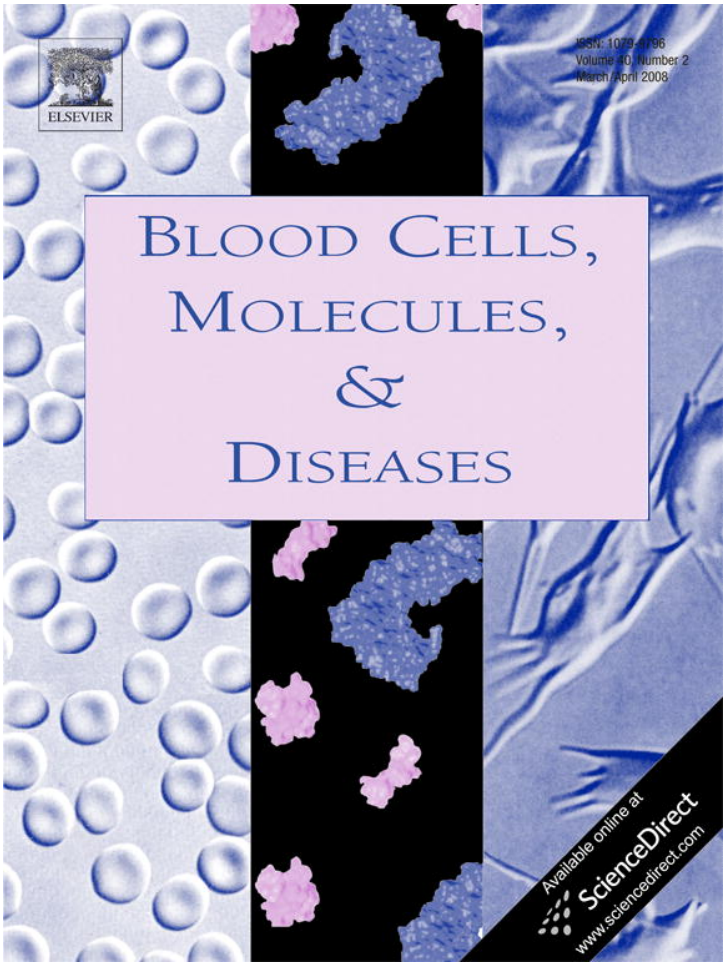

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Hematologically important mutations: Shwachman–Diamond syndrome

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Abstract

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities. The Shwachman–Bodian–Diamond syndrome (*SBDS*) gene was identified as a causative gene for SDS in 2003, and genetic analyses of SDS have been performed. Over the last 4 years, a number of different mutations affecting the *SBDS* gene have been described. In this report, a summary of documented SDS associated mutations is provided.

Keywords: SBDS; SBDSP; Shwachman–Diamond syndrome; Mutations

Shwachman–Diamond syndrome (SDS; MIM# 260400) is a rare autosomal recessive disorder, described for the first time in 1964 [1], characterized by the association of exocrine pancreatic and bone marrow dysfunctions. Other systemic findings (skeletal, liver and psychomotor) and/or problems secondary to bone marrow dysfunction may also be detected [1–4]. Intermittent or persistent neutropenia is the most common hematologic finding, but anemia and thrombocytopenia can also been present in approximately 40% of the patients [1–5].

In 2002, fine mapping identified the locus for SDS in band 7q11. More recently (2003), Boocock et al. [6] identified 18 positional candidate genes in this locus, and examined eight of them for occurrence of SDS-associated changes. They found alterations only in a previously uncharacterized gene. This gene, designated *SBDS* (Shwachman–Bodian–Diamond syndrome), is composed of five exons spanning 7.9 kb. The authors also described a pseudogene (SBDSP; MIM# 607444), with 97% homology to SBDS [5–7]. *SBDS* comprises five exons spanning 7.9 kb, with a 1.6 kb transcript that translates into a protein of 250 amino acids [6,7]. The SBDS protein is a member of a highly conserved family with orthologs in several species. Although its function remains to be elucidated, studies revealing ubiquitous expression with accumulation in the nucleolus in a cell-cycle-dependent manner, as well as structural and co-expression studies in the yeast orthologs, provide strong evidence for its role in ribosome biogenesis [7,8].

In the molecular analysis of the *SBDS* gene, the presence of a hotspot region in and around exon 2 has facilitated diagnosis, and direct sequencing of this region has enabled the detection of at least one mutated allele in about 90% of SDS patients [5].

Shwachman–Diamond syndrome gene mutations are shown in Table 1. The nucleotide numbers shown in this table are based on the cDNA sequence of GenBank accession number NM_016038.2. Mutation nomenclature was according to the recommendations of the Human Genome Variation Society (2005) (http://www.hgvs.org/mutnomen), using the numbering convention which assigns "1" to the A of the initiator ATG codon.

References

[1] H. Shwachman, L.K. Diamond, F.A. Oski, K. Khaw, The syndrome of pancreatic insufficiency and bone marrow dysfunction, J. Pediatr. 65 (1964) 645–663.
[2] M. Wilschanski, E. Hoeven, J. Phillips, B. Shuckett, P. Durie, Shwachman–Diamond syndrome presenting as hepatosplenomegaly, J. Pediatr. Gastroenterol. Nutr. 19 (1994) 111–113.

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Table 1
SBDS gene mutations in Shwachman–Diamond syndrome

cDNA nucleotide substitution	Amino acid substitution	Mutation type	Reference	Comments
c.24C>A	p.N8K	Substitution	[6]	
c.95A>G	p.Y32C	Substitution	[9]	
c.96_97insA	p.N34fsX15	Insertion; frameshift	[6]	
c.101A>T	p.N34I	Substitution	[9]	
c.119delG	p.S41fsX17	Deletion; frameshift	[6]	
[c.129-443A>G; c.129-433G>A; c.141C>T; c.183_184TA>CT; c.201A>G; c.258+2T>C]	p.K62X	Substitution; Stop mutation	[9]	a)
c.131A>G	p.E44G	Substitution	[6]	
[c.141C>T; c.183_184TA>CT]	p.K62X	Substitution; Stop mutation	[9]	a)
[c.141C>T; c.183_184TA>CT; c.201A>G]	p.K62X	Substitution; Stop mutation	[10]	a)
[c.141C>T; c.183_184TA>CT; c.201A>G; c.258+2T>C]	p.K62X	Substitution; stop mutation	[9]	a)
c.183_184TA>CT	p.K62X	Substitution; stop mutation	[6]	a)
[c.183_184TA>CT; c.201A>G]	p.K62X	Substitution; stop mutation	[10]	a)
c.199A>G	p.K67E	Substitution	[6]	
[c.201A>G; c.258+2T>C]	p.C84fsX3	Substitution; frameshift	[9]	a)
c.258+2T>C	p.C84fsX3	Substitution; frameshift	[6]	a)
c.258+1G>C	p.C84fsX3	Substitution; frameshift	[6]	
c.258+374_459+250del	p.I87_Q153del	Gross deletion	[11]	b)
c.259-1G>A	No cDNA studies performed	Predicted splice mutation	[12]	
c.260T>G	p.I87S	Substitution	[6]	
c.291_293TAAdelinsAGTTCAAGTATC	p.D97_K98delinsEVQVS	Deletion; insertion	[6]	
c.292_295delAAAG	p.E99fsX20	Deletion; frameshift	[10]	a)
c.307_308delCA	p.Q103fsX8	Deletion frameshift	[9]	
c.362A>C	p.N121T	Substitution	[13]	
c.377G>C	p.R126T	Substitution	[6]	
c.428C>G	p.S143W	Substitution	[12]	
c.505C>T	p.R169C	Substitution	[6]	
c.523C>T	p.R175W	Substitution	[13]	
c.624+1G>C	No cDNA studies performed	Predicted splice mutation	[9]	
c.635T>C	p.I212T	Substitution	[6]	
c.652C>T	p.R218X	Substitution; stop mutation	[9]	

a) These mutations result from conversion events between *SBDS* and *SBDSP* genes. b) Alu-mediated homologous recombination is the mechanism proposed for this mutation.

[3] H. Ginzberg, J. Shin, L. Ellis, J. Morrison, W. Ip, et al., Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar, J. Pediatr. 135 (1999) 81–88.
[4] S. Goobie, M. Popovic, J. Morrison, et al., Shwachman–Diamond syndrome with exocrine pancreatic dysfunction and bone marrow failure maps to the centromeric region of chromosome 7, Am. J. Hum. Genet. 68 (2001) 1048–1054.
[5] M. Popovic, S. Goobie, J. Morrison, et al., Fine mapping of the locus for Shwachman–Diamond syndrome at 7q11, identification of shared disease haplotypes, and exclusion of TPST1 as a candidate gene, Eur. J. Hum. Genet. 10 (2002) 250–258.
[6] G.R.B. Boocock, J.A. Morrison, M. Popovic, et al., Mutations in SBDS are associated with Shwachman–Diamond syndrome, Nat. Genet. 33 (2003) 97–101.
[7] A. Savchenko, N. Krogan, J.R. Cort, et al., The Shwachman–Bodian–Diamond syndrome protein family is involved in RNA metabolism, J. Biol. Chem. 280 (2005) 19213–19220.
[8] M.K. Austin, R.J. Leary, A. Shimamura, The Shwachman–Diamond SBDS protein localizes to the nucleolus, Blood 106 (2005) 1253–1258.
[9] E. Nicolis, A. Bonizzato, B.M. Assael, M. Cipolli, Identification of novel mutations in patients with Shwachman–Diamond syndrome, Hum. Mutat. 25 (2005) 410.
[10] E. Nakashima, A. Mabuchi, Y. Makita, et al., Novel SBDS mutations caused by gene conversion in Japanese patients with Shwachman–Diamond syndrome, Hum. Genet. 114 (2004) 345–348.
[11] E. Costa, F. Duque, J. Oliveira, P. Garcia, I. Gonçalves, L. Diogo, R. Santos, Identification of a novel AluSx-mediated deletion of exon 3 in the *SBDS* gene in a patient with Shwachman–Diamond syndrome, Blood Cells Mol. Diseases 39 (2007) 96–101.
[12] H. Taneichi, H. Kanegane, T. Futatani, et al., Clinical and genetic analyses of presumed Shwachman–Diamond syndrome in Japan, Int. J. Hematol. 84 (2006) 60–62.
[13] M. Erdos, K. Alapi, I. Balogh, G. Oroszlan, E. Rakoczi, J. Sumegi, L. Marodi, Severe Shwachman–Diamond syndrome phenotype caused by compound heterozygous missense mutations in the SBDS gene, Exp. Hematol. 34 (2006) 1517–1521.