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Germ-Line Mosaicism Simulates Genetic Heterogeneity in Wiskott-Aldrich Syndrome

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Summary

The Wiskott-Aldrich syndrome (IMD2) is an X-linked recessive immunodeficiency. Initial linkage studies mapped the disease locus on the proximal short arm of the X chromosome, a localization which was further refined to the interval framed by DXS7 and DXS14. We have recently shown that a novel hypervariable locus, DXS255, is very closely linked to the disease gene and is likely to be, at present, the marker closest to the disease gene. The analysis of one family, however, displayed conflicting linkage results, as all of the informative markers situated in the Xp11-q22 region appeared to recombine with the disease locus in two "phase-known" meioses. We have shown by X-inactivation studies that the segregation of the disease through three obligate carrier females in this family originates from a grandpaternal mosaicism, which accounts for the apparent recombinations. This shows that germ-line mosaicism can simulate genetic heterogeneity in linkage studies.

Introduction

The Wiskott-Aldrich syndrome (WAS) (IMD2; McKusick 30100 [McKusick 1988]) is a severe X-linked recessive disorder characterized by eczema, thrombocytopenia with small-size platelets, and multiple infections (Wiskott 1937; Aldrich et al. 1954). Immunodeficiency involving both T and B cell functions is a common feature. It is characterized by low antigen-induced lymphocyte proliferation and by defective antibody production associated with low serum IgM levels. In the absence of bone marrow transplantation, the syndrome is usually lethal within the first decade of life (Parkman et al. 1978).

The underlying intrinsic molecular defect has not yet been characterized, although two heavily O-glycosylated proteins have been shown to be missing on the platelets (GP1b) and on the lymphocytes (GPL115, sialophorin) (Parkman et al. 1981; Remold-O'Donnell et al. 1984). The latter is possibly involved in T cell activation (Mentzer et al. 1987). cDNAs for sialophorin, however, have been cloned and mapped to chromosome 16 (Pallant et al. 1989; Shelley et al. 1989): the corresponding gene therefore cannot be a candidate locus for the gene(s) involved in the disease.

It has recently been shown that nonrandom X inactivation is found in platelets and T and B lymphocytes, as well as in monocytes and granulocytes of heterozygous carrier females, suggesting that the selection takes place at an early stage of the haematopoietic ontogeny and affects most of the peripheral blood cell types (Gealy et al. 1980; Kohn et al. 1987; Fearon et al. 1988; Greer et al. 1989). The heterozygous females present neither clinical nor immunological abnormalities.

The definition of closely linked RFLP markers is a desirable goal for carrier and prenatal diagnosis. A first genetic analysis was performed in order to determine the subchromosomal location of the IMD2 locus on the human X chromosome (Peacocke and Siminovitch 1987). This demonstrated linkage between IMD2 and two polymorphic loci, DXS7 and DXS14, that map to the proximal short arm of the X chromosome. Kwan et al. (1988) showed, with a high probability against all other orders, that the disease gene is located between these two markers. We recently reported that the hyper-

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variable locus DXS255 (Fraser et al. 1987, 1989) is very closely linked to the disease locus, no recombination being detected in 24 informative meioses (de Saint-Basile et al. 1989). Segregation data in a 3-generation family, however, showed recombinations in two phase-known meioses, with all of the informative RFLP markers located within a region which spanned from Xp11 to Xq22.3. This result suggested that a mutation at a second locus could be responsible for the expression of the disease in this family. Similarly, genetic heterogeneity has been described in retinitis pigmentosa, for which an autosomal (RP_1) and two X-linked loci (RP2 and RP3) have been defined (McKusick 1988; Mandel et al. 1989).

A transmission of the disease by the phenotypically normal grandfather nevertheless remained to be considered as a possibility in this family, because the carrier status of the grandmother was not formally proved. We therefore performed X-inactivation analyses and demonstrated that in this particular family the disease indeed was transmitted on the X chromosome of the grandfather, who was thus mosaic for the mutation in his somatic or germ cells.

Cases of germ-line mosaicism have previously been identified, for instance, in Duchenne muscular dystrophy (Bakker et al. 1987; Darras and Francke 1987; Darras et al. 1988; Wood and McGillivray 1988) and, more recently, in a boy with mild ornithine transcarbamylase deficiency (Maddalena et al. 1988). We discuss the implications of this phenomenon both with respect to genetic mapping studies and with respect to genetic counseling.

Subjects and Methods

Family M

The family consulted at the Hôpital des Enfants Malades, Paris. The diagnosis of WAS has been ascertained by clinical and immunological investigations according to the World Health Organization Committee on Immunodeficiency Criteria (Rosen et al. 1983).

The propositus, III9, developed eczema and a thrombocytopenic purpura at the age of 1 year. By the age of 14 years he had developed recurrent infections of the lower and upper respiratory tract, osteomyelitis, and severe bleedings including epistaxis and cerebromeningeal hemorrhage leading to paresis and hematemesis. His platelet count was 10,000–30,000/μl, with normal granulocyte and lymphocyte counts. Immunological studies showed borderline serum Ig levels: IgG 12.9 g/liter, IgM 0.32 g/liter, and increased IgA and IgE levels (3.78 g/liter and 861 microunits/ml, respectively); low isoagglutinin titers were recorded. In addition, at the age of 10 years the patient was found to have an aortic dysplasia, the origin of which remains unknown.

A bone marrow transplantation was performed at age 15 years. The patient died 2 mo later from cardiac failure associated with herpes simplex encephalitis.

Two cousins (III2 and III7) died, respectively, at age 9 years from hematemeses and at age 11 years from encephalitis due to herpes simplex. A third cousin (III1) presented with aortic dysplasia at the age of 20 years. The grandfather (I2) was healthy, without any history of eczema, recurrent infections, or bleeding.

DNA Analysis

The X-chromosome inactivation study was performed as follows: 20 μg of DNA were digested to completion with *Pst*I and *Bst*XI; the digest was then divided into two 10-μg aliquots, one of which was further digested with 10 units of *Hpa*II while the other was not. Southern analysis was then performed with the PGK pSPT19.1 polymorphic probe (Keith et al. 1986) and with the hypervariable marker DXS255 (Fraser et al. 1987, 1989), according to a method described elsewhere (Oberlé et al. 1986).

Linkage Analysis

Multipoint linkage analyses were performed using program LINKMAP (version 4.7), from the program package LINKAGE (Lathrop et al. 1984, 1985), on a compatible PC-AT computer.

Results and Discussion

The gene responsible for WAS has been assigned to the Xp11 region by genetic linkage studies (Peacocke and Siminovitch 1987; Kwan et al. 1988). Data obtained by us from the analysis of five new families are in agreement with this localization (de Saint Basile et al. 1989).

The analysis of a sixth family (family M; fig. 1), however, displayed strikingly conflicting results, as recombinations occurred in two "phase-known" meioses (III1 and III8) with all of the five informative markers tested, from DXS7 (Xp11.3) to DXS17 (Xq22). This would virtually exclude, in this family, a location of the disease locus from a region spanning from Xp11 to Xq22. A multipoint linkage analysis was performed with this family by using the LINKMAP program (Lathrop et al. 1984, 1985). The resulting plot is presented in figure 2 (curve II). Lod-score values inferior

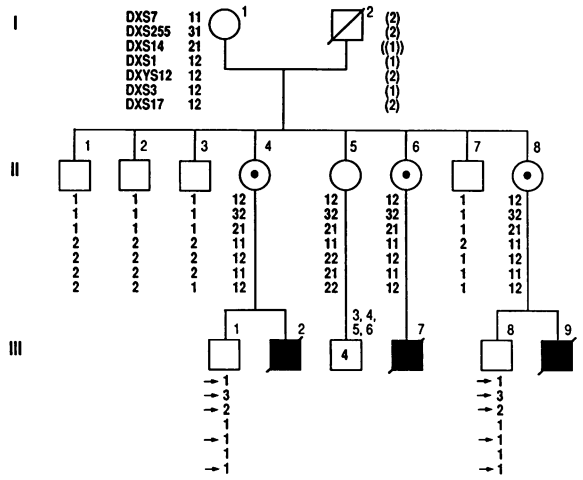

Figure 1 Family M (pedigree 96). The vertical arrangement of alleles indicates the most likely haplotype. Paternal haplotype is indicated on the right for females. In parentheses is the deduced genotype; in double parentheses is the most likely genotype (based on minimum recombination between closely linked markers). Alleles 1 and 2 denote the largest and smallest fragments, respectively. □ = male; ○ = female; ⊙ = obligatory carrier; ⊘ = deceased; ◪ = deceased affected male. Arrows indicate the apparent recombinations.

<−2 are found at most points in the map (for comparison, see the positive lod scores obtained for the five other families we have analyzed; fig. 2, curve I). This corresponds to the exclusion threshold for placing a locus in a given region and would thus indicate genetic heterogeneity for WAS. Segregation analysis was performed with polymorphic DNA markers located outside of the Xp11-q22 span, and an absence of linkage was observed, for instance, with DXS52 (Xq28) and DXS164 (Xp21), excluding as well the possibility of the existence of a second WAS locus in these two regions of the X chromosome (data not shown).

Careful examination of the pedigree suggested an alternative hypothesis to genetic heterogeneity. The grandmother (I1) was not formally proved to be a carrier, since none of her four sons are affected, a result which would have only a 6% probability of occurring if she were a carrier. Furthermore, the haplotype of markers from DXS7 to DXS17 in the two normal boys, III1 and III8, corresponds to that inherited from the grandmother I1 without recombination. This could suggest that the WAS mutation was carried on the grandpaternal haplotype, although we could not prove this directly, since the affected males are deceased. We therefore decided to undertake X-inactivation studies in order to test this hypothesis, as selective inactivation of the mutated X chromosome occurs in the peripheral blood cells of WAS carrier females.

X-inactivation studies at the DNA level rely on the use of RFLP markers that are differentially methylated on the active and inactive X chromosomes. In a first instance we have used probe pSPT19.1 from the PGK locus (Keith et al. 1986), which detects an RFLP after double restriction of human genomic DNA with enzymes *Bst*XI and *Pst*I, with allelic bands at 1.05 and 0.9 kb. The X-inactivation study was then performed by further restriction with the methylation-sensitive enzyme *Hpa*II.

Since it had previously been shown that nonrandom X inactivation occurs in most of the peripheral blood cell types of WAS carriers (Fearon et al. 1988; Greer et al. 1989), we decided to perform the X-inactivation analysis on DNA extracted from total blood samples

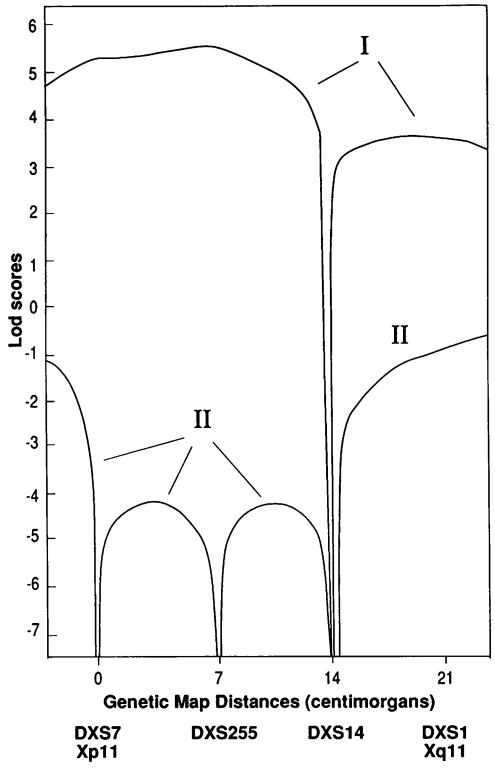

Figure 2 Multipoint lod scores. Curve I results from calculations performed with data from five pedigrees published elsewhere (de Saint-Basile et al. 1989). Curve II is derived from the analysis of family M. According to our previously published data (Arveiler et al. 1987), the genetic distance between DXS1 and DXS7 was fixed at 21 cM. Because of insufficient published data concerning the map positions of DXS14 and DXS255, the DXS1-to-DXS7 span has been arbitrarily divided into three equal intervals of 7 cM each.

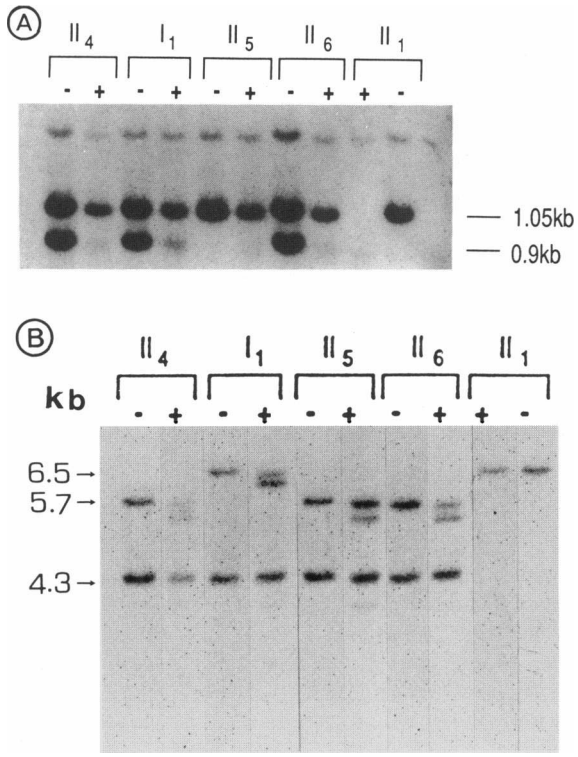

Figure 3 X-inactivation study in family M. Southern blot analysis of genomic DNA prepared from total peripheral blood of various individuals of the family, before (−) and after (+) addition of *Hpa*II (for details, see Subjects and Methods). *A*, Use of PGK probe pSPT19.1 (Keith et al. 1986). The 1.05- and 0.9-kb allelic bands are shown. *B*, Analysis performed with marker DXS255 (Fraser et al. 1987). Allelic bands at 4.3, 5.7, and 6.5 kb are shown.

of both the nonobligate-carrier grandmother (I1) and two obligate carriers (II4 and II6), as well as of individuals II5 (of uncertain status) and III1 (male used as a control). Results are displayed in figure 3*A*. The grandmother (I1) is heterozygous at the PGK locus, and both alleles persist after digestion with *Hpa*II, which suggests that she is not a carrier. The signal corresponding to allele 2 (0.9-kb band), however, appears diminished when compared with the band corresponding to allele 1 (1.05-kb band). This suggests that the maternal: paternal X-inactivation ratio in this female is quite different from the expected 50:50 value. Such cases have already been described, and similar skewed patterns are observed in about 5% of normal control females (Vogelstein et al. 1987; Fearon et al. 1988).

The obligate carriers (II4 and II6) are also heterozygous for the PGK polymorphism: allele 2 (0.9-kb band) disappears totally in the samples that correspond to both of them after addition of *Hpa*II; this shows that allele 1, which is inherited from their father (I2), is always methylated and, therefore, that the paternal X chromosome is always inactive in their peripheral blood cells. This demonstrates that the mutation was transmitted to three obligate-carrier daughters by their phenotypically normal father.

Individual II5 is homozygous for allele 1, and the X-inactivation study therefore does not give any further information with respect to her genetic status. As expected, total disappearance of the allelic band was observed in a control male sample (III1) after addition of *Hpa*II.

In order to gain information concerning the genetic status of individual II5, we have completed the X-inactivation study by using the hypervariable locus DXS255 (fig. 3*B*). Indeed, it recently has been shown (Boyd et al. 1988) that the active X chromosome is methylated at this locus. Again random X inactivation was shown in the grandmother (I1), whereas much more skewed hybridization patterns were observed in the obligate carriers (II4 and II6): selective disappearance, after addition of *Hpa*II, of the 5.7-kb allele inherited from their father I2 confirms transmission of the mutation through the normal grandfather. Persistence of both alleles in the sample corresponding to II5 indicates that this female does not carry the mutation. This unambiguously proves the existence of a germ-line mosaicism in the grandfather (I2).

Similar cases of germ-line mosaicism have been demonstrated in several families with Duchenne muscular dystrophy (DMD) (Bakker et al. 1987; Darras and Francke 1987; Darras et al. 1988; Wood and McGillivray 1988), as well as in a family with ornithine transcarbamylase deficiency (Maddalena et al. 1988), and have been suggested in a family with hemophilia A (Gitschier 1988). It should be noted that Bruton agammaglobulinemia was first claimed to show genetic heterogeneity, on the basis of segregation data which appeared to exclude the Xq21-q22 region in one family (Mensink et al. 1986, 1987). A grandpaternal mosaicism, however, recently has been demonstrated by X-inactivation studies in this family (Hendriks et al. 1989). With regard to autosomal conditions, mosaicism also has been proved in osteogenesis imperfecta type II (Byers et al. 1988) and has been suggested in other dominant diseases, such as achondrodysplasia (Fryns et al. 1983; Opitz 1984; Reiser et al. 1984) (for a review on mosaicism, see Hall 1988).

Germ-line mosaicism is probably not restricted to a few disease loci. This has important consequences for linkage analyses, since such cases might falsely sug-

gest heterogeneity by creating apparent phase-known recombinants. Undetected cases might also increase artificially the genetic map distances between RFLP markers and a disease locus. This might account, in part, for the apparent high rate of recombination previously reported, within the DMD locus, between intragenic markers and the DMD mutation (Davies et al. 1987), although recent data (Chen et al. 1989) show high rates of recombination in and around the DMD locus, independently of mosaicism.

The possibility of germ-line mosaicism has obvious implications for genetic counseling, since it means that the recurrence risk for the mutation is not zero and since it can lead to misinterpretation of the segregation data of polymorphic markers. This phenomenon should be taken into account when the disease appears to segregate for only 1 or 2 generations, and prenatal diagnosis should be proposed even to women with a low risk of being carriers when a direct detection of the mutation is possible (such as for deletions in the DMD gene). It should be noted that mosaicism can only be demonstrated if the mutation is directly detectable (as in DMD) or, in the case of X-linked diseases, if X-inactivation studies allow one to define unambiguously the chromosome that carries the mutation.

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