A variant of von Willebrand disease (vWD) was identified in six members of a kindred spanning four generations. The proband was a 46-year-old woman with a lifelong history of bleeding, a prolonged bleeding time (>15 minutes), markedly elevated von Willebrand factor (vWF) antigen (vWF:Ag = 2.09 U/mL), slightly reduced ristocetin cofactor activity, and a plasma vWF multimer pattern similar to that of vWD type IIC. Similar findings were observed in her three children, mother, and brother. In affected family members, platelet and plasma vWF multimer patterns were discrepant with higher molecular weight multimers observed in platelet vWF. Following a 1-Des-amino-8-D-arginine vasopressin (DDAVP) challenge, the proband failed to normalize her bleeding time even though vWF:Ag rose by 70% and higher molecular weight multimers were increased slightly. Genetic studies were consistent with autosomal dominant inheritance of a mutation within the vWF gene. By sequencing of cloned genomic DNA, mutations were excluded in exons 4, 5, 14, and 15, which encode regions of the vWF propeptide proposed to be important in multimer biosynthesis. Mutations also were excluded in exons 28 to 31, which encompass the known mutations that cause vWD types IIA, IIB, and B. This new variant of vWD, characterized by autosomal dominant inheritance, a qualitative defect that resembles vWD type IIC, and increased plasma vWF:Ag, was tentatively designated vWD type IIC Miami.

VON WILLEBRAND DISEASE (vWD) is the most common bleeding disorder of humans. The phenotypic expression of this condition ranges from very mild to life-threatening hemorrhaging. Patients with vWD are usually divided into three groups. Type I vWD is characterized by quantitative deficiency of von Willebrand factor (vWF) and by autosomal dominant inheritance. Type III vWD is characterized by a virtual absence of vWF and by autosomal recessive inheritance. Type II vWD is characterized by normal to decreased plasma levels of vWF and the residual vWF is functionally abnormal. In most type II variants, SDS-agarose gel electrophoresis shows a loss of high molecular weight multimers, thereby distinguishing these variants from type I and type III vWD. The subtypes (A to H) of type II vWD are distinguished on the basis of specific functional defects or by details of the multimer pattern.

Type IIC vWD was described in 1982 by Ruggeri and colleagues in a patient with low vWF:Ag and ristocetin cofactor (RCoF) activity and was inherited as an autosomal recessive disorder. By multimeric analysis, the repeating triplet pattern of normal plasma vWF was replaced by one major band with a single faint intervening band, and the smallest multimer was relatively increased. Four unrelated families have been reported to be affected by recessive vWD with a similar phenotype. Some variation was observed in the number of intervening bands for plasma vWF multimer patterns, and in the degree of abnormality for platelet vWF multimer patterns, suggesting that vWD type IIC may be heterogeneous. The molecular basis for the recessive type IIC variants is not known.

Within a pedigree comprising 16 individuals, spanning four generations, we have identified 6 patients with vWD in which the multimeric analysis of plasma vWF is consistent with the type IIC phenotype. In contrast to the reported cases classified as vWD type IIC, this new variant is inherited as an autosomal dominant disorder and all affected persons in this family have markedly increased plasma vWF:Ag levels with slightly reduced plasma vWF RCoF. In addition, the platelet vWF multimeric pattern demonstrates higher molecular weight multimers than previously noted in propositi with recessive vWD type IIC.

Detailed genetic analysis strongly suggests that this dominant type IIC variant is caused by a mutation within, or closely linked to, the vWF gene. By DNA sequencing, mutations in exon 28 of the vWF gene were excluded, which indicates that the mechanism for this new variant differs from that causing vWD types IIA and IIB.

MATERIALS, METHODS, AND CASE HISTORY

Materials and Methods

Collection and handling of blood samples. For phenotypic studies, blood samples were collected in 1/10 volume of 3.8% sodium citrate with or without a protease inhibitor cocktail consisting of 0.1 mmol/L leupeptin, 5.0 mmol/L EDTA, and 6 mmol/L N-ethylmaleimide (Sigma, St Louis, MO). For genetic studies, blood samples were anticoagulated with EDTA. Platelet lysates were prepared essentially as previously described except that the platelet suspension (1 x 10^5/L) was lysed with 1/40 volume of 20% Triton-X 100 for 1 minute.

From the Department of Pathology, University of Miami School of Medicine, Miami, FL, and the Departments of Medicine, Biochemistry, and Molecular Biophysics, Howard Hughes Medical Institute, and The Jewish Hospital of St Louis, Washington University, St Louis, MO.

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Address reprint requests to Marlies R. Ledford, BS, MT (ASCP) SH, Department of Pathology, University of Miami School of Medicine, PO Box 016960 (R-5), Miami, FL 33101.

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hour at 37°C. Platelet counts and mean platelet volume (MPV) were determined with a Coulter STKR (Coulter Corp, Hialeah, FL).

**Assays of vWF function and concentration.** Ivy bleeding times (BT) were performed using a Surgicutt device (International Technidyne Corp, Edison, NJ). Ristocetin-induced platelet agglutination (RIPA) and RCoF activity assays were performed by standard aggregometric methods using ristocetin concentrations of 0.4 to 1.5 mg/mL and 1.0 mg/mL, respectively. For the RCoF assay, lyophylized platelets were from Bio/Data Corp, and a CAP (College of American Pathologists, Chicago, IL) reference vWF preparation was used for establishing a standard curve. Botrocetin and lyophylized platelets for botrocetin cofactor assay were kindly provided by American Diagnostica, Inc (Greenwich, CT). The assay was performed on a PAP-4 aggregometer (Bio/Data Corp, Horsham, PA) using botrocetin at a final concentration of 5 U/mL, lyophylized platelets adjusted to 8 x 10⁹/L, and normal pooled plasma (30 donors) for calibration. vWF:Ag was determined with an ELISA kit (Diagnostica Stago, American Bioproducts Co, Parsippany, NJ) and also by the method of Laurell using a polyclonal rabbit anti-human vWF antibody (Diagnostica Stago).

**Electrophoretic analysis of vWF structure.** Multimeric analysis of plasma and platelet vWF was performed by two methods: (1) autoradiography, using an F(ab')₂ rabbit anti-human vWF antibody (Diagnostica Stago) and (2) electrophoretic, using the same polyclonal antibody as for the Laurell method and a horseradish peroxidase-conjugated goat anti-rabbit affinity-purified IgG (Cal-Biochem, La Jolla, CA) as the secondary antibody. LGT VII agarose (Sigma) was used at concentrations of 1.4% or 2.0% as indicated.

Subunit composition of plasma vWF was determined in a gel system similar to that used for multimer analysis except that samples contained 5% 2-mercaptoethanol and were heated for 1 minute at 100°C. 5.0% NuSeive GTG agarose was used for the running gel and 1.0% IsoGel was used for the stacking gel (FMC Corp, Rockland, ME).

**Other assays.** Activated partial thromboplastin time (APTT) and one-stage factor VIII:C assays were performed on a Coag-AMate X2 (Organon Teknika, Durham, NC) using Organon Teknika reagents and reference plasma. Factor VIII:C was also assayed by a chromogenic substrate method using a commercially prepared kit with substrate CBS 48.03 (Diagnostica Stago).

**Analysis of PCR-amplified DNA.** Genomic DNA was prepared from peripheral blood leukocytes. Polymerase chain reaction (PCR) was performed using a Perkin Elmer–Cetus (Norwalk, CT) DNA Thermal Cycler as previously described. Primers used for amplification of exon 28 were No. 226, TGC GAA TAT GGA AGT CAT TG; No. 227a, CCG ATC CT1 CCA GGA CGA AC; and No. 375a, TCT TGG CAG ATG CAT GTA GC. PCR-amplified fragments of exon 28 using primers 226 and 227a were digested with BstEII (New England Biolabs, Beverly, MA), electrophoresed on a 1% agarose gel, and visualized by staining with ethidium bromide. Analysis of intron 40 variable number of tandem repeat (VNTR) polymorphism was performed as previously described.

**Case History.** The proband of family M, a 46-year-old white woman, was referred in March 1990 to evaluate a lifelong bleeding diathesis before elective minor surgery. Initial studies were: BT > 15 minutes (normal [N] < 8 minutes), APTT = 30 seconds (upper limit of N = 170)

Values for BT, VIII:C, vWF:Ag, and RCoF are summarized in Table 1. The six affected family members had prolonged bleeding times (>15 minutes) and normal platelet counts. These individuals had markedly elevated plasma vWF:Ag levels by ELISA and also by the Laurell technique (data not shown). Plasma RCoF activity was variable among the six affected members ranging from low to within normal limits; however, the ratio of vWF:Ag to RCoF was ~4.6:1 for the affected members compared with ~1.2:1 for the unaffected family members. All individuals were ABO blood group type O except II-4, III-1, and III-4, who were type A. The six affected family members had normal VIII:C levels, although the ratio of vWF:Ag to VIII:C was increased (~2.3:1). RIPA with concentrations of 0.8 to 1.5 mg/mL ristocetin was normal in all tested individuals, with no enhanced responsiveness to low-dose ristocetin (0.4 mg/mL). Plasma botrocetin cofactor activity was 58% and 78% for II-3 and III-1, respectively. Representative data for platelet vWF from three affected members (II-3, III-1, III-3) showed platelet vWF:Ag levels above the normal range and normal platelet RCoF activity. Platelet vWF from III-1 demonstrated 35% botrocetin cofactor activity.

For the six affected individuals, analysis of plasma vWF
Fig 1. Pedigree and genetic studies for dominant vWD type IIC family M. Roman numerals denote generations. Arabic numbers indicate individuals within each generation, and the arrow denotes the proband. Filled symbols identify family members with elevated levels of vWF:Ag and a type IIC multimer pattern. Letters a, b, c, d correspond to alleles of a VNTR marker system (for details see legend to Fig 3). C+, T- identifies a polymorphism at nucleotide 4641 of the vWF exon 28. PCR amplification of exon 28 was performed using primers 226 and 227a. Product fragments were digested with BstEII to produce a fragment of 1,090 bp (T-) or 1,045 bp (C+). The aC haplotype appears to be linked to the vWD type IIC phenotype in family M.

multimers in 1.4% low gelling temperature (LGT) agarose gels (Fig 2A) revealed loss of the highest molecular weight multimers, no intervening bands, and an increase in the smallest multimer, with the latter two findings also observed using 2% LGT agarose gels (data not shown). In Fig 2B, platelet vWF from representative affected family members, in an intermediate resolution gel, clearly demonstrates the presence of high molecular weight multimers that are comparable to normal plasma but not to normal platelet vWF. Densitometric scans (data not shown) showed high molecular weight multimers totaling 58% and 50% for normal platelet vWF and IIC platelet vWF, respectively. Gels of lower porosity (2.0% agarose, data not shown) consistently disclosed an intervening band between multimers 1 and 2 as well as an increase in staining intensity of lower multimers relative to normal platelet vWF. These data suggest either that limited proteolysis occurs in vivo or that multimer assembly is abnormal in this vWD variant.

The subunit composition of plasma vWF from the proband (II-3) and her affected daughter (III-1) was compared with that of normal plasma vWF and vWF from an individual with type IIA vWD. Both affected patients demonstrated proteolytic fragments comparable to those found in normal plasma vWF and type IIA vWF (data not shown).

Two marker systems were used to investigate linkage of the vWD phenotype to the vWF gene in this family. One system exploits a highly polymorphic tetranucleotide (ATCT)n repeat within intron 40.15 In Fig 3, the observed PCR product sizes are designated a to d. The second system is a C/T polymorphism in exon 28 at nucleotide 4641 numbered from the initiation codon. This polymorphism is detected by digestion with the enzyme BstEII17 that cuts the DNA (indicated by +) if C is present but does not (indicated by −) if T is present. For III-4, plasma samples were available for phenotypic characterization (Table 1), but blood cells for DNA isolation could not be obtained. All analyzed

Table 1. Laboratory Data From Family M

<table>
<thead>
<tr>
<th>Family Member</th>
<th>BT (min)</th>
<th>F VIII:C (U/mL)</th>
<th>vWF:Ag/ELISA (U/mL)</th>
<th>RCoF (U/mL)</th>
<th>vWF:Ag/ELISA (U/mL)</th>
<th>RCoF (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>&gt;15</td>
<td>1.15</td>
<td>2.90</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-1</td>
<td>8</td>
<td>1.40</td>
<td>0.90</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-2</td>
<td>&gt;15</td>
<td>1.21</td>
<td>1.50</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-3</td>
<td>&gt;15</td>
<td>1.09</td>
<td>2.44</td>
<td>0.48</td>
<td>0.47</td>
<td>0.30</td>
</tr>
<tr>
<td>II-4</td>
<td>4</td>
<td>0.86</td>
<td>0.90</td>
<td>0.67</td>
<td>0.38</td>
<td>0.43</td>
</tr>
<tr>
<td>H-5</td>
<td>6</td>
<td>0.47</td>
<td>0.66</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-6</td>
<td>6.5</td>
<td>0.50</td>
<td>0.90</td>
<td>0.77</td>
<td>0.16</td>
<td>0.14</td>
</tr>
<tr>
<td>III-1</td>
<td>&gt;15</td>
<td>0.81</td>
<td>2.17</td>
<td>0.29</td>
<td>0.39</td>
<td>0.20</td>
</tr>
<tr>
<td>III-2</td>
<td>5</td>
<td>0.47</td>
<td>0.73</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-3</td>
<td>&gt;15</td>
<td>0.78</td>
<td>2.24</td>
<td>0.39</td>
<td>0.40</td>
<td>0.28</td>
</tr>
<tr>
<td>III-4</td>
<td>&gt;15</td>
<td>1.17</td>
<td>2.38</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-5</td>
<td>8.5</td>
<td>0.94</td>
<td>1.03</td>
<td>0.68</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>III-6</td>
<td>6.5</td>
<td>0.41</td>
<td>0.67</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-7</td>
<td>9</td>
<td>0.50</td>
<td>0.80</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-8</td>
<td>4</td>
<td>0.50</td>
<td>0.50</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-1</td>
<td>1.29</td>
<td>0.98</td>
<td>0.98</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BT, bleeding time; vWF: Ag, von Willebrand factor antigen; ELISA, enzyme-linked immunosorbent assay; RCoF, ristocetin cofactor activity of von Willebrand factor.
matings were informative and the results are consistent with linkage between the aC haplotype (Fig I) and the type IIC phenotype (lod = 2.1, \( \theta = 0.00 \)). The genotype of I-2, who was not available for study, is inferred to be bT/cC.

In an attempt to identify the causative mutation, regions of the vWF gene from patient III-3 were subcloned and sequenced. Clones for both alleles were identified on the basis of heterozygosity for known DNA sequence polymorphisms. No candidate mutations were found for either allele in exons 4 to 5, exons 14 to 15, or exons 28 to 31. In particular, mutations in exon 28 known to cause vWD types IIa, IIb, and B18 were not present (data not shown).

**DISCUSSION**

The laboratory studies of the proband showed a disparity between vWF:Ag and RCoF and an absence of high molecular weight vWF multimers. The normal triplet structure of the plasma vWF multimer pattern was replaced by a single band and the smallest multimer was accentuated (Fig 2A). This pattern resembles that reported for vWD types IIC\(^{2-7}\) and IIE\(^{13}\); it is distinguished from type IIE by the prominence of the smallest multimer.\(^{19}\) On the basis of the plasma vWF multimer pattern, the disorder in family M is most similar to vWD type IIC.

The cases of vWD type IIC reported to date\(^ {3-8}\) show some phenotypic heterogeneity (Table 2). Common features include low levels of vWF:Ag, even lower RCoF activity, absent RIPA, and apparently autosomal recessive inheritance. However, differences are present among the vWF multimer patterns. Plasma vWF multimers consistently show an increase in the smallest multimer, but some patients show an absence of intervening bands\(^ {5-7}\) and others show a single faint intervening band.\(^ {3,4}\) The platelet vWF multimer pattern is more variable. For some patients, it appears to be identical to plasma vWF,\(^ {3,5}\) but in others, there are differ-
Fig 3. Analysis by PCR of the vWF intron 40 tetranucleotide (ATCT) repeat polymorphism. Following extraction with chloroform, amplified DNA products were electrophoresed on an 8% SDS-PAGE gel and stained with ethidium bromide. The molecular weight standard (MW) of 118 bp is HaeIII-digested φX174 DNA. The four observed PCR product sizes are arbitrarily designated a to d: "a" allele (99 bp) corresponds to 6 ATCT repeats. "b" allele (103 bp) corresponds to 7 ATCT repeats, "c" allele (119 bp) corresponds to 11 ATCT repeats, and "d" allele (123 bp) corresponds to 12 ATCT repeats. The "a" allele is linked to the type IIC phenotype in this pedigree.

Table 2. Comparison of Dominant and Recessive vWD Type IIC

<table>
<thead>
<tr>
<th>Patients</th>
<th>Affected individuals</th>
<th>Inheritance</th>
<th>Clinical history</th>
<th>Bleeding time</th>
<th>Factor VIII:C</th>
<th>vWF:Ag (EIA)</th>
<th>vWF:Ag RCoF</th>
<th>RIPA</th>
<th>Multimer pattern</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Autosomal dominant</td>
<td>Mild to severe</td>
<td>&gt;15 &gt;20 &gt;30 &gt;30 &gt;20 &gt;12</td>
<td>1.00 0.14 0.67 0.85 0.24 0.31</td>
<td>2.41 0.14 0.50 1.25 – 0.50</td>
<td>2.27 0.03 – 0.45 0.16 0.18</td>
<td>0.50 &lt;0.01 0.10 0.14 0.03 0.03</td>
<td>– Absent – Absent –</td>
<td></td>
</tr>
<tr>
<td>Family M</td>
<td>6</td>
<td>Autosomal recessive</td>
<td>Mild</td>
<td>&gt;20</td>
<td>0.14</td>
<td>0.14</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Presence of HMWM</td>
</tr>
<tr>
<td>Spanish</td>
<td>2</td>
<td>Autosomal recessive</td>
<td>Moderate</td>
<td>&gt;30</td>
<td>0.67</td>
<td>0.50</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Multimer 1</td>
</tr>
<tr>
<td>Swedish</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Moderate</td>
<td>&gt;30</td>
<td>0.85</td>
<td>1.25</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Same as plasma</td>
</tr>
<tr>
<td>Italian</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Moderate</td>
<td>&gt;30</td>
<td>0.24</td>
<td>0.45</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Same as plasma</td>
</tr>
<tr>
<td>French</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Severe</td>
<td>&gt;20</td>
<td>0.31</td>
<td>0.16</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Faint band for Multimer 1</td>
</tr>
<tr>
<td>English</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Moderate</td>
<td>&gt;12</td>
<td>0.50</td>
<td>0.18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: vWF:Ag, von Willebrand factor antigen; EIA, electroimmunoassay; ELISA, enzyme-linked immunosorbent assay; IRMA, immunoradiometric assay; RCoF, ristocetin cofactor activity of von Willebrand factor; RIPA, ristocetin-induced platelet agglutination; HMWM, high molecular weight multimers.

* Mean values for 6 affected persons.
† Original patient.
antigen and type IIC multimer pattern are transmitted in an autosomal dominant fashion in family M that differs from the autosomal recessive transmission described previously for vWD type IIC.

In contrast to other patients with vWD type IIC, affected members of family M have markedly elevated levels of vWF antigen (Table 2). To exclude the possibility that the high antigen levels were not representative of the phenotype, several affected individuals were tested on multiple occasions and consistently demonstrated these findings. For affected members of family M, vWF function as determined by the ristocetin cofactor assay was borderline normal to low but significantly higher than values reported for other type IIC propositi. Although VIII:C levels were normal in family M, the ratio of VIII:C to vWF:Ag was low; administration of DDAVP to the proband increased this ratio into the normal range.

In the plasma of normal individuals or of patients with vWD types IIA or IIB, vWF consists mostly of the intact 250-Kd subunit but also contains proteolytic fragments of 189, 176, and 140 Kd. Several other variants with aberrant structure of individual multimers show markedly decreased amounts of these proteolytic fragments, particularly vWD types IIC (Swedish proband), IID, and IIIE. In contrast, plasma vWF from two affected members of family M demonstrates the presence of fragments similar to those found in normal plasma vWF (data not shown). Thus, a marked decrease in intervening or satellite multimer species (Fig 2A) does not necessarily provide evidence for decreased subunit proteolysis.

Genetic analysis of family M showed complete concordance between intragenic vWF polymorphisms and the vWD phenotype, and this is consistent with a mutation in the vWF gene. If there is a single intragenic mutation, the mechanism by which it causes both defective multimer structure and high vWF:Ag levels is not obvious. In principle, the decrease in large multimers might be caused by impaired biosynthesis or by enhanced proteolysis. Our studies of plasma and platelet vWF do not provide clear evidence for either mechanism, and no explanation for the high vWF:Ag levels is apparent. One possibility is that the mutation could facilitate the transport of vWF through the endoplasmic reticulum, a process that is unusually prolonged for normal vWF. By reducing intracellular degradation or storage, such an effect could thereby increase the rate of vWF secretion.

The vWF gene of the proband was examined for mutations that might disrupt multimer biosynthesis or increase multimer degradation. The vWF propeptide is proposed to catalyze vWF multimer formation. Segments of the vWF propeptide that are encoded by exons 4 and 5 (D1 domain) and exons 14 and 15 (D2 domain) show similarity to sequences in protein disulfide isomerase, and mutagenesis of these regions abolishes multimer formation. By DNA sequencing of PCR products, mutations within these sequences were excluded (data not shown). Similarly, of the mutations that cause vWD type IIA, some impair multimer formation and others increase sensitivity to proteolytic degradation. By DNA sequencing, mutations were excluded in exons 28 to 31 (data not shown); these regions that encode for domains A1 and A2 of the mature protein include all of the currently known mutations that cause vWD type IIA, as well as those that cause vWD types IIB and B. Thus, the molecular basis of vWD in family M is different from these previously characterized variants, which suggests that the pathophysiologic mechanism also is different.

To our knowledge, this is the first report of a qualitative defect of vWF that is associated with elevated levels of vWF:Ag. The unique combination of autosomal dominant inheritance, type IIC–like multimer pattern, and high vWF:Ag appears to represent a new variant of type II vWD. Until classification can be based on either pathophysiologic mechanism or genetic defect, we propose to designate this new variant as vWD type IIC Miami to avoid the addition of new terms to the present nomenclature.

ACKNOWLEDGMENT

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REFERENCES


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New variant of von Willebrand disease type II with markedly increased levels of von Willebrand factor antigen and dominant mode of inheritance: von Willebrand disease type IIC Miami

MR Ledford, I Rabinowitz, JE Sadler, JW Kent and F Civantos