GENEReviews

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Shwachman-Diamond Syndrome

[*Shwachman Syndrome, Shwachman-Bodian-Diamond Syndrome, Pancreatic Insufficiency and Bone Marrow Dysfunction*]

Johanna M Rommens , PhD
Senior Scientist, Program in Genetics & Genome Biology
The Hospital for Sick Children
Professor, Department of Molecular Genetics
University of Toronto
j.rommens@utoronto.ca

Peter R Durie , MD, FRCPC
Division of Gastroenterology, Hepatology & Nutrition
The Hospital for Sick Children
Professor, Department of Pediatrics
University of Toronto
peter.durie@sickkids.ca

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Summary

Disease characteristics. Shwachman-Diamond syndrome (SDS) is characterized by exocrine pancreatic dysfunction with malabsorption, malnutrition, and growth failure; hematologic abnormalities with single- or multi-lineage cytopenia 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 relies on clinical findings, including pancreatic dysfunction and characteristic hematologic problems. *SBDS* is the only gene currently known to be associated with SDS. Molecular genetic testing is clinically available.

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 bi- or trilineage cytopenia. If recurrent infections are severe and absolute neutrophil counts are persistently 500/mm^3 or less, 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 to promote oral health. Consider prophylactic antibiotics and G-CSF to reduce risk of infection during complex dental procedures or orthopedic surgery. *Surveillance:* assessment of development, growth, and nutritional status every six months. Complete blood counts at least every six months. Following baseline examination, bone marrow examination every one to three years or more frequently if bone marrow changes are observed. *Agents/circumstances to avoid:* Prolonged use of cytokine and hematopoietic growth factors (such as G-CSF) should be considered with caution. Case reports have indicated that standard preparative regimens for HSCT with cyclophosphamide or cyclophosphamide and busulfan may lead to cardiac toxicity; milder ablation regimens are being considered.

Genetic counseling. SDS is inherited in an autosomal recessive manner. Most parents of children with *SBDS* mutations are carriers; however, *de novo* mutations 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 and prenatal testing for pregnancies at increased risk are possible if both disease-causing mutations in a family are known.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of Shwachman-Diamond syndrome (SDS) relies on evidence of exocrine pancreatic dysfunction and bone marrow failure with single- or multi-lineage cytopenia [Rothbaum et al 2002].

Exocrine pancreatic dysfunction can be documented with any one of the following:

- An abnormal fecal fat balance study of a 72-hour stool collection (with exclusion of intestinal mucosal disease or cholestatic liver disease) plus abnormal exocrine pancreas on imaging
- Low serum concentrations of the digestive enzymes pancreatic isoamylase and cationic trypsinogen
- Deficiency in pancreatic enzyme secretion following quantitative pancreatic stimulation testing with intravenous cholecystokinin and secretin

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]:

- 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].

Pancreatic histopathology reveals few acinar cells and extensive fatty infiltration. Pancreatic imaging studies with ultrasonography or CT reveal small size for age. In a series of persons with mutation-positive SDS, MRI revealed fatty infiltration with retained ductal and islet components [Toiviainen-Salo et al 2008].

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

- Persistent or intermittent depression of at least one myeloid lineage:
  - Neutropenia (established with an absolute neutrophil count <1,500 neutrophils /mm^3 for ≥3 measurements taken over a period of ≥3 months)
  - Thrombocytopenia (persistent, with platelet count <150,000 platelets/ mm^3)
  - Anemia (with hemoglobin concentration below the normal range for age)
- Pancytopenia (trilineage cytopenia with persistent neutropenia, thrombocytopenia, and anemia)

Bone marrow examination may reveal the following:

- Varying degrees of hypocellularity and fatty infiltration of the marrow compartments, indicating marrow failure and disordered hematopoiesis

- Maturation arrest or delay in single- or multiple-myeloid lineages
- Aplastic anemia and myelodysplasia with or without abnormal cytogenetic findings. When cytogenetic anomalies are present, they can be monosomy 7, isochromosome 7, or other chromosomal changes seen in bone marrow failure syndromes.

Studies in which patient and non-patient marrow cells are co-cultured indicate problems with both the stem cell and stromal microenvironment compartments [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.

Other. Variation in severity and clinical manifestations complicate the ability to establish a definitive diagnosis of SDS. Other primary features used in support of the diagnosis:

- Short stature
- Skeletal abnormalities
- Hepatomegaly with or without elevation of serum aminotransferase levels

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *SBDS* is the only gene presently known to be associated with SDS [Boocock et al 2003].

Other loci. A limited number (<10%) of persons with clear clinical indications of SDS do not appear to have mutations in *SBDS,* suggesting that mutations in another gene(s) may be causative.

Clinical testing

Targeted mutation analysis. In more than 90% of individuals with SDS, at least one of the mutant *SBDS* alleles has resulted from a phenomenon known as gene conversion (see Molecular Genetics). The three most common gene conversion mutations, accounting for more than 76% of disease alleles:

- c.183_184delinsCT
- c.258+2T>C
- c.[183_184delinsCT; 258+2T>C], in which both mutations occur on a single allele

In more than 62% of affected individuals, the above mutations account for both disease-causing alleles.

Sequence analysis. The common gene conversion mutations can be detected by direct sequencing of exon 2 [Boocock et al 2003], accounting for 76% of the SDS-causing alleles in more than 200 families [Author, unpublished]. Most of the other rare mutations, including splicing mutations, short insertions or deletions, and missense mutations, can be identified by direct sequencing of the five exons of *SBDS*.

Research testing

Unusual mutations that involve exon deletions [Costa et al 2007], extended conversions of exon 2 and flanking introns, or gene rearrangements involving exon 2 have been observed but may not be detected readily with routine sequencing [Author, unpublished]. In these cases, testing with methods that detect the number of copies of *SBDS* exons is necessary (e.g., quantitative PCR methods); however, their interpretations must consider the occurrence of the pseudogene. The extent of variation in the pseudogene is not known.

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
SBDS	Targeted mutation analysis	Common mutations c.183_184delinsCT, c.258+2T>C, and c.[183_184delinsCT; 258+2T>C] [1]	76% [2]	Clinical Testing
	Sequence analysis	Sequence variants, including the common mutations listed above	>90% [3]	

1. Targeted mutations, and therefore detection frequencies, may vary among laboratories.

2. Targeted mutation analysis for these three common mutations can detect at least one mutation in 90% of affected individuals.

3. If exocrine pancreatic dysfunction and characteristic hematologic abnormalities have been documented, the proportion of affected individuals with mutations in SBDS is high.

Interpretation of test results

To interpret the common gene conversion mutations identified by targeted mutation analysis, parents should be tested to determine whether the mutation(s) observed in their child are:

- **Monoallelic** (e.g., c.[183_184delinsCT; 258+2T>C] on one chromosome and a normal allele on the other chromosome)

  OR

- **Biallelic** (e.g., c.183_184delinsCT on one chromosome and c.258+2T>C on the other chromosome)

For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in a proband. If both exocrine pancreatic dysfunction and characteristic hematologic abnormalities are present, it is appropriate to proceed with molecular genetic testing of *SBDS*:

- Targeted mutation analysis for the three common mutations in exon 2 can detect at least one mutation in 90% of affected individuals.
- If no mutation or only one mutation is identified using targeted mutation analysis, sequence analysis of the whole coding region can be performed.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with variations in *SBDS*.

Note: (1) Although a recent publication suggested that carriers with one normal and one disease-causing *SBDS* allele may be at higher-than-average risk for aplastic anemia [Calado et al 2007], methodic problems with this study may include the following:

- Background risk of being a *SBDS* carrier (1/139) did not appear to be considered.
- Criteria for performing sequence analysis on individuals with aplastic anemia were not clearly delineated.

(2) Aplastic anemia has not been observed in *SBDS* heterozygotes (i.e., carriers) of more than 200 families with SDS [Authors, personal observation].

(3) Sequence analysis of DNA obtained from bone marrow samples from 77 persons with acute myelogeneous leukemia (AML) did not reveal any *SBDS* mutations [Majeed et al 2005].

Clinical Description

Natural History

The clinical spectrum of Shwachman-Diamond syndrome (SDS) is broad and varies among affected individuals, even sibs [Ginzberg et al 1999]. Despite this variability, both gastrointestinal and hematologic findings are observed in all affected individuals [Cipolli et al 1999, Ginzberg et al 1999].

Neonates generally do not show manifestations of SDS; however, early presentations have included acute life-threatening infections and asphyxiating thoracic dystrophy caused by rib cage restriction. Rare neonatal presentations have also included severe bone marrow failure and aplastic anemia [Kuijpers et al 2005] or 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, and recurrent infections secondary to neutropenia and impaired neutrophil chemotaxis, which are likely the most critical contributors to frequent recurrent infections, especially in young children [Dror & Freedman 2002, Stepanovic et al 2004, Kuijpers et al 2005]. Persistent or intermittent neutropenia is recognized first in almost all affected children, often before the diagnosis is made; in one series of 88 children, neutropenia was a presenting finding in 98% [Ginzberg et al 1999]. Acute and deep-tissue infections can be life threatening, particularly in young children [Cipolli 2001, Grinspan & Pikora 2005].

The risk for leukemia, typically AML, may be 15%-25% or higher in individuals with SDS than in the general population [Dror & Freedman 2002]. Although information is limited to a few studies, a retrospective survey over 25 years revealed that seven of 21 individuals with SDS developed myelodysplastic syndrome; five of the seven developed AML [Smith et al 1996]. In a more recent study, eight of 71 persons with SDS developed MDS and/or leukemia over a ten-year period [Donadieu et al 2005].

The risks for transformation with dysplastic cytologic abnormalities and AML are considered to be lifelong; AML is generally associated with poor outcome [Donadieu et al 2005]. The risk for malignancies other than AML does not appear to be increased, but information to date is limited.

Characteristic skeletal changes appear to be present in all mutation-positive individuals [Mäkitie et al 2004]; however, skeletal manifestations vary among individuals and over time. In some individuals the skeletal findings may be sub-clinical.

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].

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

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].

Hepatomegaly and liver dysfunction with elevated serum aminotransferase concentration can be observed in young children, but tend to resolve by age five years. Mild histologic changes may also be evident in 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].

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]
- Cognitive and/or behavioral problems [Cipolli et al 1999, Ginzberg et al 1999]; however, few studies have described their full extent and range [Kent et al 1990; E Kerr, personal communication].
- Immune dysfunction [Dror et al 2001]
- Kidney or urinary tract anomalies

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed with *SBDS* mutations [Mäkitie et al 2004; Kawakami et al 2005; Kuijpers et al 2005; Author, unpublished]; this is consistent with the earlier observed phenotypic variability among affected sibs [Ginzberg et al 1999].

Nomenclature

SDS has previously been known as:

- Shwachman's syndrome

- Congenital lipomatosis of the pancreas
- Shwachman-Bodian syndrome

Prevalence

It has been estimated that SDS occurs in one of 76,000 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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Features of Shwachman-Diamond syndrome (SDS) in early childhood, such as poor growth and transient neutropenia, may have multiple causes in young children.

Pancreatic dysfunction

Cystic fibrosis, which often presents with both upper-respiratory infections and exocrine pancreatic dysfunction, can be distinguished from SDS by sweat chloride testing and absence of primary bone marrow failure.

Other conditions with exocrine pancreatic dysfunction:

- Johanson-Blizzard syndrome, which can be distinguished from SDS by the characteristic anomalies, severe developmental delays, and absence of hematologic abnormalities
- Pearson bone marrow-pancreas syndrome, a rare mitochondrial disorder with both exocrine pancreatic dysfunction and bone marrow dysfunction, which can be distinguished from SDS by bone marrow examination and molecular genetic testing

Exocrine pancreatic insufficiency can also result from severe malnutrition.

Other bone marrow failure syndromes that overlap in some respects with SDS include the following:

- Diamond-Blackfan anemia
- Fanconi anemia
- Dyskeratosis congenita

These conditions and aplastic anemia can often be excluded by clinical investigations and bone marrow examination. Primary exocrine pancreatic dysfunction is not known to occur is these related syndromes.

Neutropenia

Transient neutropenia can result from medications or infections.

Clinical findings, repeated assessments of hematologic findings, and molecular genetic testing reliably distinguish SDS from Kostmann congenital neutropenia and *ELA2*-related neutropenia.

Skeletal dysplasia

Cartilage-hair hypoplasia (CHH) syndrome has gastrointestinal, skeletal, hematologic, and immunologic features. However, the skeletal anomalies of CHH can be distinguished from those of SDS, and the gastrointestinal features of CHH are secondary to complications of infections rather than to exocrine pancreatic insufficiency.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease following the initial diagnosis of Shwachman-Diamond syndrome (SDS), the following evaluations to assess the status of the pancreas, liver, bone marrow, and skeleton are recommended:

- Assessment of growth: height, weight in relation to age
- Assessment of developmental milestones (including pubertal development)
- 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, followed by confirmation with 72-hour fecal fat balance study (with discontinuation of enzyme supplementation for at least a 24-hour period)
- Assessment of serum aminotransferase levels
- Complete blood count with white cell differential and platelet count at six-month intervals (or more often as clinically indicated)
- Bone marrow examination with biopsy and cytogenetic studies at initial assessment (Note: Current practice typically involves these studies; discussions to develop uniform recommendations are ongoing.)
- Skeletal survey with radiographs of at least the hips and lower limbs

Treatment of Manifestations

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

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.

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 or less, treatment with prophylactic antibiotics and granulocyte-colony stimulation factor (G-CSF) can be considered.

Hematopoietic stem cell transplantation (HSCT) can be considered for treatment of severe pancytopenia, bone marrow transformation to myelodysplastic syndrome, or AML. Cells from both bone marrow and cord blood have been used. Although earlier reports indicate that survival is fair, cautious myeloablation and newer regimens show promise for improving outcomes [Cesaro et al 2005; Vibhakar et al 2005; Sauer et al 2007; R Harris, personal communication].

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

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.

Although cognitive, learning, and behavioral features of SDS have been less well investigated than other aspects, remedial interventions are considered beneficial [E Kerr, personal communication].

For pregnancies in women with SDS, high-risk pregnancy care including consultation with a hematologist is recommended.

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 [M Glogauer, personal communication].

Prophylactic antibiotics and G-CSF may be especially helpful when interventions such as complex dental procedures or orthopedic surgery are being considered.

Surveillance

The following is recommended given the intermittent nature of some features of SDS and the evolution of the phenotype over time [Rothbaum et al 2002]:

- Developmental and growth assessment every six months
- Assessment of nutritional status every six months and measurement of serum concentration of vitamins to evaluate effectiveness of or need for pancreatic enzyme therapy
- Complete blood counts with white blood cell differential and platelet counts at least every six months, or more frequently if infections are recurrent and debilitating
- Current practice is to repeat bone marrow examinations every one to three years following the baseline examination. These should be more frequent if changes in bone marrow function or cellularity are observed.

  Note: Discussions to develop uniform recommendations are ongoing.
- Monitoring for orthopedic complications resulting from growth during childhood with bone density measurements and x-rays of hips and knees during the most rapid growth stages

Agents/Circumstances to Avoid

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

Some drugs, such as cyclophosphamide or cyclophosphamide and busulfan, typically used in standard preconditioning or preparative regimens for bone marrow transplantation 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].

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Shwachman-Diamond syndrome (SDS) is inherited in an autosomal recessive manner. The mode of inheritance of SDS in individuals without identified *SBDS* mutations is unknown.

Risk to Family Members

Parents of a proband

- The parents of an affected child are usually heterozygotes (i.e., carriers of one mutant allele).
- Occasionally, only one parent is a carrier as the affected child has one inherited and one *de novo SBDS* allele.
- Heterozygotes are asymptomatic. See Genetically Related Disorders.

Sibs of a proband

- **When both parents are known to be carriers**
  - At conception, each sib of an affected individual has 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.
  - Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- **When the proband has one inherited and one *de novo* mutation**. At conception, each sib of an affected individual has a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic. See Genetically Related Disorders.

Offspring of a proband. The offspring of an individual with SDS are obligate heterozygotes (carriers) for a disease-causing mutation. 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 of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is possible once the mutations have been identified in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Shwachman-Diamond Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
SBDS	7q11	Ribosome maturation protein SBDS

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Shwachman-Diamond Syndrome

260400	SHWACHMAN-DIAMOND SYNDROME; SDS
607444	SBDS GENE; SBDS

Table C. Genomic Databases for Shwachman-Diamond Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
SBDS	SBDS	51119 (MIM No. 607444)	SBDS

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Normal allelic variants: The *SBDS* locus involves a total of five exons and spans less than 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]. Some of the normal allelic variants reflect the sequence of the pseudogene (*SBDSP)*, indicating that they may have arisen by gene conversion events between the gene and the pseudogene.

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

At least one allele in >90% of individuals with Shwachman-Diamond syndrome (SDS) has a mutation that apparently arose by gene conversion. The gene conversion event occurred between the functional *SBDS* gene and a nonfunctional pseudogene copy (*SBDSP),* which has 97% sequence identity to *SBDS*. The high sequence identity between these two genes facilitates gene conversion, a phenomenon whereby a small segment of *SBDS* is replaced by a segment copied from the *SBDSP* pseudogene. Therefore, this segment of *SBDS* has sequence variants typical of the pseudogene; the variants that inactivate normal *SBDS* gene expression and/or translation of normal protein are pathogenic.

The three most common converted pathologic alleles:

- c.183_184delinsCT
- c.258+2T>C
- c.[183_184delinsCT; 258+2T>C].

  Note: This allele has a longer converted segment with both variants occurring on one allele.

These three alleles account for more than 76% of disease-causing alleles.

Other alleles with more extensive converted regions involving exon 2, neighboring introns, and exon 1 have also been found [Authors, unpublished]. The rare c.297_300delAAGA mutation is also likely the consequence of gene conversion with *SBDSP* but involves only the exon 3 region.

More than 38 novel sequence variants identified in the five exons of *SBDS* are consistent with loss-of-function alterations [Boocock et al 2003; Nakashima et al 2004; Woloszynek et al 2004; Nicolis et al 2005; Maserati et al 2006; Taneichi et al 2006; Author, unpublished]. Seven have been found in multiple, apparently unrelated, families (see Table 2).

Except for one reported case to date, affected individuals with rare mutations occur as compound heterozygotes with one of the three common gene conversion mutations. In the one exception, an individual with a clinical diagnosis of SDS had two rare missense alleles in exons 3 and 4, respectively [Erdos et al 2006].

Table 2. *SBDS* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequence
Normal	c.141C>T [2]	p.(=) [4]	NM_016038.2 NP_057122.2
	c.201A>G [2]	p.(=)	
	c.635T>C [3]	p.Ile212Thr	
	c.651C>T	p.(=)	
Pathologic	c.119delG	p.Ser41AlafsX18	
	c.183_184delinsCT [2] (c.183TA>CT)	p.Lys62X	
	c.[183_184delinsCT; 258+2T>C] [2]	p.Lys62X	
	c.258+1G>C	--	
	c.258+2T>C [2]	p.Cys84TyrfsX4	
	c.297_300delAAGA [2]	p.Glu9AspfsX20	
	c.377G>C	p.Arg126Thr	
	c.505C>T	p.Arg169Cys	
	c.624+1G>C	--	
	c.652C>T	p.Arg218X	

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions
2. Likely the consequence of gene conversion with *SBDSP*
3. Initially reported to be a possible pathogenic allele
4. The designation p.(=) means that the protein has not been analyzed, but no change is expected.

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

The modeling of several of the identified missense mutations onto the three-domain structure of the solved archael SBDS protein ortholog supports the likelihood that they are pathogenic [Savchenko et al 2005, Shammas et al 2005]. The SBDS protein is thought to play a role in

RNA metabolism and ribosome biogenesis, and more recent genetic studies of the yeast homolog support a role in 60S ribosomal subunit biogenesis and translational activation [Menne et al 2007].

Abnormal gene product: The mutations identified in individuals with SDS led to prematurely truncated proteins, splicing aberrations, and missense alterations. These mutations 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.Lys62X), 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.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Shwachman's Syndrome Italian Association
Post office nr. 10025625
Via S. Anna 15/A – 62010
Montecassiano (MC)
Italy
Email: aiss@shwachman.it
www.shwachman.it

Shwachman-Diamond Support UK
9 Tippett Close
Nuneaton Warwickshire CV11 4SU
United Kingdom
Phone: 02476 345199
Email: enquiries@shwachman-diamondsupport.org
www.shwachman-diamondsupport.org

Shwachman-Diamond Syndrome Canada
2152 Gatley Road
Mississauga ON L5H 3L9
Canada
Phone: 866-462-8907
Email: sdscanada@sympatico.ca
www.shwachman.org

Shwachman-Diamond Syndrome Foundation
127 Western Avenue
Sherborn MA 01770
Phone: 877-737-4685; 614-939-2324
Fax: 970-255-8293
Email: 4sskids@shwachman-diamond.org
www.shwachman-diamond.org

National Cancer Institute (NCI)
Email: LisaLeathwood@Westat.com

Inherited Bone Marrow Failure Syndromes

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Boocock GR, Morrison JA, Popovic M, Richards N, Ellis L, Durie PR, Rommens JM. Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nat Genet* 2003;33:97–101. [PubMed: 12496757]

Calado RT, Graf SA, Wilkerson KL, Kajigaya S, Ancliff PJ, Dror Y, Chanock SJ, Lansdorp PM, Young NS. Mutations in the SBDS gene in acquired aplastic anemia. *Blood* 2007;110:1141–6. [PubMed: 17478638]

Cesaro S, Oneto R, Messina C, Gibson BE, Buzyn A, Steward C, Gluckman E, Bredius R, Boogaerts M, Vermylen C, Veys P, Marsh J, Badell I, Michel G, Güngör T, Niethammer D, Bordigoni P, Oswald C, Favre C, Passweg J. Haematopoietic stem cell transplantation for Shwachman-Diamond disease; a study from the European Group for blood and marrow transplantation. *Br J Haematol* 2005;131:231–6. [PubMed: 16197455]

Cipolli M. Shwachman-Diamond syndrome: clinical phenotypes. *Pancreatology* 2001;1:543–8. [PubMed: 12120235]

Cipolli M, D'Orazio C, Delmarco A, Marchesini C, Miano A, Mastella G. Shwachman's syndrome: Pathomorphosis and long-term outcome. *J Pediatr Gastroenterol Nutr* 1999;29:265–72. [PubMed: 10467990]

Costa E, Duque F, Oliveira J, Garcia P, Gonçalves I, Diogo L, Santos R. Identification of a novel AluSx-mediated deletion of exon 3 in the SBDS gene in a patient with Shwachman-Diamond syndrome. *Blood Cell Molec & Diseases* 2007;39:96–101.

Donadieu J, Michel G, Merlin E, Bordigoni P, Monteux B, Beaupain B, Leverger G, Laporte JP, Hermine O, Buzyn A, Bertrand Y, Casanova JL, Leblanc T, Gluckman E, Fischer A, Stephan JL. Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry. *Bone Marrow Transplant* 2005;36:787–92. [PubMed: 16151425]

Dror Y, Freedman MH. Shwachman-Diamond syndrome: an inherited preleukemic bone marrow failure disorder with aberrant hematopoetic progenitors and faulty microenvironment. *Blood* 1999;94:3048–54. [PubMed: 10556188]

Dror Y, Freedman MH. Shwachman-diamond syndrome. *Br J Haematol* 2002;118:701–13. [PubMed: 12181037]

Dror Y, Ginzberg H, Dalal I, Cherepanov V, Downey G, Durie P, Roifman CM, Freedman MH. Immune function in patients with Shwachman-Diamond syndrome. *Br J Haematol* 2001;114:712–7. [PubMed: 11553003]

Durie PR, Rommens JM (2004) Shwachman-Diamond syndrome. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR (eds) Pediatric Gastrointestinal Disease 4th ed. BC Decker Inc, Lewiston, NY, pp 1624-33

Erdos M, Alapi K, Balogh I, Oroszlan G, Rakoczi E, Sumegi J, Marodi L. Severe Shwachman-Diamond syndrome phenotype caused by compound heterozygous missense mutations in the SBDS gene. *Exp Hematol* 2006;34:1517–21. [PubMed: 17046571]

Ginzberg H, Shin J, Ellis L, Morrison J, Ip W, Dror Y, Freedman M, Heitlinger LA, Belt MA, Corey M, Rommens JM, Durie PR. Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. *J Pediatr* 1999;135:81–8. [PubMed: 10393609]

Goobie S, Popovic M, Morrison J, Ellis L, Ginzberg H, Boocock GR, Ehtesham N, Betard C, Brewer CG, Roslin NM, Hudson TJ, Morgan K, Fujiwara TM, Durie PR, Rommens JM. Shwachman-Diamond syndrome with exocrine pancreatic dysfunction and bone marrow failure maps to the centromeric region of chromosome 7. *Am J Hum Genet* 2001;68:1048–54. [PubMed: 11254457]

Grinspan ZM, Pikora CA. Infections in patients with Shwachman-Diamond syndrome. *Pediatr Infect Dis J* 2005;24:179–81. [PubMed: 15702050]

Ho W, Cheretakis C, Durie P, Kulkarni G, Glogauer M. Prevalence of oral diseases in Shwachman-Diamond syndrome. *Spec Care Dentist* 2007;27:52–8. [PubMed: 17539220]

Ip WF, Dupuis A, Ellis L, Beharry S, Morrison J, Stormon MO, Corey M, Rommens JM, Durie PR. Serum pancreatic enzymes define the pancreatic phenotype in patients with Shwachman-Diamond syndrome. *J Pediatr* 2002;141:259–65. [PubMed: 12183724]

Kawakami T, Mitsui T, Kanai M, Shirahata E, Sendo D, Kanno M, Noro M, Endoh M, Hama A, Tono C, Ito E, Tsuchiya S, Igarashi Y, Abukawa D, Hayasaka K. Genetic analysis of Shwachman-Diamond syndrome: phenotypic heterogeneity in patients carrying identical SBDS mutations. *Tohoku J Exp Med* 2005;206:253–9. [PubMed: 15942154]

Kent A, Murphy GH, Milla P. Psychological characteristics of children with Shwachman syndrome. *Arch Dis Child* 1990;65:1349–52. [PubMed: 1702966]

Kuijpers TW, Alders M, Tool AT, Mellink C, Roos D, Hennekam RC. Hematologic abnormalities in Shwachman Diamond syndrome: lack of genotype-phenotype relationship. *Blood* 2005;106:356–61. [PubMed: 15769891]

Majeed F, Jadko S, Freedman MH, Dror Y. Mutation analysis of SBDS in pediatric acute myeloblastic leukemia. *Pediatr Blood Cancer* 2005;45:920–4. [PubMed: 16007594]

Mäkitie O, Ellis L, Durie PR, Morrison JA, Sochett EB, Rommens JM, Cole WG. Skeletal phenotype in patients with Shwachman-Diamond syndrome and mutations in SBDS. *Clin Genet* 2004;65:101–12. [PubMed: 14984468]

Maserati E, Minelli A, Pressato B, Valli R, Crescenzi B, Stefanelli M, Menna G, Sainati L, Poli F, Panarello C, Zecca M, Curto FL, Mecucci C, Danesino C, Pasquali F. Shwachman syndrome as mutator phenotype responsible for myeloid dysplasia/neoplasia through karyotype instability and chromosomes 7 and 20 anomalies. *Genes Chromosomes Cancer* 2006;45:375–82. [PubMed: 16382447]

Menne TF, Goyenechea B, Sanchez-Puig N, Wong CC, Tonkin LM, Ancliff PJ, Brost RL, Costanzo M, Boone C, Warren AJ. The Shwachman-Bodian-Diamond syndrome protein mediates translational activation of ribosomes in yeast. *Nat Genet* 2007;39:486–95. [PubMed: 17353896]

Mitsui T, Kawakami T, Sendo D, Katsuura M, Shimizu Y, Hayasaka K. Successful unrelated donor bone marrow transplantation for Shwachman-Diamond syndrome with leukemia. *Int J Hematol* 2004;79:189–92. [PubMed: 15005350]

Nakashima E, Mabuchi A, Makita Y, Masuno M, Ohashi H, Nishimura G, Ikegawa S. Novel SBDS mutations caused by gene conversion in Japanese patients with Shwachman-Diamond syndrome. *Hum Genet* 2004;114:345–8. [PubMed: 14749921]

Nicolis E, Bonizzato A, Assael BM, Cipolli M. Identification of novel mutations in patients with Shwachman-Diamond syndrome. *Hum Mutat* 2005;25:410. [PubMed: 15776428]

Nishimura G, Nakashima E, Hirose Y, Cole T, Cox P, Cohn DH, Rimoin DL, Lachman RS, Miyamoto Y, Kerr B, Unger S, Ohashi H, Superti-Furga A, Ikegawa S. The Shwachman-Bodian-Diamond syndrome gene mutations cause a neonatal form of spondylometaphysial dysplasia (SMD) resembling SMD Sedaghatian type. *J Med Genet* 2007;44:e73. [PubMed: 17400792]

Ritchie DS, Angus PW, Bhathal PS, Grigg AP. Liver failure complicating non-alcoholic steatohepatitis following allogenic bone marrow transplantation for Shwachman-Diamond syndrome. *Bone Marrow Transplant* 2002;29:931–3. [PubMed: 12080360]

Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, Fier C, Freedman MA, Kannourakis G, Kinsey S, Schwinzer B, Zeidler C, Welte K, Dale D. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. *Blood* 2006;107:4628–35. [PubMed: 16497969]

Rothbaum R, Perrault J, Vlachos A, Cipolli M, Alter BP, Burroughs S, Durie P, Elghetany MT, Grand R, Hubbard V, Rommens J, Rossi T. Shwachman-Diamond syndrome: report from an international conference. *J Pediatr* 2002;141:266–70. [PubMed: 12183725]

Sauer M, Zeidler C, Meissner B, Rehe K, Hanke A, Weltke K, Lohse P, Sykora KW. Substitution of cyclophosphamide and busulfan by fludarabine, treosulfan and melphalan in a preparative regimen for children and adolescents with Shwachman-Diamond syndrome. *Bone Marrow Transplant* 2007;39:143–7. [PubMed: 17211437]

Savchenko A, Krogan N, Cort JR, Evdokimova E, Lew JM, Yee AA, Sanchez-Pulido L, Andrade MA, Bochkarev A, Watson JD, Kennedy MA, Greenblatt J, Hughes T, Arrowsmith CH, Rommens JM, Edwards AM. The Shwachman-Bodian-Diamond syndrome protein family is involved in RNA metabolism. *J Biol Chem* 2005;280:19213–20. [PubMed: 15701634]

Schibli S, Corey M, Gaskin KJ, Ellis L, Durie PR. Towards an ideal quantitative pancreatic function test: analysis of test variables that influence validity. *Clin Gastroenterol Hepatol* 2006;4:90–7. [PubMed: 16431310]

Shammas C, Menne TF, Hilcenko C, Michell SR, Goyenechea B, Boocock GR, Durie PR, Rommens JM, Warren AJ. Structural and mutational analysis of the SBDS protein family. Insight into the leukemia-associated Shwachman-Diamond Syndrome. *J Biol Chem* 2005;280:19221–9. [PubMed: 15701631]

Smith OP, Hann IM, Chessells JM, Reeves BR, Milla P. Haematological abnormalities in Shwachman-Diamond Syndrome. *Br J Haematol* 1996;94:279–84. [PubMed: 8759887]

Stepanovic V, Wessels D, Goldman FD, Geiger J, Soll DR. The chemotaxis defect of Shwachman-Diamond Syndrome leukocytes. *Cell Motil Cytoskeleton* 2004;57:158–74. [PubMed: 14743349]

Taneichi H, Kanegane H, Futatani T, Otsubo K, Nomura K, Sato Y, Hama A, Kojima S, Kohdera U, Nakano T, Hori H, Kawashima H, Inoh Y, Kamizono J, Adachi N, Osugi Y, Mizuno H, Hotta N, Yoneyama H, Nakashima E, Ikegawa S, Miyawaki T. Clinical and genetic analyses of presumed Shwachman-Diamond syndrome in Japan. *Int J Hematol* 2006;84:60–2. [PubMed: 16867904]

Toiviainen-Salo S, Raade M, Durie PR, Ip W, Marttinen E, Savilahti E, Mäkitie O. Magnetic resonance imaging findings of the pancreas in patients with Shwachman-Diamond syndrome and mutations in the SBDS gene. *J Paediatr* 2008;152:434–6.

Vibhakar R, Radhi M, Rumelhart S, Tatman D, Goldman F. Successful unrelated umbilical cord blood transplantation in children with Shwachman-Diamond syndrome. *Bone Marrow Transplant* 2005;36:855–61. [PubMed: 16113664]

Woloszynek JR, Rothbaum RJ, Rawls AS, Minx PJ, Wilson RK, Mason PJ, Bessler M, Link DC. Mutations of the SBDS gene are present in most patients with Shwachman-Diamond syndrome. *Blood* 2004;104:3588–90. [PubMed: 15284109]

Zhang S, Shi M, Hui CC, Rommens JM. Loss of the mouse ortholog of the shwachman-diamond syndrome gene (Sbds) results in early embryonic lethality. *Mol Cell Biol* 2006;26:6656–63. [PubMed: 16914746]

Suggested Reading

Dokal I, Vulliamy T. Inherited aplastic anaemias/bone marrow failure syndromes. *Blood Rev* 2008;22:141–53. [PubMed: 18164793]

Chapter Notes

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