



Bernard-Soulier Syndrome: Mutation Analysis of *GP Ib β*

Clinical Features: Bernard-Soulier Syndrome (BSS) is a severe bleeding disorder characterized by a prolonged bleeding time, thrombocytopenia, and extremely large platelets. Patients have a decreased number of giant platelets, and their blood is unable to clot following a cut because of abnormal platelet function and the platelets do not adhere to each other, leading to increased bleeding time. Median age of first symptom is around 15 months of age with postvaccination bleeding, nosebleeds, bleeding gums, and/or bleeding following tooth extraction. Other symptoms such as gastrointestinal bleeding and bleeding into the skin causing petechiae, or small red dots, may occur later in life. Women are at risk of hemorrhaging during menses. Heterozygotes may have about half the normal platelet expression level, but will not have bleeding episodes (1).

Diagnosis: Patients should be differentiated from idiopathic thrombocytopenic purpura, which also presents with prolonged bleeding time and decreased platelet counts. Laboratory tests should include a manual blood cell count because platelets may be mistaken for lymphocytes by automatic counters due to their size. A blood smear should be performed to examine the size and morphology of the platelets. BSS is unique in that ristocetin-induced agglutination will not be corrected by the addition of normal plasma (1, 2). A defect in prothrombin consumption or decreased response to thrombin can be useful in diagnosis. Flow cytometry should be used to confirm the diagnosis. Differences in some lab features between normal levels and the levels seen in a person with BSS are summarized below (2).

	Normal Level	BSS Patient
Platelet count	150,000-450,000 μ L	<30,000-200,000 μ L
Platelet diameter	1-4 μ m	4-10 μ m
Bleeding time	2-7 mins	5- <20 mins

Clinical genetic testing is available for the *GP Ib β* gene for a definitive diagnosis of BSS.

Molecular Genetics: BSS is caused by mutations in the platelet glycoprotein GP Ib-IX-V complex, which is the platelet receptor for von Willebrand factor (3). This complex is made up of four genes: *GP Iba*, *GP Ib β* , *GP IX*, and *GP V*. Mutations causing BSS have been described in all these genes excepting *GP V*. These genes occur on different chromosomes, and *GP Ib β* is located at 22q11.2. Defects in *GP Ib β* account for approximately less than 10% of patients with BSS. Patients with a 22q deletion and a mutation in *GP Ib β* have been reported with 22q deletion syndrome (DiGeorge syndrome) and BSS (4). The *GP Ib β* gene is involved in correct assembly and cell surface targeting of the GP IbV/IX complex (1).

Resources:

Web-based resources for patient information may be found at:

- www.bernardsoulier.org: Ireland-based website with facts about BSS and names of BSS experts for additional information.
- www.niacmd.net: The National Information and Advice Centre for Metabolic Diseases supports over 700 diseases internationally. A message forum is available there for patients to ask questions and to find others affected by the same rare disorders.

Inheritance: Bernard-Soulier syndrome is a rare autosomal recessive disorder, occurring in less than 1 in 1,000,000 live births in European, North American, and Japanese populations (1). The incidence may vary depending on ethnic origin. BSS has been reported often in offspring of consanguineous parents (1). Recurrence risk for a future affected child is 25%.

Test methods: We offer mutation analysis of all coding exons and intron/exon boundaries of *GP Ib β* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *GP Ib β* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype.

The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

GPIIb mutation analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$400
CPT codes:	81402 81403
Turn-around time:	4 weeks

Results: You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. López JA, Andrews RK, Afshar-Kharghan V et al. Bernard-Soulier syndrome. Blood 1998; 91: 4397-4418.
2. Lanza F. Hemorrhagic Thrombocytic Dystrophy. Orphanet Encyclopedia, 2003.
3. Yagi M, Edelhoff S, Disteche CM et al. Structural characterization and chromosomal location of the gene encoding human platelet glycoprotein Ib beta. J Biol Chem 1994; 269: 17424-17427.
4. Budarf ML, Konkle BA, Ludlow LB et al. Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velo-cardio-facial chromosomal region in 22q11.2. Hum Mol Genet 1995; 4: 763-766.

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