Identification of a Mutation in a GATA Binding Site of the Platelet Glycoprotein Ibβ Promoter Resulting in the Bernard-Soulier Syndrome*

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Bernard-Soulier Syndrome (BSS) is a rare congenital bleeding disorder due to absent or decreased expression of the glycoprotein Ib-IX-V (GpIb-IX-V) receptor complex on the platelet surface. To date, only mutations in GpIbα or GpIX have been reported in patients with BSS. GpIbβ differs from the other proteins in this receptor in that the gene is more complex, and an alternative form is expressed in cells of non-megakaryocytic lineage, including endothelial cells. It appears that the megakaryocytic and endothelial cell mRNA species are transcribed from different start sites and have different proximal promoter regions. We have identified a patient with BSS who has a deletion on one chromosome 22, resulting in velocardiofacial syndrome. The GpIbβ gene has been mapped to this deleted (22q11.2) region of chromosome 22. The patient has greatly reduced levels of GpIbβ mRNA and no detectable platelet GpIbβ protein, suggesting that his BSS results from a mutation in his remaining GpIbβ allele. Sequence analysis revealed that the coding region of GpIbβ is normal, but the 5’-upstream region contains a C to G transversion at base −133 from the transcription start site used in megakaryocytes. The mutation changes a GATA consensus binding site, disrupts GATA-1 binding to the mutated site, and decreases promoter activity by 84%. Thus, in this patient, Bernard-Soulier syndrome results from a deletion of one copy of GpIbβ and a mutated GATA binding site in the promoter of the remaining allele, resulting in decreased promoter function and GpIbβ gene transcription.

The glycoprotein Ib-IX-V complex (GpIb-IX-V) acts as a receptor on the platelet surface to bind von Willebrand factor and initiate platelet adhesion. In platelets, GpIb is a heterodimer composed of disulfide-linked GpIbα (143 kDa) and GpIbβ (24 kDa). GpIX and GpV are associated noncovalently in the membrane with GpIb in a 1:1 and 1:0.5 stoichiometry, respectively (1). The GpIbβ gene is alternatively processed in megakaryocytes versus endothelial and other cells. It appears that different transcription start sites are used to produce platelet versus endothelial cell mRNA species (2, 3). GpIbα, GpIbβ, GpIX, and GpV all belong to a family of proteins known as the leucine-rich glycoprotein (LRG) family. The proteins in this family contain highly conserved leucine-rich repeats, which are thought to mediate protein-protein interactions (1).

Abnormalities in the GpIb-IX-V complex result in the moderate to severe bleeding disorder, Bernard-Soulier Syndrome (BSS). BSS is usually inherited in an autosomal recessive manner and is characterized by thrombocytopenia, enlarged platelets, and decreased or absent GpIb-IX-V on the platelet surface. Except in the one family with an apparent autosomal dominant variant of the disorder (4), heterozygotes for the disorder do not have a bleeding diathesis (5). A number of the mutations responsible for BSS have been elucidated. To date, nine published cases have been analyzed at the molecular level. Seven cases have identified mutations in GpIbα. Three patients were identified as having a nonsense mutation producing a truncated GpIbα protein (6–8), and three patients have mutations that changed a conserved amino acid within a LRG repeat (4, 9, 10). One patient was identified as having a mutation that changed a cysteine residue in GpIbα involved in disulfide bonding (11). Two of the nine cases have identified mutations in GpIX, both of which changed an amino acid in the LRG repeat or its flanking region (12, 13). No mutations have been reported in GpIbβ in a BSS patient.

The GpIbβ gene has been localized to chromosome 22q11.2 (2, 14). This is within a region in 22q11 that is deleted in 90% of patients with DiGeorge syndrome, 85% of patients with velocardiofacial syndrome and 20% of patients with conotruncal heart defects (15, 16). DiGeorge syndrome is characterized by both thymic and parathyroid hypoplasia or aplasia, as well as conotruncal heart defects. Patients with velocardiofacial syndrome have heart defects, palatal abnormalities, learning disabilities, and atypical facies. This region of 22q11 has been termed the “DiGeorge chromosomal region.” The majority of patients have large deletions (>1 megabases). The defect responsible for these syndromes is thought to cause abnormal migration of the cephalic neural crest cells. The cephalic neural crest cells contribute to the development of thymus, parathyroid, and conotruncus of the heart. The DiGeorge chromosomal region is a “gene-rich” region under intensive investigation. The GpIbβ gene is located in the middle of this region (17). The BSS patient reported in this study has a microdeletion in the DiGeorge chromosomal region of one allele of chromo-
some 22, which is presumably responsible for his developmental abnormalities (17). Because of this deletion, he also is lacking one allele of the GpIb gene. As reported previously (17), he was diagnosed with BSS presenting with congenital thrombocytopenia, large platelets, markedly decreased ristocetin-induced platelet aggregation, and markedly reduced GpIb protein on the platelet surface by flow cytometry. Analysis of patient platelet lysates by Western blotting revealed that GpIb protein was decreased compared with normal platelets, and GpIb protein was not detected. In addition, GpIb and GpX mRNA were readily amplified from the patient’s platelet RNA by reverse transcription PCR, but GpIb mRNA was only detected at very low levels (17). We report that in this patient BSS results from a mutation in the promoter region of the remaining GpIb allele that alters a GATA binding consensus site. In vitro, the mutation disrupts GATA-1 binding to this site and results in a 6-fold decrease in promoter function.

MATERIALS AND METHODS

Genomic DNA Isolation and Southern Analysis—Genomic DNA was isolated from 5 ml of citrated blood as described previously (18). Samples of 10 ng of DNA were cut with various restriction enzymes: SaeI, Sall, and PstI (Promega Corp., Madison, WI). After running the digests on a 1% agarose gel, the gel was exposed to 32-P-methylated herring sperm DNA for 5 min. The DNA was then soaked in 1 m NaOH for 30 min followed by 2 m NaCl, 0.5 m Tris-HCl, pH 8.3, and then 30 min. The DNA was transferred to a nylon membrane (Hybond-N+; Amersham Corp.), by Southern blotting in 10 × SSC overnight. The DNA was fixed to the membrane with 32-P-UV irradiation. The blots were prehybridized for at least 1 h at 65 °C in 1 × NaCl, 0.1% SDS, 1.5 mg/ml herring sperm DNA, 10 ng/ml human placent DNA, and 10% dextran sulfate and then hybridized with a radiolabeled GpIb cDNA probe and a 1:200 dilution of a radiolabeled GpX cDNA probe to a final hybridization solution with an additional 1.5 mg/ml herring sperm DNA. The blots were washed to high stringency (0.1 × SSC, (SSC: 2.25 m NaCl, 0.225 m sodium citrate), 0.1% SDS, 1 × EDTA, 10 mm sodium phosphate, pH 6.8, at 68 °C and analyzed by autoradiography.

PCR of Genomic DNA and Sequencing—Overlapping fragments of both the patient’s and a normal GpIb allele were amplified by PCR for cloning and sequencing. Each PCR contained 200 ng of genomic DNA, 1 μg each of primer, 0.2 μM dNTP, 10% dimethyl sulfoxide, 10 mm Tris-HCl, pH 8.3, 50 mm KCl, 1.5 mm MgCl2, 0.01% gelatin, 2 μm dithiothreitol, and 2.5 units of Taq polymerase (Perkin-Elmer). The reactions were subject to 30 cycles of 94 °C 1 min, 55 °C 1 min, and 72 °C 2 min, followed by a 10-min extension at 72 °C. The primers used to amplify fragments of the GpIb gene were: 715–724 and 1218–1200, 1281–1300 and 1766–1747, 1041–1061 and 1435–1454, and 2168–2151 (numbering from endothelial GpIb gene). The primer sequences were 5′-GAT GTG CTG GTA TC-3′ and 5′-GCC GAT GCT GCA TCC-3′ (nucleotide 1059–1040, numbering from endothelial GpIb cDNA reported by Kelly et al. (21)). Each of the PCR products was cloned into the pCR II vector using the TA cloning kit (Invitrogen, San Diego, CA). The polymerase chain reaction (PCR) was performed with the primers used for cloning. The sequences reported by Kelly et al. (21) were confirmed in all cases. The DNA sequence reported by Kelly et al. (21) was confirmed in all cases. The 2168–2151 fragment of the GP Ib promoter was amplified from genomic DNA using the PCR conditions described above. The GpIb primers used were 677–694 and 1059–1040 with linkers for Sall on the forward primer and XbaI on the reverse primer. The 384-base pair product was digested with XbaI and Sall and cloned into pCAT Basic linearized with the same enzymes. The A4 construct contains a 623-base pair piece of the GpIb promoter, nucleotides −573 to 50 in the pCAT Basic vector (22).

Cell Transfection and CAT Assay—Human erythroleukemia (HEL) cells were transfected by the method of Bernhard et al. (23). 1 × 107 HEL cells growing in log phase were pelleted and washed with 10 ml of transfection buffer (30.8 mM NaCl, 120.7 mM KCl, 8.1 mM Na2HPO4, 1.46 mM KH2PO4, 5 mM MgCl2). The cells were resuspended in 350 μl of transfection buffer and transferred to 0.4 μM Gene Pulser electroporation cuvettes (Bio-Rad). 60 μg of plasmid DNA was dried under vacuum, resuspended in 40 μl of transfection buffer, and added to the cells. After gentle mixing, the cuvette was placed on ice for 15 min. The cells were then electroporated at 960 microfarads and 0.25 kV in a Bio-Rad gene pulser (Bio-Rad). The cuvette was kept on ice for 12 min, then at room temperature for 15 min. The mixture was then added to 20 ml of RPMI 1640 (Life Technologies, Inc.) with 10% fetal bovine serum (HyClone, Langan, UT) and 0.1 mM gentamycin (Life Technologies, Inc.) and grown for 0.5% CO2 overnight. The cells were then harvested for the CAT assay.

CAT assays were performed as described (24) and evaluated by autoradiography in a Medical Dynamics, Sunnyvale, CA). The CAT assay was performed as described (24) and evaluated by autoradiography at 70 °C. Quantitative analysis of the CAT assay was performed using a PhosphorImager and ImageQuant software (Molecular Dynamics, Sunnyvale, CA). Nuclear Extract Preparation—HEL cells were propagated in RPMI 1640 (Life Technologies, Inc.) with 10% fetal bovine serum (HyClone), and CHRF-288 (25) cells were cultured in Fischer’s medium (Life Technologies, Inc.) with 20% horse serum (Life Technologies, Inc.) at 37 °C in 5% CO2. The nuclear extracts were prepared according to the method of Bernhard et al. (26). The HEL and CHRF-288 cell extracts were prepared using Dr. Jaime Caro (Cardeza Foundation, Thomas Jefferson University, Philadelphia, PA).

Electrophoretic Mobility Shift Assays—The sequences of the double stranded oligonucleotides used in the gel shift studies are noted with only the top strand shown: (GpIb normal) 5′-TGT GCT ATC TCG CCG TGC AGC GCG-3′; (GpIb mutant) 5′-TGT GCT ATG TCG CCG TGC AGC GCG-3′. The oligonucleotides were labeled for 30 min at 37 °C in a reaction containing 3.5 pmol of oligonucleotide, 30 μCi of [γ-32P]ATP (DuPont NEN) and 10 units of T4 polynucleotide kinase (New England Biolabs, Beverly, MA) in 70 μl Tris-HCl, pH 7.5, 10 μg MgCl2, 5 μm dithiothreitol. The labeled probes were purified using the XtraSpin spin column kit (Pierce). Before adding probe, the binding reactions containing 3–12 μg of nuclear extract and 0.5 μg of poly(dI-dC) (di-dC) (Pharmacia Biotech Inc.) in 10 μl Tris-HCl, pH 7.5, 50 mm KCl, 1 × EDTA, 1 × dithiothreitol, 15% glycerol were preincubated for 10 min at room temperature as described by Uzan et al. (27). 4 × 106 cpm of labeled oligonucleotide was added, and the reactions were incubated for 20 min at room temperature. After addition of antibody a second incubation was added after the probe and incubated for an additional 45 min at room temperature. The antibodies used were a monoclonal anti-GATA-1 (Santa Cruz Biotechnology, Santa Cruz, CA) and a polyclonal anti-GATA-2 antibody supplied by Dr. Stuart Orkin (Children’s Hospital, Boston, MA). The samples were analyzed on 5% polyacrylamide, 2.5% glycerol gels that were run at 5°C × 100 V × 1500 G (28). The DNA bands were visualized with a Bio-Rad gel imaging system.

RESULTS

Southern blot analysis—The patient’s remaining GpIb allele was analyzed by Southern blot analysis to determine if the gene was grossly normal. Genomic DNA from both the patient and a control sample was digested with Sall, Sall, and PstI. The autoradiograph of the digests probed with radiolabeled GpIb DNA are shown in Fig. 1A. The bands seen in the digests of the patient’s DNA are identical to the control sample, so the patient has no large deletions or rearrangements in his GpIb gene. Although the same amount of genomic DNA was analyzed, there is a decrease in the intensity of the bands in the patient lanes of Fig. 1A compatible with the loss of one GpIb allele. Fig. 1B shows the control digested with radiolabeled GpX cDNA. The GpX gene maps to chromosome 3 (20), which is unaffected in this patient, so the intensity of the band in the patient lane of Fig. 1B is similar to the control, indicating that Unlike GpIb, both alleles of GpXI are present.

Sequence analysis of the GpIb gene—Overlapping frag-
allel-specific PCR was used to confirm the mutation identified in the patient's GpIbβ promoter. This method is based on the finding that a mismatch between the most 3' nucleotide of the primer and the target sequence prevents amplification under certain conditions. Thus, by utilizing a primer in which the mutation is at the 3' end, one can differentiate normal from mutant sequence in genomic DNA. The results are shown in Fig. 4. When control DNA was amplified with both the normal primer set (primers 1A and 2), the 259-base pair product was amplified with the normal primers, indicating that the patient has only the mutant allele. These results show that the patient's promoter mutation, which was initially identified from a PCR subclone, is present in the patient's genomic DNA.

GpIbβ Promoter Studies—Studies were performed using a CAT assay to determine if the altered GATA binding site in the patient's promoter has any effect on gene transcription in HEL cells. HEL cells are a megakaryocytic cell line that is known to express GpIb (28) and has been used in studies of transcriptional regulation of genes expressed in megakaryocytes (27). The GpIbβ promoter constructs, diagrammed in Fig. 5, encompass nucleotides −276 to +108 of the gene with the normal having a C at nucleotide −133 and the patient having a G at this position. A promoter construct of the GpIbβ promoter was used as a positive control and the CAT vector with no promoter was used as a negative control. The constructs were transfected into HEL cells, which were assayed for CAT activity 72 h post-transfection. The amount of CAT enzyme produced, which is noted as the percent conversion of chloramphenicol to its acetylated forms, reflects promoter activity. As shown in Fig. 5, the normal GpIbβ construct had more activity than the patient's GpIbβ promoter construct. In six independent experiments, the patient's GpIbβ promoter activity was decreased by 84 ± 13% (mean ± S.D.) compared with that of the normal promoter.

GpIbβ Promoter Binding Studies—To identify which nuclear proteins are binding to the GpIbβ promoter in the region with the patient's mutation, we performed electrophoretic mobility shift assays. The promoter oligonucleotides used in these assays are noted in the blocked sequence in Fig. 6. The 24-mers include nucleotides −141 to −118 of the promoter with the
normal having a C at position −133 and the patient having a G at this position. Nuclear extracts from CHRF-288, a megakaryoblastic cell line, HEL, or HeLa cells, an epithelial cell line, were incubated with radiolabeled normal patient or Sp1 consensus oligonucleotides, then further incubated with an antibody to GATA-1 or GATA-2 when noted. The samples were analyzed by gel electrophoresis, and the results are shown in Fig. 6. A protein from either CHRF or HEL nuclear extracts bound to the normal oligonucleotide, but not to the patient oligonucleotide. In competition studies, it was demonstrated that the protein binding the normal oligonucleotide could not be competed off with a 35-fold excess of the mutated oligonucleotide, but the binding could be inhibited with only 1.5-fold of the unlabeled normal oligonucleotide (data not shown). As shown in Fig. 6, the binding complex between the nuclear protein and the normal oligonucleotide was shifted after incubation with a monoclonal antibody to GATA-1, but not with a polyclonal antibody to GATA-2, which is known to supershift. In addition, HeLa nuclear protein extract, which contains GATA-2, but not GATA-1 (29), did not bind either the normal or patient oligonucleotide, but did bind to Sp1 as a control. These results suggest that the GATA-1 protein is binding to the normal GATA consensus site, but is unable to bind to the patient’s mutated GATA site.

**DISCUSSION**

In this study, we have identified the first case of Bernard-Soulier syndrome that can be attributed to a mutation in the GpIbβ gene. The patient has only one allele of GpIbβ, because of a large deletion at 22q11.2 containing the other allele. His remaining allele contains a C to G transversion at nucleotide −133 from the megakaryocytic transcription start site that mutates a GATA consensus binding site. In vitro, the mutation disrupts GATA-1 binding at this site and decreases transcription of the gene by 84%. We propose that the mutation identified in the promoter region of the platelet GpIbβ gene is responsible for causing BSS in this patient.

In classic BSS, it has appeared that the absence of one of the components of the complex affects the expression of the other proteins. This concept is supported by co-transfection studies using GpIbα, GpIbβ, and GpIκ in heterologous cells (30), where the expression of all three components was necessary for stable, functional expression of the receptor in the membrane. The ability of a mutation in the gene encoding either GpIbα or GpIκ has been demonstrated to affect the expression of other proteins of the complex in patients with BSS. We now demonstrate that this is also true with GpIbβ.

The GpIbβ gene is more complex than the other genes encoding the proteins of this complex. An alternative form of the gene is expressed in non-megakaryocytic cells, including endothelial cells. Endothelial cells and other tissues express a larger GpIbβ mRNA species that produces a protein larger (approximately 45 kDa) than the platelet protein (2). The function of this larger protein is unknown, but it has been shown to be present in human umbilical vein endothelial cells (2), a human glioma cell line, and mouse brain tissue by Western blotting with a polyclonal antibody directed against the platelet GpIbβ protein. The mutation identified in this patient, which is located in the promoter region of the platelet GpIbβ gene, is located in the coding region of the endothelial cell GpIbβ cDNA. However, the mutation results in a conservative amino acid change (Leu62 → Val), suggesting that the endothelial cell mRNA and protein species may still be synthesized in this patient. Studies are under way to determine if the endothelial cell mRNA is still transcribed in this patient, while the platelet GpIbβ mRNA is affected by the mutation.

As noted previously, obligate heterozygotes for BSS do not, in general, have bleeding manifestations. It is possible that clinical manifestations of heterozygotes for BSS could vary depending on the subunit affected. However, patients with syndromes associated with a microdeletion on one chromosome 22q11, 2

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2 F-Y. Tsai and S. H. Orkin, personal communication.

3 B. A. Konkle, F. Meloni, and S. S. Shapiro, unpublished data.
which would include GpIbβ, have not been noted to be thrombocytopenic or have bleeding disorders (31). We have evaluated platelet counts and GpIbα protein in 11 patients with a 22q11.2 microdeletion and found no consistent difference between the patients and normal controls (data not shown). Thus it appears that the loss of one GpIbβ allele alone is not sufficient to produce a bleeding disorder, but that these patients may be at greater risk to develop BSS through a single mutation of the remaining GpIbβ allele.

This case of BSS is unique because it is the first described natural occurring mutation of a GATA promoter element in a megakaryocytic gene, demonstrating the importance of this regulatory element in megakaryocyte gene expression. In vitro studies have identified the GATA consensus binding sequence as an important element for the transcription of megakaryocyte-specific genes. The genes for platelet factor 4, GpIbα, and GpIbβ all contain GATA binding sites in their promoter regions that are necessary for efficient transcription (27, 32–34). The two members of the GATA family of proteins expressed in the megakaryocytes are GATA-1 and GATA-2, both of which bind to the (A/T)GATA(A/G) consensus sequence (35). Although the roles of GATA-1 and GATA-2 in erythroid development have been, at least in part, elucidated, the roles of these factors in non-erythroid cells is less clear. From studies of GATA-2 gene disruption in mice, we know that GATA-2 is important for maintenance of early hematopoietic progenitors and possibly stem cells (36). Studies of GATA-1 gene disruption in mice have shown that GATA-1 is not required for megakaryocyte or platelet formation (37). However, the potential role of GATA-1 or GATA-2 in the modulation of megakaryocyte gene expression has not been elucidated. Our study suggests that GATA-1 binding is necessary for efficient GpIbβ transcription.

The platelet GpIbβ gene has three GATA consensus binding sites in the promoter region. The first and most proximal to the transcription start site is located between nucleotides –37 and –34. The second site, which is mutated in this BSS case, is located between nucleotides –136 and –133. The third and most distal site is located between nucleotides –146 and –143 (14). This BSS patient demonstrates that the second GATA binding site is important for GpIbβ promoter function. A mutation at this GATA sequence, while the other two sites are normal, decreases promoter function 6-fold. Ongoing studies evaluating GATA binding to the GpIbβ promoter suggest that the patient’s mutation may also affect binding to the adjacent GATA site at nucleotide –146. It is possible that the GATA proteins bind these two adjacent sites cooperatively. Studies are continuing to determine which GATA proteins are binding to the other motifs and what effect a mutation at these sites has on promoter function. In addition, we intend to extend our promoter studies to include sequence further 5’ to identify other positive or negative regulatory elements that are important for GpIbβ promoter function.

This case of Bernard-Soulier syndrome is also unique, because it can be attributed to a GpIbβ gene mutation in combination with a chromosome 22 deletion. Classical BSS is almost always inherited in an autosomal recessive manner. This patient’s chromosomal abnormality results in haploinsufficiency, which contributes to his phenotype by masking a defect in the GpIbβ gene on the non-deleted chromosome. Microdeletions in 22q11.2 are present in the majority of patients with DiGeorge and velocardiofacial syndrome (15, 16). Although several candidate genes have been identified, the identified gene(s) contributing to the manifestations of these syndromes have not been elucidated. Although the loss of one GpIbβ allele does not appear to result in a bleeding abnormality, an unknown function of the gene may contribute to these developmental syndromes.

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