

SHORT REPORTS

X linked recessive thrombocytopenia

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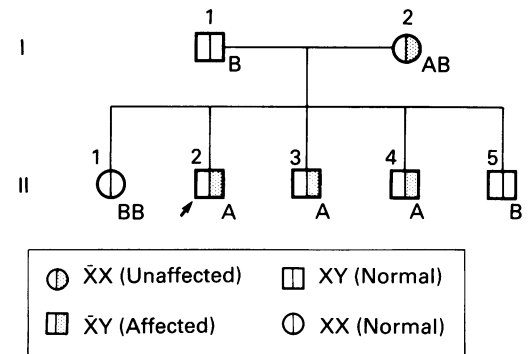
Abstract

A Saudi Arab boy presented in early childhood with thrombocytopenia, morphologically large and normal sized platelets, increased mean platelet volume, and a hypermegakaryocytic bone marrow. There was no clinical and laboratory evidence of any significant immunological abnormalities. Similar findings in two other brothers suggested strongly that they were all suffering from an X linked recessive thrombocytopenic disorder. Results of DNA analysis with the probe M27 β are consistent with X linkage and indicate also that the locus of the relevant gene lies close to or is identical to the locus of the gene for the Wiskott-Aldrich syndrome (WAS). Because of various features which include the presence of large and normal sized platelets (rather than small platelets) and freedom from significant immune deficiencies, it is likely that the X linked recessive thrombocytopenia in this family is an isolated entity quite distinct from the classical WAS phenotype. However, a modified expression of the WAS gene producing a mild phenotypic variant cannot be excluded entirely.

(J Med Genet 1993;30:968-9)

An accurate aetiological diagnosis is a prerequisite for appropriate and effective management of thrombocytopenia in infancy and childhood. Family studies and X chromosome mapping showed that a young Saudi Arab boy who had been treated as a case of essential autoimmune thrombocytopenic purpura (EATP) for several years without response was suffering from X linked recessive thrombocytopenia. His abnormal gene was shown to be identical to or close to the Wiskott-Aldrich syndrome (WAS) gene.

II-2 (figure) who is now 13 years old first bled excessively after neonatal circumcision. From the age of 6 months he experienced recurrent bouts of epistaxis and was diagnosed as suffering from EATP at the age of 3 years. Despite numerous standard forms of therapy, including high dose steroids, his platelet counts remained low ($< 10 \times 10^9/l$ to $33 \times 10^9/l$, $\bar{x} 24 \times 10^9/l$) and minor bleeding episodes persisted. Further evaluation showed similar but less severe bleeding episodes in his 9 year old (II-3) and 6 year old (II-4) brothers who were also found to be moderately severely thrombocytopenic (platelet counts of II-3: 22



Pedigree of Saudi Arab family with X linked recessive thrombocytopenia. A and B refer to the alleles identified by the M27 β (DXS255) probe. Allele A cosegregates with thrombocytopenia in an X linked recessive manner; allele B cosegregates with a normal platelet count.

to $58 \times 10^9/l$, $\bar{x} 41 \times 10^9/l$; II-4: 35 to $74 \times 10^9/l$, $\bar{x} 47 \times 10^9/l$). Stained blood films showed relatively large granular platelets with an increased mean platelet volume (MPV) in II-2 and II-4 and a normal MPV in II-3. Other haematological parameters in these three brothers were normal. His sibs II-1 (aged 15 years) and II-5 (aged 2 years) and his parents I-1 (aged 36 years) and I-2 (aged 34 years) were all clinically and haematologically normal. Results of immunological studies on the proband and his mother (I-2) included repeatedly normal absolute lymphocyte counts and normal ABO alloagglutinin titres, with only a minimal reduction of serum IgM and C4 of II-2. These results suggested that the proband and his two affected brothers were suffering from one of the hereditary thrombocytopenias, possibly X linked recessive thrombocytopenia (XLRT).¹ X chromosome DNA analysis was performed on the blood of both parents and all the children with the hypervariable marker M27 β (DXS255), which is closely linked to the WAS locus.^{2,3} The results showed complete cosegregation with the M27 β probe (figure) and no evidence of recombination with it.

The clinical, haematological, and immunological data of the affected family members are at variance with classical WAS and are probably diagnostic of isolated XLRT,¹ which has been considered by some investigators to represent an attenuated variant of WAS⁴ and by others as a separate genetic entity.⁵ The XLRT gene has been located on the short arm of the X chromosome in the region of the WAS locus or loci,¹ while DNA sequences of the WAS gene have been mapped to two separate but closely linked loci on the proximal part of the short

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Received 28 January 1993.
Revised version accepted
26 May 1993.

arm of the X chromosome.⁶ These findings have reinforced the speculation that XLRT and WAS are intimately related and are probably caused by different mutations at the same locus or loci.¹ The figure shows the inheritance by II·2, II·3, and II·4 of the DXS255 allele A from their unaffected (presumably carrier) mother (I·2) and of the allele B by the unaffected brother (II·5) consistent with the hypothesis that the phenotype is linked to a mutation at the putative XLRT/WAS locus. By this hypothesis the sister (II·1) should not transmit the condition to her offspring, provided that there has been no recombination between DXS255 and the mutant gene at the XLRT/WAS locus.

We thank Dr Ian Craig for the M27 β (DXS255) probe, Tracey Flint for technical

assistance, and Ranjana Haleangadi for the typescript.

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