of therapeutic techniques for FA such as hematopoietic stem cell transplantation and posttransplant care, more patients are surviving and being followed up for longer periods than before. With the prospect of a significantly extended lifespan, we must be prepared to treat problems related to nonhematological conditions that were previously considered secondary and to devise a follow-up plan for those patients. There is a critical need for nation-wide studies in order to assemble more genetic and clinical data to develop cost-effective diagnostic strategies that are optimal for Korean FA patients.

## Diamond-Blackfan anemia

Diamond-Blackfan anemia (DBA, MIM# 105650) is an inherited congenital BMF syndrome characterized by hypoproliferative anemia, associated physical malformations, and

a predisposition to cancer. The hallmark of classical DBA is normochromic macrocytic anemia with reticulocytopenia and the absence or insufficiency of erythroid precursors in an otherwise normocellular bone marrow (Fig. 3A)[3]. The disease is rare, with a reported incidence of 7 per million live births, and the anemia usually occurs in early infancy, with more than 90% of the patients being diagnosed before the age of 1 year[22]. Most DBA cases are sporadic, but the disease can be inherited with an autosomal dominant mode of inheritance. Although anemia is the most prominent feature, the disease is also associated with congenital malformations, mainly involving the head, upper limbs, heart, and the urogenital system, and growth retardation in approximately 50% of patients[3]. The clinical and hematologic manifestations in 56 Korean DBA patients were assessed in a previous report[23]. The annual incidence of DBA was found to be 6.6 cases per million and 74.1% were diagnosed before 1 year of age (median, 4 months). About 40% of patients showed congenital defects, including thumb deformities, ptosis, coarctation of the aorta, ventricular septal defect, and strabismus.

DBA has been associated with mutations and deletions in the large and small ribosomal protein (RP) genes, and genetic aberrations have been detected in approximately 50%–60% of patients. Since the identification of mutations in the RP *S19* gene, which was the first DBA gene to be reported, mutations in an increasing number of genes encoding RPs of both the small (RPS) and large (RPL) ribosomal subunits have been reported. At present, 10 genes encoding RPs of the small (*RPS24*, *RPS17*, *RPS19*, *RPS10*, *RPS26*, and *RPS7*) and large (*RPL35A*, *RPL5*, *RPL11*, and *RPL26*) ribosomal subunits have been described in DBA patients[24]. In the Japanese cohort, 27% of the 45 DBA patients had mutations in the RP genes, and mutations in the *RPS19* gene were detected in 11% of patients. Mutations in *RPL5*, *RPL11*, and *RPS17* were also detected[25]. A recent study investigated the genetic abnormalities in nine Korean DBA patients and noted that seven distinct mutations, including three novel mutations, were identified in three RP genes, *RPS19* (4/7), *RPS26* (2/7), and *RPS17* (1/7)[26]. Haploinsufficiency of RPs results in ribosome stress and activation of the TP53 tumor suppressor pathway, which is thought to be the main cause of clinical manifestations[27]. Decreased *RPS19* mRNA expression and p53 overexpression were also seen in Korean DBA patients, supporting the idea that haploinsufficiency and p53 overactivation are the central pathways underlying the pathogenesis of DBA[26].

Clinical suspicion and molecular genetic studies—even in patients without typical anomalies—are critically needed to better understand the genetic background and genotype-phenotype correlations of DBA and to optimize the treatment strategy[28]. A clear genotype-phenotype correlation was not apparent in patients with *RPS19* mutations due to incomplete penetrance and a highly variable expression profile, even within the same family[29]. Additionally, much of our knowledge of the disease has been gained from patient registries in North America, United Kingdom, Italy, and France[22,30,31]. There have been only a few other genotype studies performed on Asian DBA patients. Among the DBA patients harboring *RPS19* mutations, *RPS19* alterations have not been correlated with any specific phenotype. When researchers compared the clinical features of the *RPS19*-mutated DBA patients in their cohort with those of the previously reported DBA patients who shared identical or associated genotypic aberrations, no apparent correlation was found within the *RPS19*-mutated patients. The whole genome approach involving WES and aCGH of the known DBA-associated genes encoding RPs has been successfully attempted and has revealed mutations in new DBA-associated genes[32,33].

Long-term follow-up in the DBA registry identified that the rate of any solid tumor or leukemia was 5.4 folds higher in DBA patients than expected in a demographically matched comparison with the general population. MDS and AML have been reported in a few patients, suggesting an increased predisposition to hematologic malignancies. There are also cases in which the disease has evolved into aplastic anemia[33]. Lymphoma and osteosarcoma developed in two Korean DBA patients[23]. It is necessary to collect further data, including information regarding management pathways, from nationwide DBA registries, along with data on molecular analyses.

## Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS, MIM #260400) is characterized by BMF, pancreatic insufficiency, and skeletal abnormalities. Features of pancreatic insufficiency are apparent early in infancy. The spectrum of hematologic abnormalities includes neutropenia, pancytopenia (~20%), MDS, and leukemia (~25%)[34]. Patients with SDS have an increased risk—as high as 30%—of developing MDS and/or AML by the age of 30 years[35]. Biallelic Shwachman-Bodian-Diamond protein (*SBDS*) gene mutations inherited in an autosomal recessive fashion are causally related to the disease[36]. SBDS plays an important role in the maturation of the 60S ribosomal subunit and, therefore, in ribosome biogenesis[37]. In over 90% of patients diagnosed with SDS, the most common mutations are c.258+2T>C, followed by c.183_184TA>CT36). We examined the characteristics of two unrelated Korean adolescent patients with diverse clinical manifestations of SDS, including short stature, neutropenia, thrombocytopenia, congenital lipomatosis of the pancreas, Legg-Calve-Perthes syndrome, congenital coxa vara, and osteoporosis. Direct sequencing of the *SBDS* gene revealed compound heterozygosity of two common mutations

(c.[183_184TA>CT];[258+2T>C]) in one patient and homozygous mutations of c.[258+2T>C];[258+2T>C] in the other patient.

Prior to the advent of genetic testing, the diagnosis of SDS was based largely on the clinical criteria of neutropenia and exocrine pancreatic insufficiency. However, patients with *SBDS* gene mutations revealed an unexpectedly broad range of clinical phenotypes at presentation. The frequency of cryptic presentations of SDS raises the likelihood that SDS is an underdiagnosed disorder. Serum trypsinogen and pancreatic isoamylase were the most sensitive measures of clinically asymptomatic pancreatic dysfunction in SDS. Normal pancreatic imaging studies and normal fecal elastase do not rule out the diagnosis of SDS[38]. An early diagnosis of SDS is necessary for the early intervention and treatment of the many clinical symptoms of this disease and to predict the hematological prognosis of patients. In the present cases, however, a conclusive diagnosis seemed to be delayed even though the patients were being followed up continuously. Therefore, clinicians should take extra efforts to ensure rapid diagnosis and to carry out additional studies to determine the functions of SBDS-related proteins.

## Severe congenital neutropenia

Neutropenia is defined as a reduction in the absolute number of neutrophils in the blood circulation below $1.5 \times 10^9/L^{-1}$ in children over 1 year and below $2.0 \times 10^9/L^{-1}$ in children aged between 2 and 12 months[39,40]. SCN, as its name indicates, is characterized by profound peripheral neutropenia ($<0.5 \times 10^9/L^{-1}$) for at least 3 months, whether intermittent or permanent. Patients with the congenital disorder usually present with recurrent, life-threatening infections in infancy. Patients who are diagnosed with SCN usually show maturation arrest in the early stages of neutrophil development in the bone marrow (Fig. 3B). In addition, SCN is commonly considered as a preleukemic syndrome, since the cumulative incidence for leukemia exceeds 25% after 20 years of observation. Leukemia occurs in both subtypes (autosomal dominant and recessive) of SCN[41]. Bone marrow examination usually reveals characteristic maturation arrest of myeloid precursors at the promyelocyte stage of differentiation.

SCN is inherited in autosomal dominant, autosomal recessive, X-linked, and sporadic patterns. Heterozygous neutrophil elastase gene (*ELA2*) mutations are the most frequent cause of SCN and are present in patients with sporadic and familial forms of SCN[42,43]. Autosomal recessive SCN is associated with biallelic mutations in the *HAX1* gene and the *G6PC3* gene[44,45]. Mutations in WAS are associated with X-linked inherited SCN[46]. Mutations in other genes (*GFI1*, *CSF3R*) are also known to be associated with SCN, demonstrating genetic heterogeneity[47,48].

Despite recent progress in gene discovery, an all-encompassing causal mechanism underlying SCN has not yet emerged. Genetic surveys in Korean SCN patients have been carried out leading to the identification of two mutations in the *ELA2* gene (p.Ala57Val and p.Gly203Arg)[49,50]. However, we recognize that the genetic profiles in the majority of our SCN cases remain unresolved and require future investigations[51].

## Conclusions

The identification of the molecular actors and the insights they provide into the involved biological pathways, have helped us to understand the pathogenesis of IBMFS. Current advances in molecular technologies have come largely through the rapid identification of new gene mutations, which account for a far broader clinical spectrum. Clinical similarities between these syndromes may originate from the close association and similarity between the underlying molecular pathology of these disorders. Genetic advances have already found application in the clinic and have led to improved diagnosis, particularly for cases wherein the clinical manifestations are atypical. Accumulating data on the Korean population have revealed the prevalence of mutated genes in IBMFS, the types of mutations involved, and the challenge in identifying the clinical characteristics of patients. Early and correct disease recognition can make for more appropriate decisions leading to improved management and prevention of long-term sequelae of the disease. In addition, with the development of parallel testing of multiple BMF genes in a single sample using NGS, comprehensive genetic testing will be available, enabling the development of appropriate screening tools, discovery of new prognostic markers, and development more specific drugs.

These findings suggest ethnic differences in phenotypic expression, a feature that has been observed previously in other genetic diseases, including FA. It also highlights the need to define the clinical-genetic spectrum in different ethnic populations.

## Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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