ELECTRONIC LETTER

Refined mapping of the gene for otopalatodigital syndrome type I

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Otopalatodigital syndrome type I (OPD-I) (MIM 31130) is a rare X linked disorder characterised by a peculiar face with supraorbital ridges, flat nasal bridge, hypertelorism, micrognathia, and cleft palate (pugilistic face) and by hand and foot deformities with spatulate distal digits and short first digits arising from the second digits (tree frog hands and feet), together with conductive deafness, short stature, and mild mental retardation.^{1,2} Affected males invariably have a distinct phenotype, and heterozygous carrier females frequently exhibit a mild phenotype with an estimated penetrance of ~80%.³⁻⁵

The gene for OPD-I has been mapped to the Xq27-28 region by linkage analyses in two families. Hoar *et al*⁶ localised the OPD-I gene to a region distal to DXS100 on Xq25, with a maximum lod score of 1.20 at $\theta=0$ for DXS86 on Xq26 and for DXS304 and DXS15 on Xq28. Biancalana *et al*⁷ assigned the OPD-I gene to a region distal to DXS539 on Xq27, with a maximum lod score of 1.99 at $\theta=0$ for DXS305 and DXS52 on Xq28, and excluded linkage to DXS86 on Xq26. These findings suggest that the gene for OPD-I resides in the approximately 12 Mb region distal to DXS539 on Xq27, with a combined lod score of 3.19. Here, we report a Japanese family with OPD-I and refine the OPD-I critical region.

CASE REPORTS

The family pedigree is shown in fig 1. Case I.1 was dead and, allegedly, had had clinical features compatible with OPD-I. Case II.3 exhibited mild but definite supraorbital ridges and bilateral short first toes. Case III.2 showed overt supraorbital ridges, bilateral short first toes, and hearing loss. Cases IV.1 and IV.2 had typical OPD-I features such as supraorbital ridges, flat nasal bridge, hypertelorism, downward slanting palpebral fissures, thick and arched eyebrows, microtia, spatulate distal digits, short first digits arising from the second digits, bilateral conductive deafness, pectus excavatum, and short stature. Mental development appeared normal in case IV.1 and mildly retarded in case IV.2. Other family members had no discernible abnormalities. The G banded karyotype was normal in lymphocytes of cases I.2, II.3, III.2, IV.1, and IV.2.

Microsatellite genotyping was performed for a total of 18 loci on Xq26-28 (fig 1), after obtaining appropriate informed consent. In brief, leucocyte genomic DNA from nine family members was amplified by the polymerase chain reaction (PCR) with fluorescently labelled forward primers and unlabelled reverse primers, and the PCR products were determined for the product size on an ABI PRISM 310 autosequencer using GeneScan (Applied Biosystems, <http://www.appliedbiosystems.com/>). The primer sequences and the PCR conditions have been reported in Genome Database (<http://www.gdb.org/>), and the locus order is primarily based on the report of the Sixth International Workshop on X Chromosome Mapping,⁷ the Génethon genetic map (<http://www.genethon.fr/>), and the Cedar Centre genetic map (<http://cedar.genetics.soton.ac.uk/pub/chromX/map.html>). Consequently, eight recombination events were observed in

four female meioses, and a haplotype pattern for eight loci on a roughly 6 Mb region between DXS8011 and DXS1108 was shared in common by two boys with the typical OPD-I phenotype (cases IV.1 and IV.2) and two obligate carrier females with a mild or overt OPD-I phenotype (cases II.3 and III.2). This particular haplotype was absent in four normal males (cases II.1, II.2, II.4, and III.1) and in one normal female who should be free from a mutant OPD-I gene (case I.2). Two point linkage analysis was performed with the program MLINK of the LINKAGE package version 5.10⁸ under the assumption of 100% penetrance in affected males and 80% penetrance in carrier females and showed a maximum lod score of 0.90 at $\theta=0$ for DXS1177, DXS15, BGN, DXS1073, and DXS8087.

The X inactivation pattern was examined in the female family members by previously described methods.^{9,10} Analysis of the methylation pattern of the *AR* gene showed that cases I.2 and II.3 had random X inactivation with the ratio of inactivation between the two X chromosomes being 60%:40% and 71%:29%, respectively; however, it was not informative in case III.2 because of lack of heterozygosity. Analysis of the methylation pattern of the *PGK1* gene indicated skewed X inactivation in case III.2. The results of the X inactivation pattern, though examined for leucocytes, were consistent with random expression of the mutant OPD-I allele in case II.3 with a mild OPD-I phenotype and preferential expression of the mutant OPD-I allele in case III.2 with an overt OPD-I phenotype.

SUMMARY

In summary, the present study suggests that the OPD-I critical region is further narrowed down from the ~12 Mb region distal to DXS539 to the ~6 Mb region between DXS8011 and DXS1108, with a combined maximum lod score of 4.09. Further studies will permit a better localisation of the gene for OPD-I.

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Abbreviations: OPD-I, otopalatodigital syndrome type I

Figure 1 Family with otopalatodigital syndrome type I (OPD-I). Black squares indicate males with the typical OPD-I phenotype, circles with a dot depict obligate carrier females with a mild or overt OPD-I phenotype, and white squares and circles represent clinically normal subjects. The loci examined at Xq26-28 are shown at the bottom right. DXYS154 and DXYS225 lie in the long arm pseudoautosomal region, and the remaining 16 loci reside in the X differential region. The alleles are arbitrary, indicated by Arabic numbers according to their sizes. The region between DXS8011 and DXS1108 is shared by affected males and females and is absent in clinically normal subjects examined.

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