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Shwachman-Diamond Syndrome

Synonym: Shwachman-Bodian-Diamond Syndrome

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Summary

Clinical characteristics

Shwachman-Diamond syndrome (SDS) is characterized by: exocrine pancreatic dysfunction with malabsorption, malnutrition, and growth failure; hematologic abnormalities with single- or multilineage cytopenias and susceptibility to myelodysplasia syndrome (MDS) and acute myelogeneous leukemia (AML); and bone abnormalities. In almost all affected children, persistent or intermittent neutropenia is a common presenting finding, often before the diagnosis of SDS is made. Short stature and recurrent infections are common.

Diagnosis/testing

The diagnosis of SDS is established in a proband with the classic clinical findings of exocrine pancreatic dysfunction and bone marrow dysfunction and/or biallelic pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS* or a heterozygous pathogenic variant in *SRP54* identified by molecular genetic testing.

Management

Treatment of manifestations: Care by a multidisciplinary team is recommended. Exocrine pancreatic insufficiency is treated with oral pancreatic enzymes and fat-soluble vitamin supplementation. Blood and/or platelet transfusions may be considered for anemia and/or thrombocytopenia associated with bi- or trilineage cytopenia. If recurrent infections are severe and absolute neutrophil counts are persistently ≤500/mm^3, treatment with granulocyte-colony stimulation factor (G-CSF) can be considered. Hematopoietic stem cell transplantation (HSCT) should be considered for treatment of severe pancytopenia, MDS, or AML.

Prevention of secondary complications: Aggressive dental hygiene should be pursued to promote oral health. Consider prophylactic antibiotics and G-CSF to reduce risk of infection during complex dental procedures or orthopedic surgery.

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Surveillance: Complete blood counts at least every three to six months; assessment of development, growth, and nutritional status every six months. Following baseline examination, repeat bone marrow examination every one to three years or more frequently if bone marrow changes are observed. Monitor for orthopedic complications with x-rays of hips and knees during the most rapid growth stages. Perform bone densitometry before puberty, during puberty, and thereafter based on individual findings. Perform neuropsychological screening in children age 6-8 years, 11-13 years, and 15-17 years.

Agents/circumstances to avoid: Prolonged use of cytokine and hematopoietic growth factors (e.g., G-CSF) should be considered with caution. Some drugs used in standard HSCT preparative regimens (e.g., cyclophosphamide and busulfan) may not be suitable because of possible cardiac toxicity.

Genetic counseling

SDS is inherited in an autosomal recessive (most commonly) or an autosomal dominant manner.

- *Autosomal recessive SDS.* SDS caused by pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS* is inherited in an autosomal recessive manner. Most parents of children with autosomal recessive SDS are heterozygotes (carriers of one pathogenic variant); however, *de novo* pathogenic variants have been reported. When both parents are known to be carriers, the sibs of a proband have a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for relatives at risk is possible if both pathogenic variants in a family are known.
- *Autosomal dominant SDS.* SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner; most such affected individuals reported to date have resulted from a *de novo SRP54* pathogenic variant.

If the pathogenic variant(s) in a family are known, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Shwachman-Diamond syndrome (SDS) **should be suspected** in individuals with some or all of the following clinical findings.

Exocrine pancreatic dysfunction, documented with any one of the following:

- Low serum concentrations of the digestive enzymes pancreatic isoamylase and cationic trypsinogen, adjusted to age (See Note.)
- Low levels of fecal elastase
- Supportive features including:
  - An abnormal fecal fat balance study of a 72-hour stool collection (with exclusion of intestinal mucosal disease or cholestatic liver disease)
  - Evidence of pancreatic lipomatosis on imaging
  - Reduced levels of fat-soluble vitamins (A, D, E, K)

Note: Exocrine pancreatic dysfunction may be difficult to detect because the production of individual pancreatic enzymes varies during childhood and because severe perturbations of enzyme levels are required to meet diagnostic criteria [Schibli et al 2006]. Additionally:

- Serum pancreatic isoamylase concentration is not reliable in children younger than age three years [Ip et al 2002].
- Serum cationic trypsinogen concentration increases to pancreatic-sufficient levels during early childhood in approximately 50% of children with SDS [Durie & Rommens 2004].

Hematologic abnormalities caused by bone marrow dysfunction and involving one or more of the following:

- Hypoproductive cytopenias. Persistent or intermittent depression of at least one lineage (for ≥2 measurements taken over a period of ≥3 months):
  - Neutropenia (absolute neutrophil count <1,500 neutrophils/mm^3)
  - Thrombocytopenia (platelet count <150,000 platelets/mm^3)
  - Anemia or macrocytosis (with hemoglobin concentration below normal range for age)
- Pancytopenia. Trilineage cytopenia with persistent neutropenia, thrombocytopenia, and anemia
- Abnormal findings on bone marrow examination:
  - Varying degrees of hypocellularity and fatty infiltration of the marrow compartments for age, indicating marrow failure and disordered hematopoiesis
  - Aplastic anemia and/or myelodysplasia with or without abnormal cytogenetic findings (which can include deletion of 20q11, monosomy 7, isochromosome 7, or other chromosomal changes seen in bone marrow failure syndromes).
  - Leukemia. In particular acute myleogenous leukemia

Other primary features [Myers et al 2014]:

- Short stature
- Skeletal abnormalities, most commonly chondrodysplasia or congenital thoracic dystrophy
- Congenital anomalies including cardiac defects, ear malformations / hearing loss, or skin rashes
- Hepatomegaly with or without elevation of serum aminotransferase levels
- Family history consistent with autosomal recessive inheritance

Establishing the Diagnosis

The diagnosis of SDS **is established** in a proband with the classic clinical findings of exocrine pancreatic dysfunction and bone marrow failure and/or biallelic pathogenic (or likely pathogenic) variants in *DNAJC21*, *EFL1*, or *SBDS* or a heterozygous pathogenic (or likely pathogenic) variant in *SRP54* identified by molecular genetic testing (see Table 1).

Note: (1) Although the diagnosis of SDS has classically relied on evidence of exocrine pancreatic dysfunction and bone marrow failure with single- or multilineage cytopenia [Rothbaum et al 2002, Dror et al 2011, Myers et al 2013a], a publication based on the North American SDS Registry reported that almost half of the 37 individuals with genetically confirmed SDS did not have this classic combination of manifestations [Myers et al 2014], indicating that the phenotypic spectrum of SDS is broader than previously thought, leading to underdiagnosis when the diagnosis is based on clinical findings alone. Myers et al [2014] found that the features supporting the diagnosis of SDS in individuals with neutropenia included bone marrow abnormalities (hypocellularity, dysplasias, and clonality for deletion 20q11), as well as the presence of congenital anomalies and a family history consistent with autosomal recessive inheritance of SDS. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of SDS is broad, individuals with the distinctive findings described in

Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SDS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of SDS, molecular genetic testing approaches can include **concurrent** or **serial single-gene testing** or use of a **multigene panel**.

Concurrent or serial single-gene testing. If available, concurrent testing of all the genes known to be associated with SDS (see Table 1) is recommended. Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Alternatively, serial single-gene testing can be done starting with *SBDS*, the gene most commonly associated with SDS. If testing of *SBDS* is not diagnostic, the other three genes can be tested in any order.

Note: Analysis of *SBDS* is complicated by the presence of a highly homologous pseudogene, *SBDSP*. Common pathogenic variants in the active *SBDS* arise from recombination and gene conversion with the pseudogene (see Molecular Genetics).

Targeted analysis for the three common *SBDS* pathogenic variants in exon 2, which are derived from *SBDS*, can be performed first:

- c.183_184delinsCT
- c.258+2T>C
- c.[183_184delinsCT; 258+2T>C] (a complex allele resulting from gene conversion with *SBDSP*)

Targeted testing of *SBDS* detects at least one pathogenic variant in 90% of affected individuals and both pathogenic variants in approximately 62% of affected individuals who have SDS associated with *SBDS* [Boocock et al 2003].

Note: Because the complex c.[183_184delinsCT; 258+2T>C] allele occurs through a gene conversion event, parental testing is needed to distinguish:

- In *cis* configuration (i.e., c.[183_184delinsCT; 258+2T>C] on the same allele)
  FROM
- In *trans* configuration (i.e., c.183_184delinsCT on one allele and c.258+2T>C on the other allele)

A multigene panel that includes *DNAJC21*, *EFL1*, *SBDS*, *SRP54*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

Note: Analysis of *SBDS* is complicated by the presence of a highly homologous pseudogene, *SBDSP*. Common pathogenic variants in the active *SBDS* arise from recombination and gene conversion with the pseudogene (see Molecular Genetics). A multigene panel not specifically designed for SDS or exome analysis may not detect common *SDBS* pathogenic variants, although pathogenic variants in one of the other genes could be detected.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of SDS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which genes are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Note: Analysis of *SBDS* is complicated by the presence of a highly homologous pseudogene, *SBDSP*. Common pathogenic variants in the active *SBDS* arise from recombination and gene conversion with the pseudogene (see Molecular Genetics). Exome analysis may not detect common *SDBS* pathogenic variants although pathogenic variants in one of the other genes could be detected.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Shwachman-Diamond Syndrome

Gene [1, 2]	Proportion of SDS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
EFL1	<1%	6/6 [6]	Unknown [7]
DNAJC21	<1%	3/4 [8]	1/4 [8]
SBDS	~92%	>90% [9]	<2% [10]
SRP54	<1%	3/3 [11]	Unknown [7]
Unknown [12]	<10%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, and multiplex ligation-dependent probe amplification (MLPA) and a gene-targeted microarray designed to detect single-exon deletions or duplications. Assay design is complicated by the presence of *SBDSP*.
6. Stepensky et al [2017]
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. Dhanraj et al [2017]
9. Rare pathogenic variants, such as c.297_300delAAGA, are also likely the consequence of gene conversion with *SBDSP* [Carvalho et al 2014; J Rommens, personal communication].
10. Rare whole-exon deletions [Costa et al 2007], extended conversions of exon 2 and flanking introns, or gene rearrangements involving exon 2 have been observed.
11. Carapito et al [2017]
12. A limited number (<10%) of persons with clear clinical indications of SDS do not appear to have pathogenic variants in any of the known genes, suggesting that pathogenic variants in another gene(s) may also be causative.

Clinical Characteristics

Clinical Description

The clinical spectrum of Shwachman-Diamond syndrome (SDS) is broad and varies among affected individuals, including sibs [Ginzberg et al 1999]. Earlier studies suggested that gastrointestinal and hematologic findings were observed in all affected individuals [Cipolli et al 1999, Ginzberg et al 1999]; with wider use of molecular genetic testing, however, this belief has been challenged (see Diagnosis) [Myers et al 2014].

Presentation. Neonates generally do not show manifestations of SDS; however, early presentations have included acute life-threatening infections, severe bone marrow failure, aplastic anemia [Kuijpers et al 2005], asphyxiating thoracic dystrophy caused by rib cage restriction, and severe spondylometaphyseal dysplasia [Nishimura et al 2007].

More commonly, SDS presents in infancy with failure to thrive and poor growth secondary to exocrine pancreatic dysfunction.

It should be noted, however, that the presentation of SDS varies greatly, with nearly half of individuals in the North American SDS Registry presenting without classic neutropenia and steatorrhea [Myers et al 2014].

Exocrine pancreatic dysfunction resulting from severe depletion of pancreatic acinar cells is a classic feature of SDS, with the majority of dysfunction identified within the first year of life, often in the first six months. Manifestations vary widely from asymptomatic to severe dysfunction with significant malabsorption of nutrients, steatorrhea, and failure to thrive.

For unclear reasons, in many individuals manifestations resolve with age, with as many as 50% being able to discontinue pancreatic enzyme supplementation with normal fat absorption by age four years even when enzyme secretion remains deficient [Mack et al 1996].

A general acinar defect has also been identified, with increased parotid acinar dysfunction in persons with SDS compared to controls [Stormon et al 2010]. In a study of histologic changes in gastrointestinal mucosal biopsies of symptomatic individuals with SDS, Shah et al [2010] identified duodenal inflammation in more than 50%, suggesting a possible enteropathic component to their disease. This enteropathy may contribute to vitamin deficiencies observed in some individuals with SDS despite nutritional supplementation and enzymatic replacement [Pichler et al 2015].

Pancreatic histopathology reveals few acinar cells and extensive fatty infiltration. Pancreatic imaging studies with ultrasonography or CT may reveal small size for age. In a series of individuals with SDS in whom *SBDS* pathogenic variants had been identified, MRI revealed fatty infiltration with retained ductal and islet components [Toiviainen-Salo et al 2008b]. Normal imaging studies do not rule out the diagnosis of SDS as these abnormal findings may emerge over time [Myers et al 2014].

Hematologic abnormalities. Neutropenia and impaired neutrophil chemotaxis are likely the most critical contributors to recurrent infections seen in young children [Dror & Freedman 2002, Stepanovic et al 2004, Kuijpers et al 2005]. Despite impaired neutrophil chemotaxis, individuals with SDS maintain the ability to form empyema and abscess, in contrast to other disorders of neutrophil chemotaxis [Aggett et al 1979, Rothbaum et al 1982]. Acute and deep-tissue infections can be life threatening, particularly in young children [Cipolli 2001, Grinspan & Pikora 2005]. Persistent or intermittent neutropenia is recognized first in almost all (88%-100%) affected children, often before the diagnosis of SDS is made [Ginzberg et al 1999].

Although anemia and thrombocytopenia are also seen in the majority of individuals with SDS, these findings may be intermittent or clinically asymptomatic. Severe aplastic anemia with pancytopenia occurs in a subset of individuals. The French Severe Chronic Neutropenia Registry found that 41 (40%) of 102 individuals with SDS

demonstrated significant hematologic manifestations, including those with intermittent severe cytopenias and 21 with persistent severe cytopenias (9 classified as malignant, 9 as nonmalignant, and 3 progressing from nonmalignant to malignant) [Donadieu et al 2012].

The risk for myelodysplasia (MDS) or progression to leukemia – typically acute myelogeneous leukemia (AML) – is significant in individuals with SDS; however, data remain limited with specific reports varying by definition of MDS and cohort age.

- One 25-year survey revealed that seven of 21 individuals with SDS developed myelodysplastic syndrome; five of these seven developed AML [Smith et al 1996].
- In 55 individuals with SDS in the French registry, rates of transformation to MDS/AML were 18.8% and 36.1% at 20 years and 30 years, respectively [Donadieu et al 2012].
- The Severe Congenital Neutropenia International Registry (SCNIR) reported an overall incidence of 8.1% of MDS/AML in 37 individuals with SDS over a ten-year period, representing a 1% per year rate of progression to MDS or AML [Dale et al 2006, Rosenberg et al 2006].
- A cumulative transformation rate of 18% was reported in 34 individuals with SDS by the Canadian Inherited Bone Marrow Failure Study (CIBMFS) [Hashmi et al 2011].

Of note, the above findings contrast with other reports from the Israeli (3 individuals) [Tamary et al 2010] and NIH (17 individuals) [Alter et al 2010] registries in which no one developed MDS/AML. Conclusions remain difficult given the small sample sizes; however, these differences may be attributable to cohort age [Myers et al 2013a].

The risk for malignant transformation involving dysplasia or AML is considered to be lifelong, with AML generally associated with poor outcome [Donadieu et al 2005]. To date, reported malignancies other than AML have been rare; they include isolated case reports of bilateral breast cancer [Singh et al 2012], dermatofibrosarcoma [Sack et al 2011], pancreatic adenocarcinoma, and CNS lymphoma [Sharma et al 2014].

It is well recognized that individuals with SDS may develop certain characteristic cytogenetic clonal changes, such as del(20)(q11) and i(7)(q10), in the absence of overt MDS or AML. It has been suggested that these changes may persist and fluctuate over time without high risk of progression to MDS/AML [Cunningham et al 2002, Crescenzi et al 2009, Maserati et al 2009]. Novel cytogenetic abnormalities in the presence or absence of classic del(20)(q11) and i(7)(q10) have been reported in a cohort of 91 Italian individuals with SDS, including unbalanced structural anomalies of chromosome 7, complex rearrangements of the del(20)(q), and unbalanced translocation with partial trisomy 3q and partial monosomy 6q [Valli et al 2017].

Studies in which patient and non-patient marrow cells are co-cultured indicate problems with both the stem cell compartments and stromal microenvironment [Dror & Freedman 1999]. These findings, together with the wide range of abnormalities seen in the bone marrow, are consistent with SDS being a bone marrow failure syndrome.

Growth. Children with adequate nutrition and pancreatic enzyme supplementation have normal growth velocity and appropriate weight for height; however, approximately 50% of children with SDS are below the third percentile for height and weight [Durie & Rommens 2004].

Characteristic skeletal changes appear to be present in all individuals with a molecularly confirmed diagnosis [Mäkitie et al 2004]; however, skeletal manifestations vary among individuals and over time. In some individuals the skeletal findings may be subclinical.

Cross-sectional and longitudinal data from the study of Mäkitie et al [2004] revealed the following:

- Delayed appearance of secondary ossification centers, causing bone age to appear to be delayed
- Variable widening and irregularity of the metaphyses in early childhood (i.e., metaphyseal chondrodysplasia), followed by progressive thickening and irregularity of the growth plates

- Generalized osteopenia

Of note, the epiphyseal maturation defects tended to normalize with age and the metaphyseal changes tended to progress (worsen) with age [Mäkitie et al 2004].

Further skeletal findings can include rib and joint abnormalities, the latter of which can result from asymmetric growth and can be sufficiently severe to warrant surgical intervention.

Additionally, low-turnover osteoporosis has been reported as a feature of SDS. Toiviainen-Salo et al [2007] reported bone abnormalities in ten of 11 individuals with genetically confirmed SDS including reduced bone mineral density by Z-scores. Vertebral compression fractures were reported in three. Vitamin D and K deficiencies, both detrimental to bone health, were each identified in six individuals. It is important to ensure accurate measurement of bone mineral density, as adults with SDS have short stature and may have an incorrectly reported low bone mineral density due to low height Z-score [Shankar et al 2017].

Hepatomegaly and liver dysfunction with elevated serum aminotransferase concentration can be observed in young children but tend to resolve by age five years [Toiviainen-Salo et al 2007]. Elevated bile acids were reported in one Finnish study in seven of 12 individuals with SDS, three of whom had persistent or intermittent elevation over time, raising concern for ongoing cholestasis [Toiviainen-Salo et al 2009]. Mild histologic changes may also be evident in liver biopsies, and although they do not appear to be progressive, it has been noted that liver complications have occurred in older individuals following bone marrow transplantation [Ritchie et al 2002].

Cognitive/psychological. Individuals with SDS have also been recognized to have cognitive and/or behavioral impairment as well as structural brain changes [Kent et al 1990, Cipolli et al 1999, Ginzberg et al 1999, Toiviainen-Salo et al 2008a, Perobelli et al 2012, Booij et al 2013].

Kerr et al [2010] compared the neuropsychological function of 32 children with SDS with age- and sex-matched children with cystic fibrosis and sib controls. On a number of measures, those with SDS displayed a far wider range of abilities than controls, from severely impaired to superior. Approximately 20% of children with SDS demonstrated intellectual disability in at least one area, with perceptual reasoning being most affected. They were also far more likely than the general population to have the diagnosis of pervasive developmental disorder (6% vs 0.6%). Attention deficits were also more common in children with SDS and in their unaffected sibs than in children with cystic fibrosis.

Other possible findings

- Ichthyosis and eczematous lesions
- Oral disease including delayed dental development, increased dental caries in both primary and permanent teeth, and recurrent oral ulcerations [Ho et al 2007]
- Endocrine dysfunction including congenital hypopituitarism [Jivani et al 2016], diabetes, and growth hormone deficiency [Myers et al 2013b]
- Immune dysfunction [Dror et al 2001]
- Congenital anomalies including: cardiac, gastrointestinal, neurologic, urinary tract/kidney, or eye and ear anomalies [Myers et al 2014]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed for any of the genes associated with SDS.

Nomenclature

Previously used terms for SDS:

- Shwachman's syndrome
- Congenital lipomatosis of the pancreas
- Shwachman-Bodian syndrome

Prevalence

It has been estimated that SDS occurs in one of 77,000 births based on the observation that it is approximately 1/20th as frequent as cystic fibrosis in North America [Goobie et al 2001].

SDS occurs in diverse populations including those with European, Indian, aboriginal (North America), Chinese, Japanese, and African ancestry.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS*.

Heterozygous *SRP54* pathogenic variants may also be associated with isolated congenital neutropenia [Bellanné-Chantelot et al 2018].

Differential Diagnosis

Features of Shwachman-Diamond syndrome (SDS) (e.g., poor growth and transient neutropenia) may have multiple causes in young children (see Table 2).

Table 2. Disorders to Consider in the Differential Diagnosis of Shwachman-Diamond Syndrome (SDS)

Disorder / Clinical Circumstance	Gene(s)	MOI [1]	Clinical Features of the Disorder / Comments	
			Overlapping w/SDS	Distinguishing from SDS
Cystic fibrosis (CF)	*CFTR*	AR	CF often presents w/ both upper-respiratory infections & exocrine pancreatic dysfunction.	In CF: • ↑ sweat chloride values • No primary bone marrow failure
Johanson-Blizzard syndrome (JBS) (OMIM 243800)	*UBR1*	AR	Exocrine pancreatic dysfunction	In JBS: • Anomalies & severe DDs • No hematologic abnormalities
Severe malnutrition	NA	NA	Failure to thrive	In severe malnutrition: • Clinical picture consistent w/inadequate caloric/protein intake • No underlying syndromic diagnosis • No exocrine pancreatic dysfunction
Pearson marrow-pancreas syndrome (PMPS) (OMIM 557000)	See footnote 2.	mt	Exocrine pancreatic dysfunction & bone marrow dysfunction	In PMPS: • Normal cellularity in bone marrow, w/distinct cytoplasmic vacuolization in myeloid precursors • mtDNA contiguous-gene deletions/ duplications

Table 2. continued from previous page.

Disorder / Clinical Circumstance	Gene(s)	MOI [1]	Clinical Features of the Disorder / Comments	
			Overlapping w/SDS	Distinguishing from SDS
SPINK1-related severe infantile isolated exocrine pancreatic insufficiency [3]	*SPINK1*	AR	Exocrine pancreatic dysfunction	No bone marrow failure or neutropenia
Diamond-Blackfan anemia (DBA)	18 genes	AD XL	Bone marrow failure	In DBA: • Progressive macrocytic anemia w/ reticulocytopenia • Normal cellularity bone marrow w/markedly ↓ or absent erythroid precursors • No primary exocrine pancreatic dysfunction
Fanconi anemia (FA)	21 genes	AR AD XL	Bone marrow failure	In FA: • Progressive pancytopenia w/positive chromosome breakage studies • Variable cellularity of bone marrow w/↓ precursors • No primary exocrine pancreatic dysfunction
Dyskeratosis congenita (DC)	11 genes	XL AD AR	Bone marrow failure	In DC: • Abnormally shortened telomere length • Variable cellularity of bone marrow w/↓ precursors • No primary exocrine pancreatic dysfunction
Medications or infections	NA	NA	Neutropenia	Neutropenia caused by medications or infections is transient.
Kostmann congenital neutropenia (OMIM 610738)	*HAX1*	AR	Neutropenia	In Kostmann congenital neutropenia: • Severe neutropenia • On hematologic testing: early myeloid arrest at promyelocyte/ myelocyte stage, w/atypical nuclei & cytoplasmic vacuolization
ELANE-related neutropenia [4]	*ELANE*	AD	Neutropenia	In *ELANE*-related neutropenia: • Severe neutropenia w/mutation of *ELANE* • On hematologic testing: isolated neutropenia

Table 2. continued from previous page.

Disorder / Clinical Circumstance	Gene(s)	MOI [1]	Clinical Features of the Disorder / Comments	
			Overlapping w/SDS	Distinguishing from SDS
Cartilage-hair hypoplasia (CHH)	*RMRP*	AR	Skeletal dysplasia	In CHH: • Short at birth, w/abnormal long-bone growth. ↑ incidence of scoliosis, abnormal pubertal growth spurt, & global dysfunction of skeletal growth (axial & appendicular) • Gastrointestinal features are due to complications of infection (vs to exocrine pancreatic insufficiency in SDS).

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; mt = mitochondrial; NA = not applicable; XL = X-linked

1. Ordered by relative frequency if multiple modes of inheritance

2. Pearson marrow-pancreas syndrome is caused by mtDNA contiguous gene deletions/duplications (OMIM 557000).

3. Venet et al [2017]

4. ELANE-related neutropenia includes cyclic neutropenia and severe congenital neutropenia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual following the initial diagnosis of Shwachman-Diamond syndrome (SDS), current consensus practice typically recommends the following evaluations to assess the status of the pancreas, liver, bone marrow, and skeleton [Dror et al 2011].

- Assessment of growth: height, weight in relation to age
- Assessment of nutritional status to determine if supplementation with pancreatic enzymes is necessary and/or effective:
  - Measurement of fat-soluble vitamins (vitamin A, 25-OH-vitamin D, and vitamin E) or their related metabolites
  - Measurement of prothrombin time (to detect vitamin K deficiency)
- Assessment of serum concentration of the digestive enzyme cationic trypsinogen and, if sufficiency is observed, subsequent confirmation with a 72-hour fecal fat balance study (with discontinuation of enzyme supplementation for at least a 24-hour period)
- Pancreatic imaging by ultrasound
- Complete blood count with white cell differential and platelet count
- Measurement of iron, folate, and B_{12}
- Bone marrow examination with biopsy and cytogenetic studies at initial assessment
- Immunoglobulins and lymphocyte subpopulations
- Skeletal survey with radiographs of at least the hips and lower limbs
- Bone densitometry as clinically indicated
- Assessment of serum aminotransferase levels
- Assessment of developmental milestones (including pubertal development) with neuropsychological evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A multidisciplinary team including specialists from the following fields is recommended: hematology, gastroenterology, clinical genetics, orthopedics, endocrinology, immunology, dentistry, child development, psychology, and social work as needed [Dror & Freedman 2002, Rothbaum et al 2002, Durie & Rommens 2004, Dror et al 2011, Myers et al 2013a].

Exocrine pancreatic insufficiency can be treated with the same oral pancreatic enzymes commonly used in treatment of cystic fibrosis; dose should be based on results of routine assessment of pancreatic function and nutritional status. Steatorrhea often resolves in early childhood, but pancreatic enzyme levels can remain low; routine monitoring (see Surveillance) is recommended.

Supplementation with fat-soluble vitamins (A, D, E, and K) is recommended.

Hematologic abnormalities. Blood and/or platelet transfusions may be considered for anemia and bi- or trilineage cytopenia.

If recurrent infections are severe and absolute neutrophil counts are persistently ≤500/mm^3, treatment with prophylactic antibiotics and granulocyte-colony stimulation factor (G-CSF) can be considered with caution (see Agents/Circumstances to Avoid).

Hematopoietic stem cell transplantation (HSCT) should be considered for treatment of severe pancytopenia, bone marrow transformation to myelodysplastic syndrome, or acute myelogeneous leukemia (AML). Chemotherapy can be utilized as a bridge to HSCT in individuals with SDS and AML; however, sustained complete remission is problematic and prompt continuation to HSCT remains imperative. Although earlier reports indicate that survival is fair, cautious myeloablation and newer reduced-intensity regimens have demonstrated improved outcomes in small cohorts [Cesaro et al 2005, Vibhakar et al 2005, Sauer et al 2007, Bhatla et al 2008].

Note: Bone marrow abnormalities are not treated unless severe aplasia, myelodysplastic changes, or leukemic transformation are present.

Skeletal abnormalities. Skeletal manifestations of SDS may range from clinically asymptomatic to severe, and can evolve or progress over time. Severe manifestations such as asphyxiating thoracic dystrophy due to rib cage restriction will require subspecialty care including pediatric pulmonary and orthopedic specialists. Other rib and joint abnormalities may require surgical intervention if severe, and consultation with an orthopedic surgeon familiar with SDS may be beneficial for those with skeletal dysplasia.

Evaluate for treatment for low bone density if indicated by bone densitometry.

Growth. Children with poor growth and delayed puberty benefit from ongoing consultation with an endocrinologist, who may also consult with orthopedists regarding possible surgical management of asymmetric growth and joint deformities.

Other. Cognitive, learning, and behavioral complications can be features of SDS, and remedial interventions are considered beneficial.

Prevention of Secondary Complications

Frequent dental visits to monitor tooth development and oral health are recommended to reduce the incidence of mouth ulcers and gingivitis. Home care should include aggressive dental hygiene with topical fluoride treatments to help prevent dental decay.

Prophylactic antibiotics and G-CSF may be especially helpful when interventions such as complex dental procedures or orthopedic surgery are being considered (see Agents/Circumstances to Avoid).

Surveillance

The following are recommended given the intermittent nature of some features of SDS and the evolution of the phenotype over time [Rothbaum et al 2002, Dror et al 2011, Myers et al 2013a]:

- Complete blood counts with white blood cell differential and platelet counts at least every three to six months, or more frequently if peripheral blood counts are changing or infections are recurrent and debilitating
- Bone marrow examinations every one to three years following the baseline examination, and more frequently if changes in bone marrow function or cellularity are observed
- Assessment of nutritional status every six months and measurement of serum concentration of vitamins to evaluate effectiveness of or need for pancreatic enzyme therapy
- Monitoring for orthopedic complications with x-rays of hips and knees during the most rapid growth stages
- Bone densitometry before puberty, during puberty, and thereafter based on individual findings. Results must be interpreted in the context of stature and pubertal status.
- Developmental assessment every six months from birth to age six years and growth every six months
- Neuropsychological screening in children age 6-8 years, 11-13 years, and 15-17 years

Agents/Circumstances to Avoid

Prolonged use of cytokine and hematopoietic growth factors such as G-CSF is cautioned against in view of their potential contribution to leukemic transformation [Rosenberg et al 2006].

Some drugs (e.g., cyclophosphamide and busulfan) used in standard HSCT preparative regimens may not be suitable because of possible cardiac toxicity [Mitsui et al 2004, Cesaro et al 2005, Vibhakar et al 2005, Sauer et al 2007].

Evaluation of Relatives at Risk

It is appropriate to evaluate as early as possible the older and younger sibs of a proband in order to identify those who will benefit from treatment and preventive measures. This can also potentially prevent asymptomatic affected sibs from being used as bone marrow transplant donors. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Testing for exocrine pancreatic dysfunction and evidence of bone marrow failure with single- or multilineage cytopenia if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

For pregnancies in women with SDS, high-risk pregnancy care including consultation with a hematologist is recommended [Alter et al 1999]. Women with SDS are at increased risk for recurrent miscarriages, but the rates of elective abortion, live birth, and spontaneous miscarriage are comparable to the general population [Giri et al 2018].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Shwachman-Diamond syndrome (SDS) caused by pathogenic variants in *EFL1*, *DNAJC21*, or *SBDS* is inherited in an autosomal recessive manner. SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are usually heterozygotes (i.e., carriers of one SDS-related pathogenic variant).
- Occasionally, only one parent is a carrier as the affected child has one inherited and one *de novo* pathogenic variant. Approximately 10% of *SBDS* pathogenic variants are *de novo* [Steele et al 2014]. The rate of *de novo* pathogenic variants for the other genes is not known.
- Heterozygotes (carriers) are asymptomatic. See Carrier Detection.

Sibs of a proband

- When both parents are known to be carriers, each sib of an affected individual has, at conception, a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- When the proband has one inherited and one *de novo* pathogenic variant, each sib of an affected individual has, at conception, a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic. See Carrier Detection.

Offspring of a proband

- The offspring of an individual with autosomal recessive SDS are obligate heterozygotes (carriers) for a pathogenic variant in one of the genes associated with SDS.
- In the rare event that the reproductive partner of the proband is a carrier, the offspring are at a 50% risk of being affected and a 50% risk of being carriers.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant. (If one variant is *de novo*, this risk only applies to the sibs of the carrier parent.)

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Note that carriers are clinically asymptomatic:

- Although it has been suggested that carriers (heterozygotes) with one pathogenic *SBDS* allele may be at higher-than-average risk for aplastic anemia [Calado et al 2007], aplastic anemia has not been observed among *SBDS* heterozygotes (i.e., carriers) in more than 200 families with SDS [J Rommens, unpublished; North American SDS Registry; Author, unpublished].
- Sequence analysis of DNA obtained from bone marrow samples from 77 persons with acute myelogeneous leukemia (AML) did not reveal any *SBDS* pathogenic variants [Majeed et al 2005]. Subsequently, in a larger cohort of 160 children with AML, heterozygous *SBDS* pathogenic variants were present at similar frequencies to those of healthy blood donor controls, and no homozygous or compound heterozygous pathogenic variants were identified [Aalbers et al 2013].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- To date, most individuals diagnosed with *SRP54*-related SDS have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *SRP54* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent is known to have the *SRP54* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the *SRP54* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SRP54* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *SRP54*-related SDS because of the theoretic possibility of reduced penetrance in a parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with *SRP54*-related SDS has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the SDS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Associazione Italiana Sindrome di Shwachman**
  Italy
  Email: aiss@iol.it
  www.shwachman.it
- **Shwachman-Diamond Syndrome Canada**
  Canada
  Phone: 866-462-8907
  Email: info@shwachman.org
  www.sdscanada.ca
- **Shwachman-Diamond Syndrome Foundation**
  Phone: 888-825-7373
  Email: info@shwachman-diamond.org
  www.shwachman-diamond.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**
  Phone: 800-518-8474
  Email: NCI.IBMFS@westat.com
  www.marrowfailure.cancer.gov
- **Shwachman-Diamond Syndrome Registry**
  www.shwachman-diamond.org/sds-registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Shwachman-Diamond Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DNAJC21	5p13.2	DnaJ homolog subfamily C member 21		DNAJC21	DNAJC21
EFL1	15q25.2	Elongation factor-like GTPase 1		EFL1	EFL1
SBDS	7q11.21	Ribosome maturation protein SBDS	SBDS database SBDSbase: Mutation registry for Shwachman-Diamond syndrome	SBDS	SBDS
SRP54	14q13.2	Signal recognition particle subunit SRP54		SRP54	SRP54

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Shwachman-Diamond Syndrome (View All in OMIM)

260400	SHWACHMAN-DIAMOND SYNDROME 1; SDS1
604857	SIGNAL RECOGNITION PARTICLE, 54-KD; SRP54
607444	SBDS RIBOSOME MATURATION FACTOR; SBDS
617048	DNAJ/HSP40 HOMOLOG, SUBFAMILY C, MEMBER 21; DNAJC21
617941	SHWACHMAN-DIAMOND SYNDROME 2; SDS2

Molecular Pathogenesis

Schwachman-Diamond syndrome (SDS) is caused by pathogenic variants in the *DNAJC21*, *EFL1*, *SBDS*, or *SRP54*. The majority of cases are associated with *SBDS*, which encodes SBDS, a protein that plays a central role in ribosome biogenesis. Interestingly, the genes more recently found to be associated with SDS – *DNAJC21*, *EFL1*, and *SRP54* – all play a role in ribosome biogenesis and function.

DNAJC21

Gene structure. *DNAJC21* is ubiquitously expressed. It is located on the short arm of chromosome 5 (5p.13.2). It contains at least 12 exons and spans more than 25.6 kb. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Sequence analysis of *DNAJC21* (involved in ribosomal biogenesis) revealed the pathogenic variants p.Lys34Glu and p.Gln174Ter [Dhanraj et al 2017].

Table 3. *DNAJC21* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.520C>T	p.Gln174Ter	NM_001012339.2
c.100A>G	p.Lys34Glu	NP_001012339.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *DNAJC21* encodes a protein with a common isoform of 531 amino acids. Studies of the yeast homolog support the role for *DNAJC21* in ribosome biogenesis.

Abnormal gene product. Deletion of the yeast *DNAJC21* homolog *Jjj1* leads to reduced levels of mature ribosomes and dysfunctional 60S ribosome subunit biogenesis.

EFL1

Gene structure. *EFL1* has 13 exons and is located on chromosome 13q. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Homozygous pathogenic variants in *EFL1* have been associated with disease. Two affected individuals homozygous for p.Met882Lys and four affected individuals homozygous for p.Arg1095Gln have been described [Stepensky et al 2017].

Table 4. *EFL1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2645T>A	p.Met882Lys	NM_024580.5 NP_078856.4
c.3284G>A	p.Arg1095Gln	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *EFL1* is a partner for SBDS protein and is involved in the formation of mature ribosomes. *ELF1* interacts with the 60S ribosomal subunit to prevent premature association of the ribosomal subunits in the nucleus.

Abnormal gene product. Pathogenic variants in *EFL1* do not disrupt protein folding but rather prevent release of the protein from the 60S subunit, resulting in abnormal ribosomes with altered translating capabilities.

SBDS

Gene structure. *SBDS* has five exons and spans <9 kb. Notable aspects of the gene are its pericentromeric location on chromosome 7q and occurrence within a 305-kb segment that appears duplicated and inverted, 5.8 megabases (Mb) distally [Boocock et al 2003]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Some of the benign variants reflect the sequence of the pseudogene *SBDSP*, indicating that they may have arisen by gene conversion events between the gene and the pseudogene.

Pathogenic variants. The abnormalities identified in individuals with SDS lead to prematurely truncated proteins, splicing aberrations, and missense alterations.

At least one allele in more than 90% of individuals with Shwachman-Diamond syndrome (SDS) has a pathogenic variant in exon 2 that apparently arose by gene conversion, a process by which a small segment of the functional gene, *SBDS*, is replaced by a segment copied from the highly homologous nonfunctional pseudogene *SBDSP*. As a result, this segment of *SBDS* has sequence variants (typical of the pseudogene) that inactivate normal *SBDS* gene expression and/or translation of normal protein.

The three most common pathogenic alleles resulting from gene conversion and accounting for more than 76% of disease-causing alleles in more than 200 families are the following [J Rommens, unpublished]:

- c.183_184delinsCT

- c.258+2T>C
- c.[183_184delinsCT; 258+2T>C], in which both pathogenic variants occur on one allele

Nearly 100 novel sequence variants identified in the five exons of *SBDS* are consistent with loss-of-function alterations [Boocock et al 2003, Nicolis et al 2005, Maserati et al 2006, Taneichi et al 2006]. Seven have been found in multiple, apparently unrelated families (see Table 5).

Except for one reported case to date, affected individuals with rare pathogenic variants are compound heterozygotes with one of the three common pseudogene-derived pathogenic variants. In the one exception, an individual with a clinical diagnosis of SDS had two rare missense variants, in exon 3 and exon 4 [Erdos et al 2006].

Table 5. *SBDS* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.119delG	p.Ser41AlafsTer18	NM_016038.2 NP_057122.2
c.183_184delinsCT [2] (c.183TA>CT)	p.Lys62Ter	
c.[183_184delinsCT; 258+2T>C] [2]	p.Lys62Ter	
c.258+1G>C	--	NM_016038.2
c.258+2T>C [2]	p.Cys84TyrfsTer4	NM_016038.2 NP_057122.2
c.297_300delAAGA [2]	p.Glu9AspfsTer20	
c.377G>C	p.Arg126Thr	
c.505C>T	p.Arg169Cys	
c.624+1G>C	--	NM_016038.2
c.652C>T	p.Arg218Ter	NM_016038.2 NP_057122.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Likely the consequence of gene conversion with *SBDSP*

Normal gene product. *SBDS* encodes a highly conserved protein of 250 amino acids that appears to occur in all animals, plants, and archaea [Boocock et al 2003]. The structural analysis of an archaeal ortholog indicates that the SBDS protein contains three domains [Savchenko et al 2005, Shammas et al 2005].

The SBDS protein is believed to play a role in RNA metabolism and ribosome biogenesis. Studies have demonstrated SBDS protein association with the large 60S ribosomal subunit, as well as association with multiple ribosomal proteins [Ganapathi et al 2007, Ball et al 2009]. Genetic studies of the yeast homolog also support a role in 60S ribosomal subunit biogenesis and translational activation [Menne et al 2007]. Recent studies examining the interaction of SBDS with the GTPase elongation factor-like 1 (ELF1) [Finch et al 2011] endorse a model in which SBDS initiates the joining of the 40S and 60S subunits for active translation through the creation of the active 80S ribosome.

In addition to its role in ribosomal biogenesis, SBDS protein has been implicated in mitochondrial function. Reduced expression of *SBDS* decreases mitochondrial membrane potential and increases the production of reactive oxygen species, which may contribute to SDS pathophysiology [Henson et al 2013].

Abnormal gene product. The pathogenic variants identified in individuals with SDS led to prematurely truncated proteins, splicing aberrations, and missense alterations. These pathogenic variants are predicted to result in absence or loss of function of the SBDS protein. Despite the relatively common occurrence of the null allele c.183_184delinsCT (p.Lys62Ter), no homozygotes have been reported. This is consistent with the observations of a mouse model in which complete loss of both *Sbds* alleles was not compatible with life [Zhang et al 2006]. It is therefore anticipated that some residual activity of the SBDS protein is required for development to occur.

SRP54

Gene structure. *SRP54* is located on chromosome 14q and contains 14 exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. *De novo* pathogenic variants p.Thr115Ala, p.Thr117del, and p.Gly226Glu have been described in individuals with the SDS phenotype [Carapito et al 2017].

Table 6. *SRP54* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.677G>A	p.Gly226Glu	NM_003136.3
c.343A>G	p.Thr115Ala	NP_003127.1
c.349_351delACA	p.Thr117del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. SRP54 is involved in protein translation. It is part of a single RNA molecule made up of six polypeptides (SRP9, SRP14, SRP19, SRP54, SRP68, and SRP72). SRP54 plays a central role in the ribonucleoprotein complex signal pathway facilitating signal sequencing at the endoplasmic reticulum surface.

Abnormal gene product. Pathogenic variants in *SRP54* lead to both quantitative and qualitative disruption of secreted and membrane-bound protein synthesis, along with changes in cellular protein content.

Chapter Notes

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