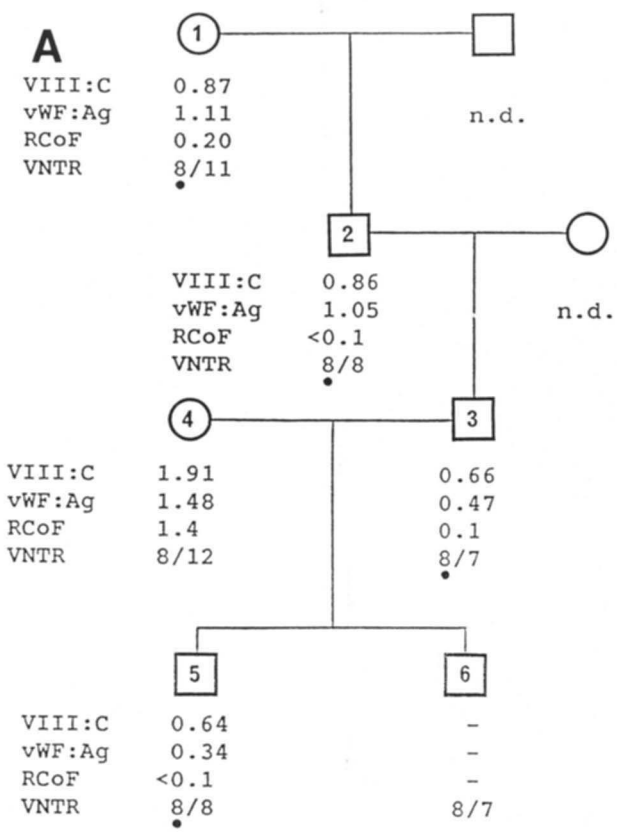
RAPID NEONATAL DIAGNOSIS OF TYPE IIB VON WILLEBRAND DISEASE USING THE POLYMERASE CHAIN REACTION

To the Editor:

The term von Willebrand disease (vWD) defines a very heterogeneous bleeding disorder that results from quantitative and/or qualitative defects of the von Willebrand factor (vWF) molecule.[1,2] Diagnosis of vWD based on phenotypic data often proves difficult. Therefore, genotypic diagnosis, eg, by gene tracking with restriction fragment length polymorphisms (RFLP) in the von Willebrand gene, has been attempted in many affected families and studies have clearly shown their utility.[3,4] Recently, Peake et al[5] and Bignell et al[6] reported a highly informative variable number of tandem repeat (VNTR) region in intron 40 of the vWF gene that can be amplified by the polymerase chain reaction (PCR). The investigators demonstrated the usefulness of diagnosis of vWD types III, I, and IIa.

The following presentation shows the application of this technique for genotypic analysis in a family with vWd type IIB. Four members of this family (nos. 1, 2, 3, and 5) are affected with type IIB vWD as indicated by an abnormal multimeric structure of the vWF, increase in platelet aggregation in the presence of ristocetin, and a normal vWF antigen. The family (except no. 5) has been reported in detail previously.[7] We could show that in this vWD type IIB family the defective vWF gene segregated with the vWF VNTR 8 allele (see Fig 1). The 2-year-old boy (no. 5), who had already



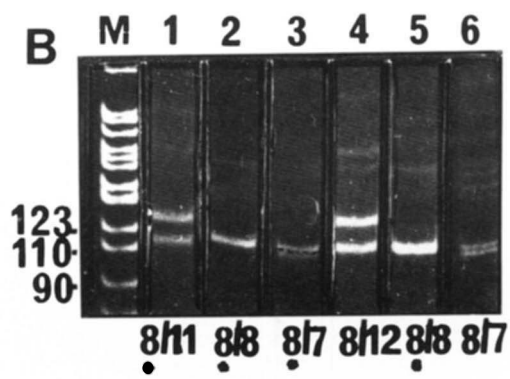


Fig 1. Family tree (A) and vWF-VNTR polyacrylamide (PAA) gel analysis (B). The numbers above the gel tracks correspond to the numbers in the family tree. PAA gel: Track M shows *Msp* I markers; sizes are given in base pairs. Tracks 2 and 5 show homozygous vWF VNTR 8, tracks 3 and 6 show heterozygous vWF-VNTR 7/8 pattern, and tracks 1 and 4 show heterozygous vWF-VNTR 8/11 and 8/12, respectively. The family tree shows the data for F VIII:C, vWF:Ag, and vWF RCoF in units per milliliter.

experienced extensive mucosal bleeding after oral trauma, was homozygous for the vWF VNTR 8 marker. His plasma ristocetin cofactor activity was less than 0.1 U/mL, vWF antigen was 0.34 U/mL, and F VIII:C activity was 0.64 U/mL. These data unequivocally confirmed that he had inherited the mutant paternal allele (see Fig 1). The family has now requested rapid diagnosis of a newborn boy to be immediately prepared for emergency. PCR amplification of leukocyte DNA in blood of the baby showed that he has inherited the paternal vWF VNTR 7 marker and is therefore, with high certainty, not affected. Our studies demonstrate the usefulness of the vWF VNTR markers also for gene tracking studies in families with type IIB vWD, providing that appropriate family studies have been conducted.

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