

Type 3 von Willebrand Disease

A case report of a homozygous partial VWF gene deletion

C Cooper, N Al Hasso, J Drummond, E Thompson, R Treacy and J Whittaker
 East Anglian Medical Genetics Service, Molecular Genetics, Addenbrookes NHS Foundation Trust, Cambridge

Introduction

Type 3 von Willebrand disease (VWD), the most severe and rare form of the disorder, is inherited in an autosomal recessive manner. It manifests itself as a total or virtually complete deficiency of von Willebrand factor (VWF) and a consequential deficiency of Factor VIII (FVIII) resulting in severe defects in both primary and secondary haemostasis. Patients have severe bleeding symptoms from birth including haemarthroses and soft tissue bleeding. Null alleles account for 80-90% of the mutations in type 3 VWD with small and large deletions accounting for 18 and 12%, respectively. Here we present the case of a one year old girl born to first cousins of Pakistani origin, referred for VWF gene screening for confirmation of suspected type 3 VWD.

Materials & Methods

Fluorescent sequencing analysis using Mutation Surveyor of exons 2-52 of the VWF gene. Duplex PCR of exons 2-5 in the index case and multiplex ligation-dependent probe amplification (MLPA) of exons 2-52 using kits P011-B1 and P012-B1 from MRC Holland (Amsterdam, the Netherlands) in the index case and parents. VWF and FVIII levels were tested by our local haemostasis laboratory and provided with the referral.

Results

PCR amplification and sequencing of exons 2-5 failed repeatedly in the index case but no other potentially pathogenic mutations were detected in exons 6-52. Duplex PCR and MLPA confirmed a homozygous deletion of exons 2-5 (Figures 1 and 2) consistent with her plasma test results provided (see Table 1) and diagnosis of type 3 VWD. Carrier testing in her parents confirmed they are heterozygous for the deletion (Figure 3).

Figure 1: Duplex PCR of exons 2-5 of the VWF gene

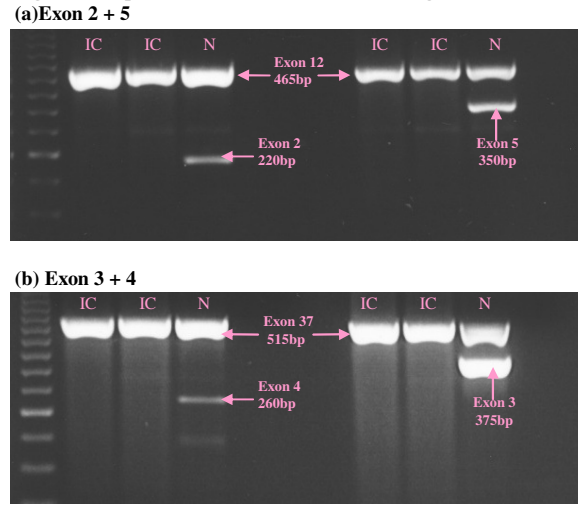


Figure 2: MLPA analysis results in the Index Case

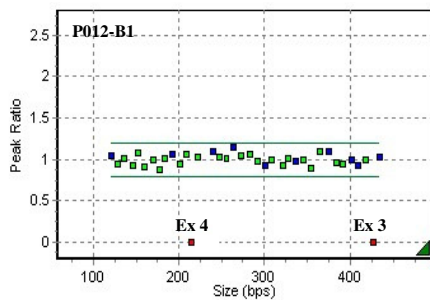
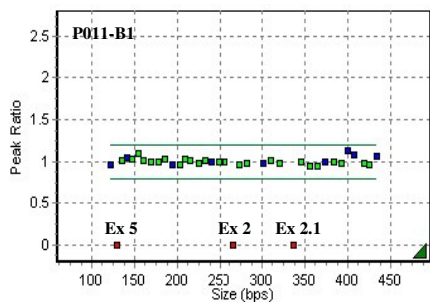
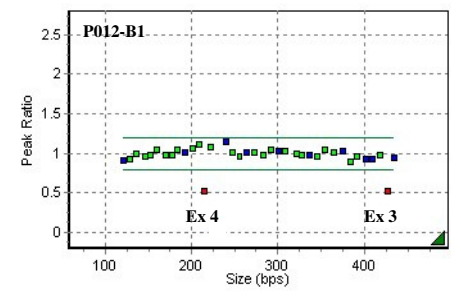
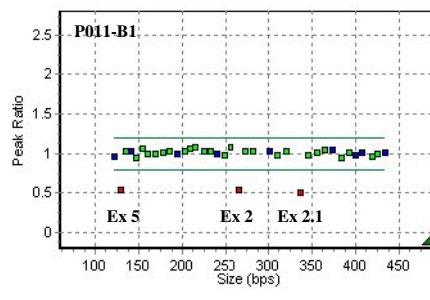


Table 1: VWF and FVIII levels in Index Case and Parents

Test	Index Case	Mother	Father	Reference Range
FVIII:C (IU/ml)	0.02	0.96	0.92	0.57-1.41
VWF:Ag (IU/ml)	0.06	0.46	0.42	0.53-1.49
VWF:Act (IU/ml)	ND	0.45	0.41	0.43-1.26

Figure 3: Example MLPA analysis results from Parent



Discussion

This case highlights that type 3 and type 1 VWD have a different molecular basis. Type 1 VWD is not just the heterozygous state of a type 3 VWD mutation. In this family, the parents are asymptomatic with borderline VWF levels and do not clinically have type 1 VWD. Furthermore, it illustrates the importance of dosage analysis in the testing repertoire allowing confirmation of a homozygous deletion in an affected patient and carrier and/or prenatal testing in the parents and other family members. Before the integration of the molecular haemostasis service with the regional molecular genetics laboratory we would have been unable to offer dosage analysis. This is now part of our testing portfolio for VWD and other haemostasis disorders (visit www.cuh.org.uk/moleculargenetics for further details).