REVIEW ARTICLE

# Shwachman-Diamond syndromes: clinical, genetic, and biochemical insights from the rare variants

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## Abstract

Shwachman-Diamond syndrome is a rare inherited bone marrow failure syndrome characterized by neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities. In 10-30% of cases, transformation to a myeloid neoplasm occurs. Approximately 90% of patients have biallelic pathogenic variants in the *SBDS* gene located on human chromosome 7q11. Over the past several years, pathogenic variants in three other genes have been identified to cause similar phenotypes; these are *DNAJC21*, *EFL1*, and *SRP54*. Clinical manifestations involve multiple organ systems and those classically associated with the Shwachman-Diamond syndrome (bone, blood, and pancreas). Neurocognitive, dermatologic, and retinal changes may also be found. There are specific gene-phenotype differences. To date, *SBDS*, *DNAJC21*, and *SRP54* variants have been associated with myeloid neoplasia. Common to *SBDS*, *EFL1*, *DNAJC21*, and *SRP54* is their involvement in ribosome biogenesis or early protein synthesis. These four genes constitute a common biochemical pathway conserved from yeast to humans that involve early stages of protein synthesis and demonstrate the importance of this synthetic pathway in myelopoiesis.

## Introduction

Shwachman-Diamond syndrome (SDS) is a rare inherited bone marrow failure syndrome (IBMFS), which occurs in 1/75,000 live births.[1] The syndrome is characterized by neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities (reviewed by Burroughs, Woolfrey, and Shimamura[2]). Other common manifestations include failure to thrive, transient hepatitis, attention deficit disorder, and eczema.[3-5] In 10-30% of cases, transformation to a myeloid neoplasm, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurs.[6] Prognosis is poor for patients with SDS and MDS/AML due to therapy-resistant disease and treatment-related toxicities.[7]

Approximately 90% of patients with SDS have biallelic pathogenic variants in the Shwachman-Bodian-Diamond syndrome gene (*SBDS*) located on chromosome 7q11. Complicating the sequence analysis is the presence of a pseudogene, *SBDSP1* with 97% homology to *SBDS*. The most common pathogenic variants are c.258+2T>C and c.183_184TA>CT. In a cohort of 158 unrelated individuals with SDS, 89% of patients had at least one allele mutated due to gene conversion with the pseudogene, and 60% of patients had two of these converted alleles. (The cis/trans orientation of the alleles were not determined).[8] Half were compound heterozygotes for c.258+2T>C and c.183_184TA>CT.

Over the past several years, pathogenic variants in three other genes have been identified in children with SDS-like disease: DnaJ heat shock protein family (Hsp40) member C21 (*DNAJC21*),[9,10] signal recognition particle 54 (*SRP54*),[11,12] and elongation factor-like GTPase 1 (*EFL1*).[13] Common to these three genes and *SBDS* is their involvement in protein synthesis. SBDS, EFL1, and DNAJC21 are proteins that affect ribosome biosynthesis. SBDS co-operates with the GTPase EFL1 to catalyze the release of eukaryotic translation initiation factor 6 (eIF6) from the pre-60S subunit. Release of eIF6 is essential for the assembly of the 80S ribosomal subunit from the 40S SSU (small subunit) and the 60S LSU (large subunit).[14,15] SRP54 facilitates the emergence of the nascent polypeptide in ribosome-associated signal recognition particle (SRP). Genotype-phenotype correlations among the variants of *SBDS*, *DNAJC21*, *SRP54*, and *EFL1* have not been comprehensively discussed.

We used PubMed to identify published case reports or series with SDS caused by *DNAJC21*, *SRP54*, and *EFL1* pathogenic variants. We searched for publications through to February 10, 2023, limited to human subjects, used the terms "DNAJC21", "SRP54", and "EFL1", and extracted clinical information. We identified 17 publications that described 63 individual patients with Shwachman-Diamond-like syndromes.[9-13,16-27] We excluded those that were genetically diagnosed with asymptomatic carriers of SDS-associated variants and whose phenotypes were not described in the reports. Some phenotype data were not available, and the values below were calculated based on the number of cases with data for that specific phenotype. This review will use the terms Shwachman-Diamond-like syndrome or Shwachman-Diamond syndromes.

## Clinical features

The affected genes among the 63 SDS-like patients were: *SRP54* 33 cases (52%), *DNAJC21* 17 cases (27%), and *EFL1* 13 cases (21%) (Table 1). Disease was inherited as either autosomal recessive (*DNAJC21* and *EFL1*) or autosomal dominant (*SRP54*). Distribution plots of pathogenic/likely pathogenic variants are shown for *DNAJC21*, *EFL1*, and *SRP54* (Figure 1). About half of the patients with *DNAJC21* variants harbored biallelic missense mutations; one-third had biallelic null variants. In patients with *EFL1* variants, compound heterozygous missense mutations were most frequent, with a few harboring compound missense and null variants. Three patients with *EFL1* variants were found to have somatic uniparental disomy of the *EFL1* locus in the hematopoietic cells. This generated homozygosity for the relatively milder variant, which conferred selective advantages.[25] No patients harbored biallelic null variants. (This feature of having no biallelic null variants has also been observed in patients with *SBDS*.) Patients' characteristics are described in Table 2. The median age at diagnosis in the genetic groups was 1.2, 0.4, and 0.2 years in *DNAJC21*, *SRP54*, and *EFL1*, respectively. The male to female ratio was 1:1, 2:1, and 1:1.2 in *DNAJC21*, *SRP54*, and *EFL1*, respectively.

The central hematologic hallmark of SDS is neutropenia with different degrees of severity. The bone marrow (BM) is generally hypocellular with a lower frequency of $CD34^+$ cells as well as myeloid precursors through the metamyelocyte stage.[28] *Sbds* deletion through downregulation of the gene in *Cebpa*-expressing murine cells also suggested that SBDS is critical for full myelocyte survival and differentiation.[29] Almost all (93%) of the patients with mutated *SRP54* showed maturation arrest of myeloid cells in the BM, a characteristic observed in patients with severe congenital neutropenia. The variable degree of neutropenia may be due to dosage effect of mutant SRP54, mitigated partially by transcription factor X-box binding protein.[30] In contrast, this maturation arrest was not observed in patients with *DNAJC21* and *EFL1* variants. In addition, two patients (6%) with *SRP54* showed cyclic neutropenia, which is typically observed in patients with congenital neutropenia harboring *ELANE* mutations.[31]

Pancytopenia was not observed in patients with the *SRP54* variants, whereas 94% and 38% of patients with *DNAJC21* and *EFL1* variants, respectively, developed pancytopenia during their disease course. Since less than 40% of patients with SBDS variants develop pancytopenia by middle age (50 years old),[32] the incidence of pancytopenia is higher in *DNAJC21*. The cumulative incidence of severe neutropenia, thrombocytopenia, and anemia in an Italian cohort of 88 patients with SDS secondary to SBDS variants was at 30 years of age, respectively, 60% (95% Confidence Interval [CI]: 46.9-76.5), 67% (95% CI: 52.4-85.1), and 20% (95% CI: 8.4-48.7). In the Italian study with complete information, 10 patients developed MDS/myeloid leukemia and 9 patients developed BM failure (BMF) / cytopenia. The 20-year cumulative incidence of myeloid neoplasia or BMF / severe cytopenia was 10% (95% CI: 3.7-19.5) and 10% (95% CI: 4.4-17.8), respectively.[32]

Once a patient with *SBDS*-associated SDS developed MDS/AML, the prognosis was fair (median survival: 7.7 years) for those with MDS and poor (median survival: 0.99 years) for AML, with persistent neoplastic disease and infectious complications being the predominant causes of death.[7] Three-year survival for SDS patients with AML was

**Table 1.** Distribution of variant classification in the cohort.

| Gene | Patients N | Variant classification | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | +/mis | +/- | mis/mis | mis/ss | mis/- | ss/ss | ss/- | -/- |
| *DNAJC21* | 17 | 0 | 0 | 9 (53%) | 0 | 1 (6%) | 2 (12%) | 0 | 5 (29%) |
| *SRP54* | 33 | 32(97%)* | 0 | 1 (3%)** | 0 | 0 | 0 | 0 | 0 |
| *EFL1* | 13 | 0 | 0 | 10 (77%) | 0 | 3 (23%) | 0 | 0 | 0 |

+: wild-type; -: null variant (nonsense and frameshift, excluding splice site variant); mis: missense variant; ss: splice altering variant. For individual variants, see *Online Supplementary Table S1*. *Genotype +/mis included 19 patients with a single amino acid deletion in the *SRP54* gene. **The patient harbored a *de novo* recurrent (p.Gly274Asp) and a hotspot (p.Ile225Asp) variant in the *SRP54* gene.

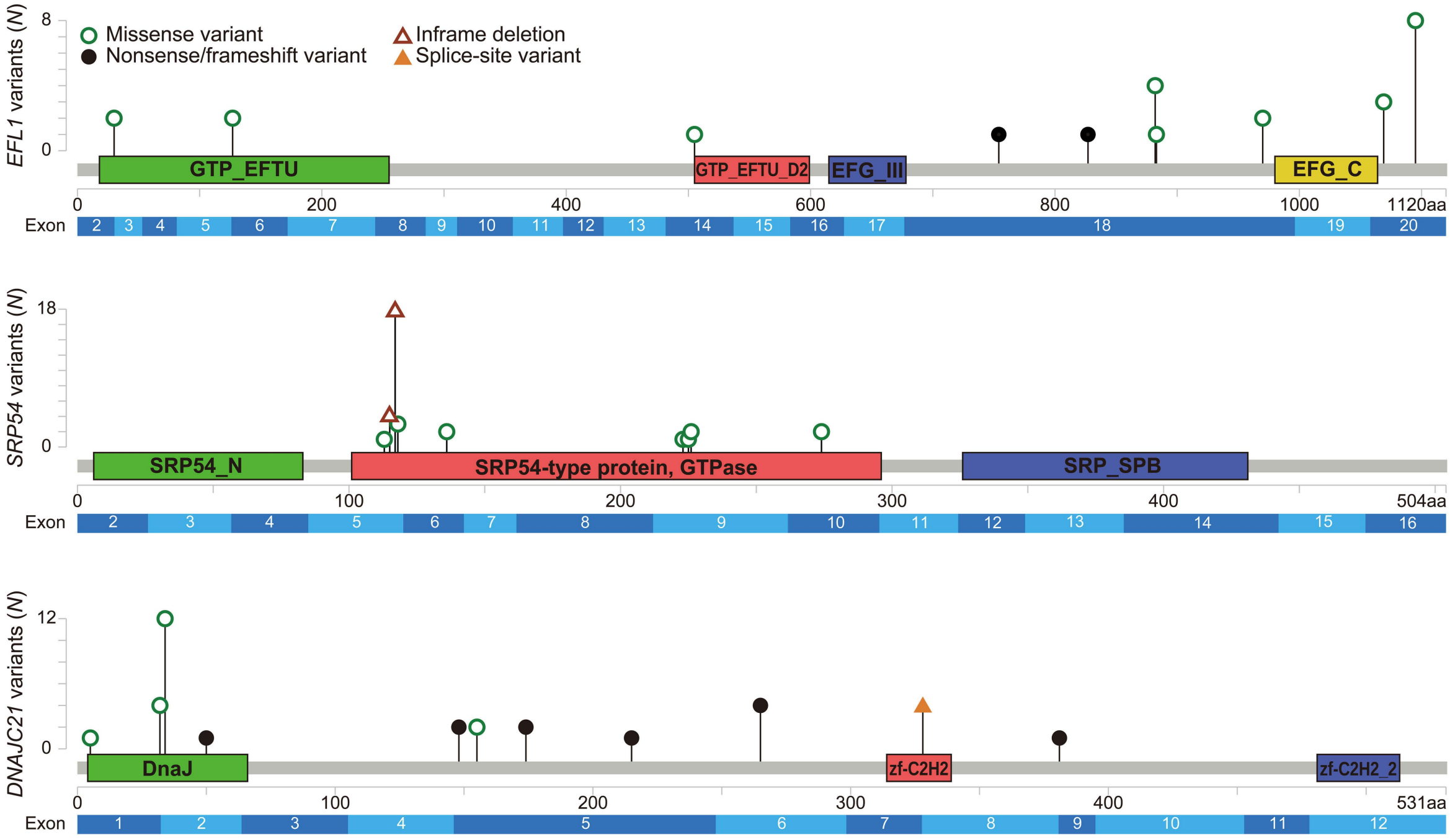


**Figure 1. Schematic of human DNAJC21, SRP54, and EFL1 showing position of disease-associated variants.** Lollipop plot indicating the locations of variants in the *DNAJC21*, *SRP54*, and *EFL1* genes. An unknown variant which resulted in loss of protein expression in a case with EFL1 was not included. Protein domains and structures were obtained from Pfam and Uniprot databases.

**Table 2.** Comparison of clinical characteristics of patients grouped by the genotypes.

| Gene | *DNAJC21* N = 17 | | | *SRP54* N = 33 | | | *EFL1* N = 13 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | % | Yes | No | % | Yes | No | % | *P* |
| Age in years at presenting symptom(s), median (range) | 1.2 (0-12) | | | 0.4 (0-20) | | | 0.2 (0-5) | | | |
| Age in years at last follow up, median (range) | 6 (1.2-14) | | | 11 (1.3-46) | | | 6 (0.6-31) | | | |
| Neutropenia | 14 | 2 | 88 | 33 | 0 | 100 | 11 | 2 | 85 | 0.043 |
| Skeletal dysplasia | 6 | 4 | 60 | 2 | 30 | 6 | 12 | 1 | 92 | <0.001 |
| Pancreatic abnormality | 6 | 6 | 50 | 8 | 24 | 25 | 13 | 0 | 100 | <0.001 |
| Recurrent/severe infection | 7 | 9 | 44 | 27 | 6 | 82 | 2 | 11 | 15 | <0.001 |
| Pancytopenia | 15 | 1 | 94 | 2 | 29 | 6 | 5 | 7 | 42 | <0.001 |
| Maturation arrest of myeloid cells | 0 | 10 | 0 | 28 | 2 | 93 | 0 | 12 | 0 | <0.000 |
| AML/MDS | 1 | 16 | 6 | 1 | 28 | 3 | 0 | 13 | 0 | 1.000 |
| Other neoplasm | 0 | 17 | 0 | 1 | 31 | 3 | 0 | 13 | 0 | 1.000 |
| IUGR/short stature | 16 | 0 | 100 | 9 | 24 | 27 | 13 | 0 | 100 | <0.001 |
| Microcephaly | 6 | 6 | 50 | 0 | 5 | 0 | 4 | 4 | 50 | 0.158 |
| CNS/cognitive symptom | 8 | 4 | 67 | 14 | 18 | 44 | 11 | 2 | 85 | 0.030 |
| Gastrointestinal symptom | 2 | 14 | 13 | 5 | 4 | 56 | 9 | 4 | 69 | 0.004 |
| Liver symptom | 3 | 7 | 30 | 2 | 2 | 50 | 6 | 7 | 46 | 0.666 |
| Cardiac abnormality | 1 | 15 | 6 | 2 | 4 | 33 | 0 | 0 | NA | NA |
| Dental/oral abnormality | 6 | 1 | 86 | 1 | 5 | 17 | 3 | 7 | 30 | 0.031 |
| Skin symptom | 12 | 4 | 75 | 1 | 28 | 3 | 1 | 12 | 8 | <0.001 |
| Retinal disease | 8 | 7 | 53 | 0 | 3 | 0 | 0 | 10 | 0 | 0.005 |
| Short telomere* | 6 | 6 | 50 | NA | NA | NA | NA | NA | NA | NA |

yrs: years; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; IUGR: intrauterine growth restriction; CNS: central nervous system; NA: not available or applicable. Fisher's exact test was used to compare phenotypes in the gene groups. *Short telomeres were defined as below the 10th percentile of the age-matched controls. Table produced using previously published data.[9-13,16-27]

11% and 51% for those with MDS.[6,7] The European Society for Blood and Marrow Transplantation - Severe Aplastic Anaemia Working Party recently performed a meta-analysis on 229 cases of allogeneic stem cell transplantation in SDS patients. They recommended regular and structured hematologic follow-up, reduction of transplant-related mortality through reduced-intensity conditioning regimens, the limitation of total body irradiation, and the early diagnosis of clonal malignant evolution and use of stem cell transplantation.[33]

Little is known about the risk of myeloid neoplasia among those with the rare genetic variants. This is likely due to the small number of patients and the relatively brief period of follow-up. Transformation to acute leukemia was reported in a patient with *DNAJC21* variants and two with an *SRP54* variant. The former, harboring a homozygous *DNAJC21* p.Pro32Ala mutation, developed acute megakaryocytic leukemia (AML-M7) at 12 years of age, when genetic studies were carried out.[9] A 15-year old boy with congenital neutropenia treated with granulocyte colony-stimulating factor presented with AML with myelodysplasia-related changes and was then diagnosed with the pathogenic variant p.Thr117del in *SRP54*. Additional genetic lesions were found: del(5q31.2), *CSF3R* p.Gln776* and *RUNX1* p.Pro113Leu. For this one case, treatment with daunorubicin/cytarabine and stem cell transplant has been successful, albeit with a short follow-up.[27] The other individual had acute lymphoblastic leukemia (ALL), even though ALL has rarely been reported in patients with SDS.[34] This patient presented with neutropenia at the age of five weeks and was subsequently identified to harbor a *de novo SRP54* p.Cys136Tyr variant. She was treated with granulocyte colony-stimulating factor from the age of four months until 10 years of age, when she was diagnosed with B-cell precursor ALL harboring aberrant expression of CD13 and CD33. Karyotype analysis showed del(5q) in the major clone with minor clones bearing del(7q). High-throughput sequencing revealed *RUNX1* (NM_001754.5:c.958C>T;p.Arg320*) and *CSF3R* (NM_156039.3:c.2302C>T;p.Gln768*) variants, but no *TP53* variants. She achieved complete remission after ALL-type induction chemotherapy and those mutations disappeared from BM cells. She received a cord blood transplant and has remained in remission for seven months.[12,35]

While predisposition to leukemia has been established in patients with SDS, there is less evidence for predisposition to non-hematologic cancers. Seven cases with solid

tumors have been reported, including 3 cases among 155 cases in the French Registry for Severe Chronic Neutropenia.[36] This study reported two cases with breast adenocarcinoma, one ovarian cancer, one pancreatic adenocarcinoma, one esophageal squamous cell carcinoma, one peritoneal carcinoma, and one dermatofibrosarcoma. All had been diagnosed in their 30s / 40s, except one who was diagnosed with dermatofibrosarcoma at the age of 17 years. Currently, no patients with *DNAJC21*, *SRP54*, and *EFL1* have been diagnosed with solid tumors. However, solid tumors in patients with *SBDS* mutations are predominantly diagnosed in adults, so patients with *DNAJC21, SRP54*, and *EFL1* variants need continuous close monitoring starting once they enter the fourth decade of life.

Another hallmark of SDS is exocrine pancreatic insufficiency, and approximately 95% of patients with *SBDS* are affected with pancreatic dysfunction associated with gastrointestinal symptoms. The developing pancreas is destined to become one of the most metabolically active secretory organs, producing approximately one liter of fluid rich in digestive enzymes every day.[37] Produced by acinar cells, these digestive enzymes are critical for absorption of macronutrients (protein and lipids). Exocrine pancreatic insufficiency results in stunted growth and malnutrition. In SDS, exocrine pancreatic insufficiency results from pancreatic acinar cell atrophy, and adipocyte replacement without appreciable inflammation.[38] Almost all patients harboring *SBDS* mutations present with pancreatic insufficiency in early life, whereas 40-60% became pancreatic sufficient over time.[3] It has been reported that lipase output changes from low/absent at the time of diagnosis to normal range, whereas amylase, trypsin and chymotrypsin activity may increase but always remains below normal values.[39] The incidence of exocrine pancreatic dysfunction was variable among patients harboring mutations in other SDS-like genes. All the patients with *EFL1* variants manifested pancreatic dysfunction, while patients with *DNAJC21* and *SRP54* variants developed pancreatic insufficiency in fewer individuals (50% and 25%, respectively). In addition, endocrine pancreatic dysfunction has been reported in some SDS cases. Although at diagnosis the incidence of Type 1 diabetes is low (3.2%), it is almost 30-fold higher than the rate of Type 1 diabetes in the general population.[40] No data are available for *EFL1* and *DNAJC21* and diabetes. Recently SRP54 levels were reported to be reduced in a murine model of diabetes,[41] suggesting that SRP54 may contribute to the impairment of pre-proinsulin synthesis due to endoplasmic reticulum stress.

Growth abnormalities are commonly observed in patients with SDS.[42] These may present as intrauterine growth restriction (IUGR) or short stature. IUGR or short stature were observed in 90% of patients with *SBDS* variants and the 50$^{th}$ percentile of the SDS population correspond to the 3$^{rd}$ percentile of the healthy population.[43] All patients with *DNAJC21* and *EFL1* variants had growth abnormalities, whereas only 28% of patients with *SRP54* variants had a history of IUGR or developed short stature.

Neurocognitive disorders, such as delayed motor and language developmental skills and limited attention span were found in more than half the children / adolescents with SDS.[44] Patients with *DNAJC21* and *EFL1* variants frequently had neurocognitive symptoms, whereas those with *SRP54* variants were less affected. Microcephaly may occur in SDS patients due to *SBDS*, but this was not consistently reported. Cardiac abnormalities, such as cardiomegaly, have been reported in SDS, but most reports did not mention this.[45,46] Other affected organs in SDS include the skin and the eye. Skin examinations showed eczema, café-au-lait spots, and hypo- or hyperpigmentation.[47] Interestingly, skin findings were common in patients with *DNAJC21*, but they were absent in patients with *SRP54* and *EFL1*. Retinal disease was observed in half of the patients with *DNAJC21* disease, but in none of the patients with *SRP54* and *EFL1* variants. The extent of these and other non-classical manifestations due to any of the SDS-associated genes and their genotype-phenotype needs further clarification, although this will be difficult due to variations in evaluation and clinical reporting.

Chemotaxis defects in SDS patients[48,49] along with neutropenia raise concern for recurrent and/or severe infection. Neutrophils isolated from SDS patients exhibit dysregulated chemotaxis due to altered F-actin polymerization capability. They may be responsive to common chemotactic stimuli; however, SDS cells cannot normally migrate towards the chemoattractant and generate random movements.[48] Patients with *SRP54* frequently had history of recurrent/severe infection. Attenuated chemotaxis in neutrophil was shown in a *srp54* knockdown zebrafish model.[11] Neutropenia was observed in all *SRP54* patients that may have been the main cause of this high frequency. On the other hand, nearly half the patients with *DNAJC21* variants had recurrent/severe infections, while patients with *EFL1* variants were less likely to develop infection; even the frequency of neutropenia was similar.

Loss of *SBDS* expression has been associated with shortened telomeres in a proportion of SDS patients.[50,51] One study showed that most patients with *DNAJC21* had short telomeres which were defined as below the 10$^{th}$ percentile of the age-matched controls,[16] while patients with *SRP54* and *EFL1* were not evaluated for shortened telomeres. One of six patients with short telomeres was below the 1$^{st}$ percentile in granulocytes and lymphocytes, and the others were between the 1$^{st}$ and 10$^{th}$ percentiles. From a diagnostic perspective, telomere studies have high sensitivity with specificity for dyskeratosis congenita (or short telomere syndrome). For individuals with neutropenia, pancreatic insufficiency, short stature and/or skeletal

anomalies, and failure to thrive, next generation sequencing of BMF syndromes that includes *SBDS*, *DNAJC21*, *EFL1*, and *SRP54* is the diagnostic test of choice. It is readily available, quick, and cost-beneficial.[52] Having ruled out cystic fibrosis, and with no pathogenic or likely pathogenic variants identified in these four genes, the next step for diagnosis is whole exome sequencing.[53] Measurement of telomere length is of limited benefit.

## Pathophysiology

In mammalian cells, more than 200 proteins, ribosomal RNA species, and up to 75% of cellular energy are devoted to producing as many as 20,000 ribosomes per minute.[54] This prodigious amount of synthetic activity is tightly regulated.[55] Protein synthesis requires ribosomal biosynthesis and ribosomal translation of mRNA into nascent polypeptides that are processed via the SRP (Figure 2). Only a minority of the 200 proteins are structural components, while the majority serve as assembly factors or chaperones. Ribosomal biogenesis begins with the import of proteins and processing of ribosomal RNA in the nucleolus. The small (40S) and large (60S) subunits are constructed and exported out of the nucleus via nuclear pores into the cytoplasm, and especially in the endoplasmic reticulum.[56] DNAJC21 binds precursor 45S ribosomal RNA and may be involved in early nuclear ribosomal RNA biogenesis and maturation of the 60S ribosomal subunit.[9] SBDS and EFL1 interact to promote the release of eIF6 to facilitate the assembly of the mature 80S ribosome. The 80S monosomes aggregate to form polysomes for more efficient translation and protein production. As the polypeptides are synthesized, they are processed and transported to organelles. For proteins directed to the endoplasmic reticulum, this process occurs co-translationally, which is mediated by the SRP complex. In eukaryotes, the SRP complex consists of six proteins arranged on a long, non-coding 7SL RNA, which help route the nascent polypeptides to the Golgi apparatus for further modification and shipping to specific subcellular compartments.[57] Two other components of the SRP complex, SRP72 and SRP19, are associated with dysgranulopoiesis.[58,59] How these fundamental and ubiquitous cellular processes that lead to protein synthesis result in specific, limited phenotypes remains poorly understood.

Mammalian cells provide tissue-specific experimental models to study the pathophysiology of SDS. In patients with *SBDS*-mutated SDS, $CD34^+$ hematopoietic cells were reduced in the BM.[60] These hematopoietic cells had impaired colony formation and long-term colony formation. BM mesenchymal stem cells from *SBDS*-mutated SDS pa-

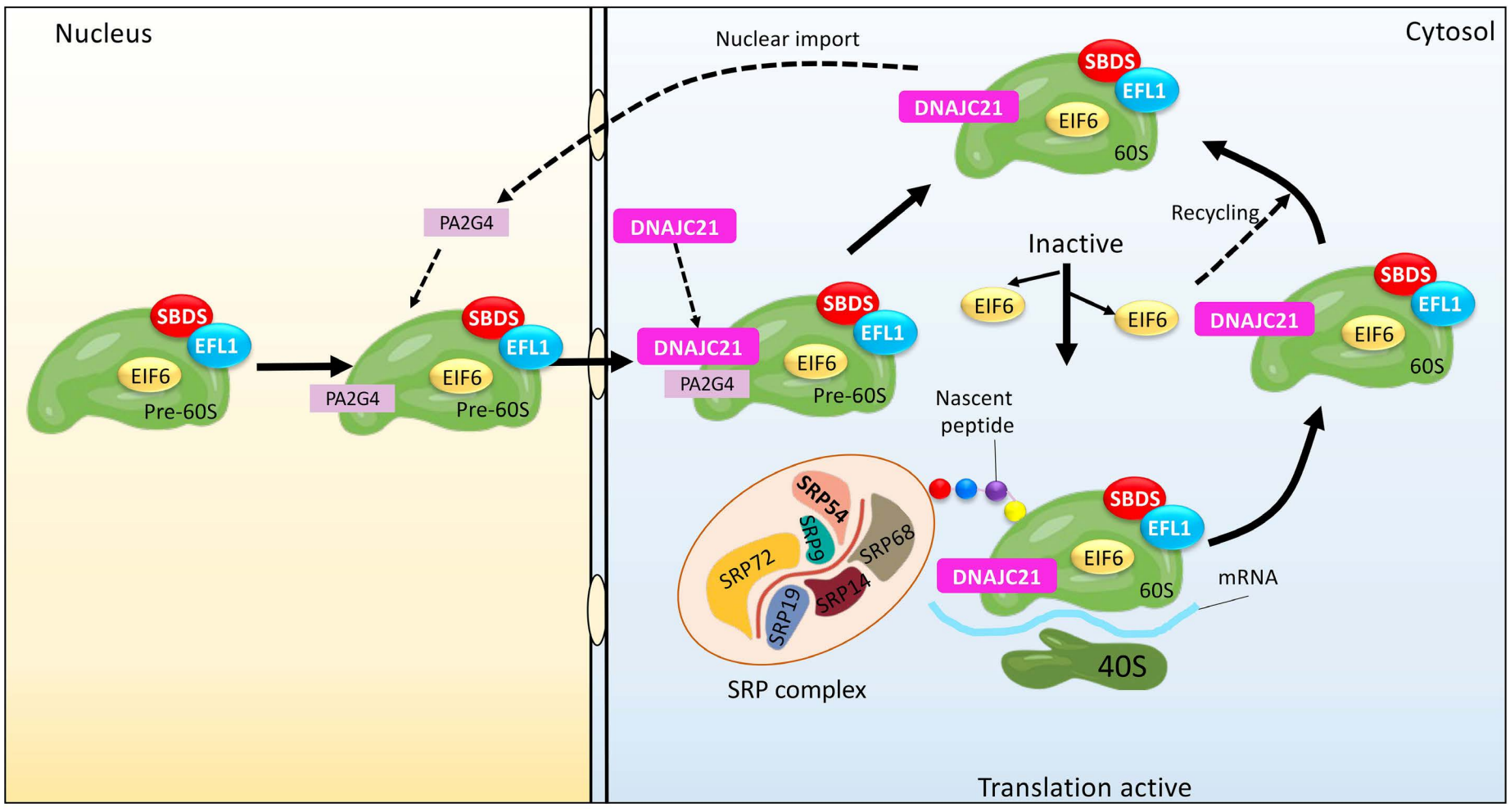


**Figure 2. Components of the Shwachman-Diamond syndrome pathway participate in ribosomal biosynthesis and initial escort by the signal recognition particle.** Ribosome maturation begins in the nucleus with the formation of the pre-60S and pre-40S subunits. These subunits traffic through the nuclear pores to the cytosol where the final steps of ribosome maturation occur, forming the 80S ready for translation of mRNA into a nascent polypeptide. The polypeptide emerges from the ribosome and is further processed via the signal recognition particle. See text for further details.

tients had reduced ability to support normal CD34+ hematopoietic cells. A role for mesenchymal cells in altering the BM microenvironment has been advanced and may contribute to dysmyelopoiesis or leukemogenesis.[61-63] Increased apoptosis was observed in SDS-derived BM in combination with p53 overexpression.[64,65] In studies of human cells, SDS patient cells were hypersensitive to low doses of actinomycin D, an inhibitor of rRNA transcription and its administration abolished nucleolar localization of SBDS.[66] Downregulation of SBDS in HEK293 cells showed alterations in both the mRNA levels and mRNA polysome loading of genes implicated in nervous system development, bone morphogenesis, and hematopoiesis.[67]

SBDS co-localizes with the mitotic spindle by immunofluorescence. Recombinant SBDS bound to purified microtubules *in vitro* resulting in microtubule stabilization both *in vitro* and *in vivo*.[68,69] Cultured cells from SDS patients exhibited an increased incidence of mitotic aberrations, characterized by multipolar spindles and centrosomal amplification, compared with controls.[68] Knockdown of *SBDS* expression with siRNA in human fibroblasts recapitulated this phenotype, but only after two weeks in culture, suggesting that the mitotic defects were a downstream result of SBDS loss. Loss of SBDS was associated with increased apoptosis when checkpoint pathways were intact but resulted in aneuploid cells when p53 was inactivated. The increased apoptosis observed in classical SDS hematopoietic progenitors has been associated with dysregulated FAS expression onto plasma membrane.[70,71] Apoptosis induced by loss of SBDS expression in human breast cancer cells can be reverted by inhibitors of caspase 8, suggesting this protease contributes to this process.[72] Loss of *SRP54* expression has been associated with p53-dependent increased apoptosis instead.[12] Little is known about the role of DNAJC21 and EFL1 in regulating apoptosis.

Patient-derived cells have limitations in that the numbers of hematopoietic cells are limited in this rare form of IBMFS. In addition, the genes more recently found to be associated with SDS (*DNAJC21*, *EFL1*, and *SRP54*) need to be further clarified, although all, including SBDS, play a role in ribosome biogenesis and function. Thus, there is a high demand for disease models to be established in SDS. The disease models caused by *DNAJC21*, *EFL1*, and *SRP54* in relationship with human disease are summarized in Table 3.

*DNAJC21* encodes a member of the DnaJ heat shock protein 40 family of proteins that contains two N-terminal tetratricopeptide repeat domains and a C-terminal DNAJ domain.[73] DNAJC21 binds the precursor 45S ribosomal RNA, which is processed to form the 18S, 5.8S and 28S rRNA.[74] DNAJC21 interacts with ZNF622 to stimulate the ATPase activity of HSPA8, promoting the release of the nuclear export receptor PA2G4 from the pre-60S ribosomal subunit.[9] Thus, DNAJC21 also participates in the maturation of the 60S subunit. In yeast, efficient removal of Tif6p (human eIF6) depends on the prior release of Arx1p (human PA2G4) by this pathway.[9] This may link DNAJC21 and SBDS-EFL1-eIF6 in the late cytoplasmic 60S ribosomal subunit maturation. The missense variant p.P32A in DNAJC21 is thought to alter the fold of the critical J domain His, Pro, Asp (HPD) motif, disrupting the interaction with HSPA8 and stimulation of its ATPase activity. The p.K34E missense variant reverses the surface charge of a key amino acid adjacent to the HPD motif and likely disrupts the interaction with HSPA8.[9]

Knockdown of DNAJC21 in HeLa cells via small interfering RNA caused cytoplasmic accumulation of PA2G4, elongated cell morphology, and cell death. Reintroduction of DNAJC21 rescued cell viability and restored normal PA2G4 trafficking. Tummala *et al.* concluded that DNAJC21 is involved in nucleolar rRNA biogenesis and in cytoplasmic recycling of nuclear export factor PA2G4 for 60S ribosomal subunit maturation.[9] In zebrafish using CRISPR / Cas9 knocking out *dnajc21*, reduced growth and abnormal yolk sac development were observed. This coincided with reduced lipid distribution in the vasculature and caudal hematopoietic tissue region at 48 hours post fertilization (hpf).[75]

SRP54 has basal GTPase activity and stimulates reciprocal GTPase activation of the SRP receptor subunit alpha (SRPRA).[11,76] SRP54 is a component of co-translational targeting of secretory and membrane proteins to the endoplasmic reticulum by SRP complex.[76] SR compaction and GTPase-mediated rearrangement of SRP receptor drive SRP-mediated co-translational protein translocation into the endoplasmic reticulum.[76] SRP54 requires the presence of SRP9/SRP14 and/or SRP19 to stably interact with RNA. In patient-derived BM cells, GTPase activity was decreased,[11] although another report showed that the same SRP54 variant (Gly226Glu) displayed basal GTPase activity and stimulates GTPase reactions with the receptor as efficiently as wild-type.[76] Differentiation of patient-derived CD34+ hematopoietic cells resulted in decreased granulocytes.[12] Patient-derived granulocytes showed increased endoplasmic reticulum stress and autophagy. In a zebrafish model using morpholino antisense oligonucleotides for *srp54*, decreased neutrophils and decreased *mpx* expression at 48 hpf was noted. Pancreas markers, *trypsin* and *ptf1a* expression at 72 hpf were also decreased.[11]

EFL1 is involved in the biogenesis of the 60S ribosomal subunit and translational activation of ribosomes.[77] Together with SBDS, EFL1 triggers the GTP-dependent release of eIF6 from 60S pre-ribosomes in the cytoplasm, thereby activating ribosomes for translation competence by allowing 80S ribosome assembly and facilitating eIF6 recycling to the nucleus,[78] where it is required for 60S rRNA processing and nuclear export. EFL1 also shows low

intrinsic GTPase activity.[77] GTPase activity is increased by contact with 60S ribosome subunits.[15]

In patient-derived fibroblasts and lymphoblastoid cell lines, release of eIF6 was impaired. Using siRNA knock-down or CRISPR/Cas9 edited HeLa cells and K562 cells, ribosome assembly was impaired.[13] RNA-seq expression profile in K562 edited to harbor patient-derived variant in *EFL1* showed different expression profiles than wild-type.

**Table 3.** Biological models for Shwachman-Diamond syndrome.

| Gene | Human cells | | Mouse | Zebrafish | Yeast |
|---|---|---|---|---|---|
| | Patient-derived cells | Cell lines | C57BL/6J | | *S. cerevisiae* |
| *DNAJC21* | Decreased proliferation by PHA/IL-2 (T cells)[9] | Morphological changes by shRNA (HeLa)[9] | NA | Reduced growth and abnormal yolk sac development, reduced lipid distribution in the vasculature and caudal hematopoietic tissue region at 48 hpf (CRISPR/Cas9 KO)[75] | NA |
| | Reduced expression of rRNA (LCL)[9] | - | - | - | - |
| | Aberrant micronuclei in CBMN-cyt assay (lymphocyte) | - | - | - | - |
| *SRP54* | Decreased GTPase activity (BM cells)[11] | Decreased GTPase activity by overexpressing the mutant protein (HEK293)[11] | NA | Decreased neutrophils; decreased *mpx* at 48 hpf, *trypsin*, and *ptf1a* expression at 72 hpf revealed using WISH and transgenic fish (MO)[11] | NA |
| | Decreased granulocytic differentiation ($CD34^+$ cells)[12] | Decreased proliferation, increased ER stress/autophagy using shRNA (HL-60)[12] | - | - | - |
| | Increased ER stress/autophagy (granulocytes)[12] | - | - | - | - |
| *EFL1* | Impaired eIF6 release (fibroblasts and LCL)[13] | Impaired ribosome assembly using siRNA and CRISPR/Cas9 (HeLa and K562)[25] | Loss of weight, decreased fat accumulation, reduced bone mass density, and decreased HSC/HSPC (N-ethyl-N-nitrosourea mutagenesis)[13] | Smaller heads and eyes, slightly bent tails; decreased neutrophils and erythrocytes (MO)[25] | Rescuing slow growth of *RIA1* (EFL1)Δ by expressing mutant *ria1*[23] |
| | - | RNA-seq expression profiles after editing by CRISPR/Cas9 (K562)[25] | *Efl1*$^{-/-}$ were embryonic lethal, while *Efl1*$^{+/-}$ and *Efl1*$^{mis/mis}$ were healthy; *Efl1*$^{mis/-}$ were small, died earlier, and developed pancytopenia (CRISPR/Cas9 KO and KI)[25] | - | Relocalization of Tif6p (eIF6) to the cytoplasm[23] |

PHA: phytohemagglutinin; CBMN Cyt: cytokinesis-block micronucleus cytome; BM: bone marrow; ER: endoplasmic reticulum; LCL: Epstein-Barr-virus-transformed lymphoblastoid cell lines; HSC/HSPC: hematopoietic stem and progenitor cells; KO: knockout; KI: knock-in of variants; hpf: hours post fertilization; WISH: whole-mount *in situ* hybridization; MO: morpholino antisense oligomers; NA: not available.

In the yeast studies, expression of patient-corresponding variant *ria1* (*EFL1* ortholog) rescued slow growth of *RIA1*-null yeast. This was associated with relocalization of Tif6p (eIF6) to the cytoplasm.[23] In mice, introduction of variants close to patient-derived variants by N-ethyl-N-nitrosourea random mutagenesis resulted in loss of weight, decreased fat accumulation, reduced bone mass density, and decreased hematopoietic stem and progenitor cells.[13] In other mice models, *Efl1*$^{-/-}$ were embryonic lethal, whereas *Efl1*$^{+/-}$ and *Efl1*$^{mis/mis}$ were healthy. *Efl1*$^{mis/-}$ were small, died earlier, and developed pancytopenia.[25] In a zebrafish model using morpholinos for *efl1*, smaller heads and eyes, and slightly bent tails were noted; neutrophils and erythrocytes were decreased in this model.[25] Zebrafish lacking *efl1* phenocopied some of the molecular and morphologic features of SDS. In addition, results from *efl1*$^{-/-}$ zebrafish were consistent with those from *sbds*$^{-/-}$ zebrafish strains, emphasizing a common molecular pathway induced by the dyad of eIF6 dissociating factors.[79]

The mechanistic target of rapamycin (mTOR) pathway is up-regulated in SBDS-deficient cells from patients. Our research group reported that mTOR phosphorylation of serine 2448 residue (activator) is significantly elevated compared to healthy control cells, possibly as a compensatory mechanism in response to energy deficiency due to ribosome impairment.[80-82] The mTOR pathway, triggered by the upstream activation of the phosphatidylinositol 3-kinase (PI3K) and AKT kinase, can induce cell proliferation through mitochondria and ribosome biogenesis.[83] Interestingly, Conn and Qian showed that constitutively activation of the complex 1 of mTOR can increase the speed of ribosomal elongation leading to decreased translation fidelity, therefore emphasizing a role of mTOR in maintaining protein homeostasis.[84] No association between SRP54, EFL1, nor DNAJC21 and mTOR has been reported so far, and this should be clarified in future studies.

## Conclusions

The initial description of SDS featured its hallmarks of exocrine pancreatic insufficiency and neutropenia.[85,86] Cloning of the gene led to the characterization of its genotypes, demonstrating the complexity because of its pseudogene in humans and its limited number of variants.[8] Since then, as many as 90% of individuals identified with the classical triad (neutropenia, exocrine pancreatic insufficiency, and skeletal anomalies) carry biallelic mutations. In 2011, consensus guidelines for the diagnosis of SDS defined the clinical diagnostic criteria with the presence of cytopenia of any given lineage and exocrine pancreas dysfunction.[87] Bone abnormalities and behavioral problems were categorized as supportive evidence. Over the last several years, pathogenic variants have been attributed to *DNAJC21*, *EFL1*, and *SRP54*. According to these guidelines, patients with *DNAJC21* (BMF syndrome-3, OMIM #617052) and *SRP54* (severe congenital neutropenia-8, OMIM #618752) may not be diagnosed as *bona fide* SDS. However, their clinical characteristics do not fit in other IBMFS categories such as dyskeratosis congenita or severe congenital neutropenia. Because of the small numbers involved, generalizations regarding phenotypes are to be made with caution.

Our review of genotype-phenotype correlations of patients with *DNAJC21*, *EFL1*, and *SRP54* may refine the clinical diagnostic criteria of SDS. Such a classification conundrum has also arisen for other BMF syndromes. Dyskeratosis congenita encompasses a range of monogenic disorders involving telomere maintenance or stability. Involving blood, skin, lung, gut or genitourinary systems, these disorders are increasingly referred to as short telomere syndromes.[88] Similar to dyskeratosis congenita in its restriction to a particular physiologic process is Fanconi anemia, which is due to one of 23 genes involved in different steps to detect and repair DNA interstrand crosslink damage. Defying thematic unity in its pathophysiology, severe congenital neutropenia is due to a number of genes that vary in their biochemical and cellular function.[89]

*SBDS*, *EFL1*, *DNAJC21*, and *SRP54* encode proteins involved in ribosome assembly and nascent polypeptide synthesis. SDS has been viewed as a ribosomopathy.[90] This term has been applied to diverse diseases with germline or somatic mutations, such as Treacher Collins syndrome, Diamond-Blackfan anemia, cartilage hair hypoplasia, and del(5q) MDS.[91] We suggest using the term Shwachman-Diamond syndromes or Shwachman-Diamond-like syndrome to denote disorders that may involve blood and/or pancreatic abnormalities, and which result from germline variants that encode proteins affecting ribosome biogenesis and early protein synthesis. The term Diamond-Blackfan anemia should be reserved for those with congenital hypoplastic anemia.

Limitations of this analysis for human phenotypes of SDS due to *DNAJC21*, *EFL1*, or *SRP54* variants include missing data from patients in the literature and the nature of the descriptive research that did not provide an adequate sample size for statistical analyses to be performed. To date, there have been few organismal models to characterize phenotypes that copy human SDS. The molecular pathways underlying these entities have fallen short on identifying precise mechanisms for developing BMF and pancreatic insufficiency. In addition, even though embryonic lethality was avoided, neoplastic transformation (the major concern for SDS patients in late adolescence-early adulthood) has not been modeled in mice or zebrafish.

Comparison of phenotypes should promote a better understanding of the disease entities covered by the term SDS. This may contribute to early diagnoses, more effec-

tive treatment options, improved surveillance for neoplastic complications, design of chemopreventive strategies, and healthier outcomes. As children, adolescents, and young adults are being diagnosed at earlier ages, and with better monitoring and management, it is likely that new manifestations of SDS will be revealed as these patients live into middle age and beyond. Understanding the molecular pathophysiology of SDS will also likely provide major new insights into the fundamental conserved mechanisms of ribosome assembly and protein synthesis, their quality control, and neoplastic transformation.

**Disclosures**

*The authors have no conflicts of interest to disclose.*

**Contributions**

*NK, VB and UO performed the research. NK analyzed the data. NK, UO, MC, VB and SJC wrote the paper.*

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**Data-sharing statement**

*All the data analyzed in this paper are available in the publications referred to in the text.*

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