Possible genetic heterogeneity in X linked hypohidrotic ectodermal dysplasia

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Abstract

Hypohidrotic ectodermal dysplasia has been mapped to Xq11-q13 by linkage studies and by a translocation in a manifesting female. We report a family with hypohidrotic ectodermal dysplasia in which the disease did not segregate with this region of the X chromosome as expected. Ten DNA probes which are localised between Xp11 and Xq22 were used in the investigation. The difficulties in diagnosing the carrier state in this condition and the possibility of non-allelic heterogeneity are discussed.

Hypohidrotic ectodermal dysplasia (HED) was first described by Thurnam¹ in 1848 and was recognised to be an X linked disorder by Thadini in 1921.² The findings in affected males are deficiency of eccrine sweat glands, anodontia or oligodontia with conical teeth, sparse scalp hair, and absent body hair. There is a distinctive face with a depressed nasal bridge and periorbital wrinkling and pigmentation.³ Subcutaneous fat is often diminished and over a third of the boys have abnormalities of the breast including absent or accessory nipples. Affected males have recurrent chest infections, failure to thrive, and life threatening prexias.

Female carriers of the disorder may have dental abnormalities, patchy scalp or body hair, breast abnormalities, and areas with sweat gland deficiency. Dental abnormalities were found in 78% of women examined in one series of 46 obligate carriers.⁴ Areas

where sweat glands are absent can be shown using the starch and iodine whole back sweat test described by Happle and Frosch.⁵

The first linkage study of HED was carried out by MacDermot *et al*,⁶ who found linkage to *DXYS1* with a lod score of 2.7 at $\theta=0.06$. Shortly after this, Kolvraa *et al*⁷ published a lod score of 2.4 at $\theta=0$ between the disease locus and *DXS146*. Further studies have confirmed a recombination distance of approximately 5 cM between the disease locus and *DXYS1*.⁸⁻¹⁰ Thirty-six families have been studied by Zonana *et al*¹⁰ generating a lod score of 14.84 at $\theta=0.01$ between the disease locus and *DXS159*, 13.44 at $\theta=0.02$ between the disease locus and *PGK1*, and 11.38 at $\theta=0.02$ between the disease locus and *DXS72*. There has been no evidence from these studies of non-allelic heterogeneity in the condition.

A manifesting female with an X;9 translocation was described at the first Human Gene Mapping meeting.¹¹ A cell line from this female was later traced and the breakpoint found to be at Xq13.1,¹² which is in keeping with the linkage data. DNA analysis has shown that the translocation breakpoint is between *DXS159* and *PGK1*.^{13 14}

We describe a family with a diagnosis of X linked HED in which the disease does not segregate with any marker from a panel of 10 polymorphic markers between Xp11 and Xq22.

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Received for publication 6 November 1989.
Revised version accepted for publication 26 January 1990.

The results for the polymorphisms detected by the probes cpX289 and pSPT/PGK are shown on the pedigree. + denotes presence and - absence of a polymorphic site. The upper probe is cpX289 (*DXS159*) and the lower probe is pSPT/PGK (*PGK1*).

Materials and methods

FAMILY MEMBERS

The pedigree of the family is shown in the figure. The affected male III·1 had few conical shaped teeth and fine, sparse hair. He had periorbital pigmentation and absent nipples. His parents gave a history of poor sweating and heat intolerance. A starch and iodine sweat test showed that although sweat pores were absent from the nape of his neck they were present over most of his back. Fingertip impressions were made in dental impression material. The sweat pore count was normal and the dermatoglyphic pattern was well preserved. In addition to the findings which led to the diagnosis of hypohidrotic ectodermal dysplasia, he had reflux nephropathy secondary to ureteric valves and had a unilateral nephrectomy because of this.

His mother lacked both mandibular first premolars and the left lateral maxillary incisor. Her right lateral maxillary incisor was abnormally pointed and both mandibular incisors were small. She had pale, fine hair and was noted to have an accessory nipple. Both subjects in generation I were reported to be normal but were not examined.

Subject II·3 lacked both upper lateral incisors. She had pale, fine hair and eczema. The third sister, II·4, lacked a right upper lateral incisor and her left upper lateral incisor had been extracted because it was small and pointed. Her appearance differed from her two sisters as she had thicker, dark hair. Her sons, dizygotic twins, have no features of the condition.

A whole back sweat test was carried out on all three sisters and was normal. Dental x rays were examined from all four women. There was definite taurodontism in subject II·1 and a suggestion of taurodontism in subjects I·2, II·3, and II·4.

Using the criteria of two missing or abnormally shaped teeth as diagnostic of carrier status when there is a family history, all three sisters were diagnosed as carriers. The accessory nipple in subject II·1 was further evidence that she is a gene carrier.

DNA ANALYSIS

The probes used to detect restriction fragment length polymorphisms are shown in the table. Details of all of these probes are given in the report of the Ninth International Workshop on Human Gene Mapping.¹⁶ The probe pLG3¹⁷ was used to confirm paternity. DNA extraction, restriction endonuclease digestion, electrophoresis, blotting, and hybridisation were carried out by standard procedures.¹⁸

Results

The haplotype results are shown in the table. The order of loci (*DXS146-DXS1-DXS106-DXS159-PGK1-DXS72-DXYS1-DXS3-DXS94-DXS17*) is based on studies of somatic cell hybrids, deletions, and recombinant chromosomes.^{13 14 19 20} Recombinations have occurred within this haplotype in four out of six female meioses. In the meiosis leading to II·1 a recombination has occurred between *DXS72* and *DXYS1*. In the meiosis leading to II·4 a recombination has occurred between *DXYS1* and *DXS3*. In the meiosis leading to III·1 a recombination has occurred between *DXYS1* and *DXS94*. Finally, in the meiosis leading to III·2 a recombination has occurred between *DXS106* and *PGK1*.

The three sisters have inherited the same maternal X chromosome at the *DXYS1* locus, but not for the haplotype from *DXS72* to *DXS146* or for the *DXS3* locus, the first locus tested distal to *DXYS1*. Their mother is not heterozygous for polymorphisms at *DXS94* or *DXS17*. The affected boy III·1 has inherited the region detected by *DXYS1* from his grandfather. The two normal boys in generation III also inherited this region of the X chromosome from their grandfather.

The meiosis leading to the affected male was informative for the polymorphisms detected by cpX289 and pSPT/PGK at *DXS159* and *PGK1*. The affected male inherited the grandpaternal alleles at both of these loci. The two normal males in genera-

The probes used at each loci are listed as a haplotype. + indicates the presence and - absence of a polymorphic site. The numbering of the subjects corresponds to the pedigree shown in the figure. The paternal haplotype is shown on the right for each of the females in generation II.

Locus	Probe	I·1	I·2	II·1	II·3	II·4	III·1	III·2	III·3
<i>DXS146</i>	pTAK8	+	- +	- +	++	++	+	+	+
<i>DXS1</i>	p8	+	++	++	++	++	+	+	+
<i>DXS106</i>	cpX203	-	- +	-	+	+	-	+	-
<i>DXS159</i>	cpX289*	+	- +	- +	++	++	+	+	+
<i>PGK1</i>	pSPT/PGK	+	-	- +	-	-	+	+	+
<i>DXS72</i>	pX65H7	-	+	+	-	-	-	-	-
<i>DXYS1</i>	pDP34	+	+	- +	- +	- +	+	+	+
<i>DXS3</i>	19.2	+	- +	++	++	+	+	+	+
<i>DXS94</i>	pXG12	-	+	+	+	+	+	-	-
<i>DXS17</i>	S21	-	++	-	+	+	+	-	-

*The polymorphism described by Arveiler *et al*¹⁵ was detected using the probe cpX289 not cpX73. cpX289 has been reassigned *DXS159* and not *DXS162* as stated in the report of the Ninth International Workshop on Human Gene Mapping.

tion III also inherited the grandpaternal allele at *PGK1*; their mother was not informative for the polymorphism detected by cpX289 at *DXS159*.

Discussion

There is good evidence that cpX289 (*DXS159*) and pSPT/PGK (*PGK1*) flank the HED locus, but in this family neither probe segregates with the disease locus. The crucial factors in the interpretation of the information in this family are the diagnosis of HED in the affected male, the assignment of carrier status in his mother and her two sisters, and paternity.

In this family there is one boy with major abnormalities and three females with minor abnormalities of teeth and hair. The differential diagnosis is between X linked HED and an autosomal dominant ectodermal dysplasia. The diagnosis of Rapp-Hodgkin syndrome (McKusick 12940), which is autosomal dominant, was considered. The features of Rapp-Hodgkin syndrome are hypohidrotic ectodermal dysplasia associated with clefting of the lip or palate, narrow nose, small mouth, short stature, and dystrophic nails. The hair in this condition has been described as coarse, wiry, and brittle in infancy but progressive hair loss leads to baldness by the late teens.²¹⁻²³ In contrast, the affected boy in this family had sparse, fine hair, there were no signs of balding in his mother or aunts, and no family members had a cleft lip, cleft palate, or dystrophic nails. Neither were there any specific features of any other ectodermal dysplasia in this family.

The affected male in this family has many of the classical features of X linked HED but is not completely typical because his whole back sweat test and finger tip impressions show that he does have sweat pores. His hair, teeth, periorbital pigmentation, and absence of nipples, however, all support the diagnosis. Renal anomalies have not been described before in the condition and were considered a coincidental finding. The most likely diagnosis in this family, however, remains X linked HED. If this is the case it could be a new mutation in the affected male, a new mutation in his mother, or, as thought on clinical grounds, all three sisters could be gene carriers.

The mother of the affected boy is heterozygous for the polymorphisms detected by cpX289 and pSPT/PGK. Her paternity was checked using pAG3. In addition, the paternal allele for pSPT/PGK is certain as her mother is homozygous for this probe. The affected male has received the grandpaternal allele for both of these probes. One explanation is that she carries a new mutation on the paternal X chromosome. If this is correct then either her two sisters are carriers as a result of gonadal mosaicism, or they are not carriers despite the dental

abnormalities. The two normal sons of II·4, assigned a carrier on the basis of dental abnormalities, have inherited the grandpaternal haplotype for these two probes and, therefore, gonadal mosaicism alone does not account for all of the findings. This means that if II·1 carries a new mutation on the paternal X chromosome, which is compatible with the mapping information on HED, then her sisters are not carriers.

Alternative explanations for III·1 receiving the grandpaternal allele for cpX289 and pSPT/PGK are a double recombination between these probes or that the disease in this family is at a separate locus. Data from other family members are not consistent with a disease localisation between cpX289 and pSPT/PGK as the three sisters have not inherited the same maternal haplotype for probes around this region.

The prior probabilities of the women being carriers of HED are greater than the probability of their dental abnormalities being incidental findings, as only 0·6% of the population have three absent permanent teeth and only 2% have two absent permanent teeth, excluding third molars.²⁴ If all three sisters are carriers of the disorder, then a second locus for HED remains the most likely explanation. However, families from Britain, Switzerland, Finland, Denmark, France, and the United States have been studied without any suggestion of non-allelic heterogeneity.

Two recombinations have been reported between the disease locus and *DXS159*. The first recombinant subject⁹ was a 56 year old female who was assigned a carrier because she had dry skin and a slight decrease in sweat pores. The second recombinant subject was an edentulous 60 year old female who gave a history of two missing permanent teeth but whose dental records were not available for review.¹⁰ The meiosis leading to this female also showed a recombination with *PGK1*. If these females are excluded from the analysis, there have been no recombinations between the disease locus and *DXS159* or *PGK1*. It seems probable that these two women are not carriers of the disease. This highlights the difficulties of accurate assignment of carrier status.

In conclusion, there are two possible explanations of the haplotype results in this family. The first possibility is that the sisters II·3 and II·4 are not gene carriers and the second possibility is that there is non-allelic heterogeneity. Either of these explanations raises concern about counselling of females in families with HED and use of linked DNA markers for predictive testing. We suggest that if DNA information from a woman is used to assign phase within a family then more stringent criteria are required for diagnosis of carrier state.

As this family raises the possibility of a second locus for HED the use of cpX289 and pSPT/PGK for clinical testing should be treated with caution in small families where it is not possible to show that the disease is segregating with the region Xq11—q13.

We would like to thank the following for providing the probes: P Pearson, P Szabo, M Upadhyaya, D Page, Y Boyd, T Kruse, B Vogelstein, A A Jeffreys, D Drayna, G Bruns, and B Schmeckpeper. We wish to acknowledge the support of Action Research for the Crippled Child.

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