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ORIGINAL INVESTIGATION

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Nance-Horan syndrome: linkage analysis in 4 families refines localization in Xp22.31–p22.13 region

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Abstract Nance-Horan syndrome (NHS) is an X-linked disease characterized by severe congenital cataract with microcornea, distinctive dental findings, evocative facial features and mental impairment in some cases. Previous linkage studies have placed the NHS gene in a large region from DXS143 (Xp22.31) to DXS451 (Xp22.13). To refine this localization further, we have performed linkage analysis in four families. As the maximum expected Lod score is reached in each family for several markers in the Xp22.31–p22.13 region and linkage to the rest of the X chromosome can be excluded, our study shows that NHS is a genetically homogeneous condition. An overall maximum two-point Lod score of 9.36 ($\theta = 0.00$) is obtained with two closely linked markers taken together, DXS207 and DXS1053 in Xp22.2. Recombinant haplotypes indicate that the NHS gene lies between DXS85 and DXS1226. Multipoint analysis yields a maximum Lod score of 9.45 with the support interval spanning a 15-cM region that includes DXS16 and DXS1229/365. The deletion map of the Xp22.3–Xp21.3 region suggests that the phenotypic variability of NHS is not related to gross rearrangement of sequences of varying size but rather to allelic mutations in a single gene, presumably located proximal to DXS16 and distal to DXS1226. Comparison with the map position of the mouse *Xcat* mutation supports the location of the NHS gene between the GRPR and PDHA1 genes in Xp22.2.

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Introduction

Nance-Horan syndrome (NHS; MIM 302350) or cataract-dental syndrome is a rare X-linked condition (Nance et al. 1974; Horan and Billson 1974; Van Dorp and Delleman 1979; Bixler et al. 1984; Seow et al. 1985; Walpole et al 1990; Lewis 1989; Zhu et al. 1990). It is characterized by (1) bilateral congenital cataract, generally associated with microcornea or even microphthalmia, (2) distinctive dental findings consisting mainly of characteristic crown-shape anomalies of the permanent teeth and (3) evocative facial features. Mild or moderate intellectual handicap has been mentioned incidentally in some reports but we consider mental retardation to be more frequent and more severe than that recorded. Carrier females have thin posterior Y-sutural opacities or, more rarely, a true cataract and/or slight dental anomalies. The combined data of three previous linkage studies (Stambolian et al. 1990; Zhu et al. 1990; Bergen et al. 1994) have placed the NHS gene in a large region of approximately 30 cM, from DXS143 (Xp22.31) to DXS451 (Xp22.13).

To refine this localization further, we have performed two-point and multipoint linkage analysis by using highly informative microsatellite markers in four unrelated families. We report our results and discuss them in relation to the deletion map of the Xp22.3–p21.3 region and the comparative map position of the putative murine homologue.

Materials and methods

Family data

Four independent multiplex families were investigated (Fig. 1). The first two families were referred to us for inclusion in a research programme on X-linked mental retardation on the basis of mental impairment associated with congenital cataract. However, NHS was recognized because of typical dental anomalies and facial dysmorphism on physical examination. Families 3 and 4 were referred as typical NHS families. In families 1, 2 and 3, all living patients were examined by one of us and histories recorded in medical reports were evaluated. In family 4, diagnostic criteria were verified in at least one patient. Males were diagnosed as being affected on

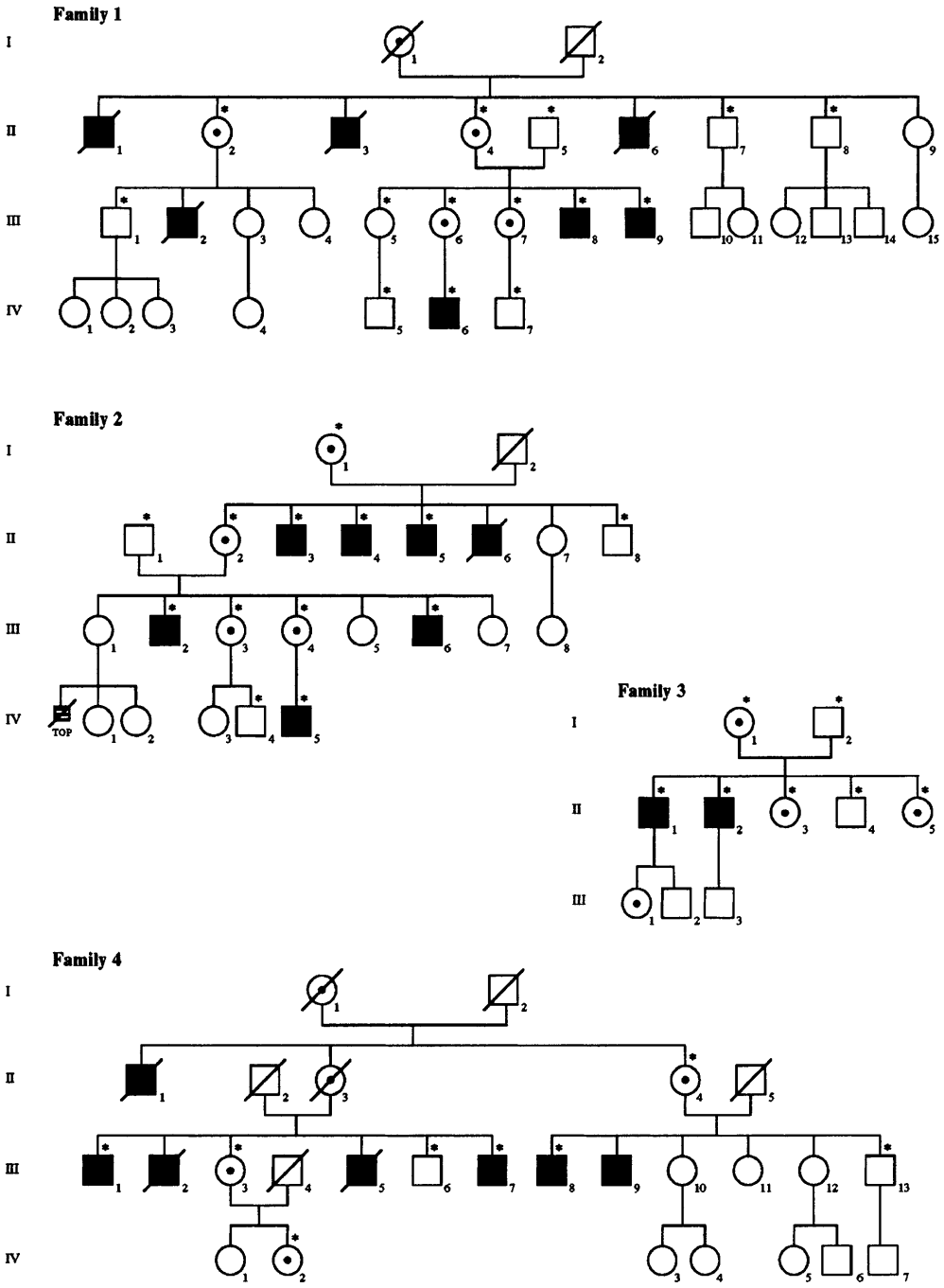


Fig. 1 Pedigrees of the four NHS families. Individuals are designated with *generation* and *pedigree numbers*. *Darkened* and *white symbols* represent affected and unaffected individuals, respectively. In family 2, termination of pregnancy (*TOP*) was justified by polymalformation. *Asterisks* indicate family members for whom DNA was available for genotypic analysis

the basis of the following major criteria: (1) history of congenital bilateral cataract, most often severe, requiring surgery and resulting in poor vision, (2) characteristic dental anomalies documented by physical examination, orthopantomograph and moulding and (3) typical facial features. Three of the families studied were typical NHS families. In family 2, the ocular and dental anomalies were less severe. All patients from families 1 and 2 had mental handicap that varied greatly in degree within the same family, some patients being profoundly retarded with autistic behaviour. High resolution R- and G-banding chromosome analysis performed in one male in each family failed to detect either gross or submicroscopic chromosomal rearrangements. Fragile-X syndrome (FRAX-A) and FRAX-E MR were excluded by the molecular technique.

Female carrier status was assessed from family history (8 obligate carriers) or clinical data (6 females; Fig. 1). Carrier status was assigned according to one or two of the following criteria: (1) posterior lenticular opacities, mostly involving the Y suture, sometimes associated with microcornea (individuals III.3 and IV.2 in family 4), and (2) typical dental anomalies that were less severe than those in the males but more obvious and more marked than the ocular stigmata in two of the women (III.7 in family 1 and II.3 in family 3). Forty-two family members were available for DNA analysis: 14 affected and 13 unaffected males, 14 carrier females and one established carrier's daughter of undetermined status who had a normal son (Fig. 1).

DNA analysis

Venous blood was collected from each consenting family member. Genomic DNA was prepared from lymphocytes according to standard procedures.

In families 1, 3 and 4, 19 single tandem repeat markers located in the previously defined candidate region were tested. However, the rest of the X chromosome was also analysed at the same time in order to exclude genetic heterogeneity. Polymorphic markers located in areas not covered in the previous studies were chosen, so that information was available every 5 cM along the X chromosome. For family 2, initially referred for a specific form of X-linked mental retardation, the whole X chromosome was studied. Finally, 51 microsatellites were used, 27 being from the Xp22.32 –p21.1 region, for the four families. Primer sequences and information were taken from the Genome Data Base (GDB, Baltimore).

The microsatellite repeats were assayed by polymerase chain reaction (PCR) amplification. PCRs were carried out in a total volume of 25 µl containing: 100 ng DNA, 50 mM KCl, 10 mM TRIS-HCl, 1.5 mM $MgCl_2$, 125 µM of each dNTP, 0.01% gelatin, 25 pmols of each primer, 1 µCi α-33P-dCTP, 1.25 IU *Taq* DNA Polymerase (Eurobio), plus 10% dimethyl sulphoxide in cases where the annealing temperature reached 65°C. The annealing temperature was optimized for each pair of primers and varied from 52°C to 65°C. An initial denaturation of 5 min at 94°C was followed by 30 cycles of 1 min at 94°C, 1 min at the annealing temperature and 2 min at 72°C and a final extension at 72°C for 7 min. Aliquots of 3 µl of the denatured product were loaded onto a 6% polyacrylamide/7.5 M urea sequencing gel. The gel was dried and subjected to autoradiography for 24 h.

Linkage study

Pairwise linkage analysis was performed by means of the LINKAGE software version 5.1. Simulation determined a maximum possible Lod score of 9.36 at a recombination frequency of $\theta = 0$ for a fully informative marker with four equally frequent alleles (3.14, 3.01, 1.20 and 2.01 for families 1, 2, 3 and 4, respectively). Normal and disease allele frequencies were set at 0.9999 and 0.0001, respectively. Disease penetrance was set at 1 in affected males. Since the proportion of symptomatic versus asymptomatic carriers was unknown, NHS was considered as an X-linked recessive condition and penetrance in females was set at 0. The MLINK and ILINK programs were used to calculate Lod scores between the disease gene and each marker. Multipoint analysis was performed with the LINKMAP option of the FASTLINK package by using the marker order DXS85–DXS16–DXS207/1053–DXS1229/365–DXS1226 according to the report of the X Chromosome Mapping Committee (Nelson et al. 1995). Recombination fractions between adjacent loci were obtained from the Genome Interactive Database (1995). Genotypes for all individuals are available upon request.

Results

We focussed our linkage study on the previously defined region of localization. However, the rest of the X chromosome was also analysed in order to exclude genetic heterogeneity. Of the 51 microsatellites tested along the whole X chromosome, only 5 were completely uninformative in all four families. Linkage to the Xp22.31–p22.13 region was confirmed, as positive Lod scores were obtained in all four families for nearly all the markers tested and, in each family, the maximum expected Lod score at $\theta = 0$ was reached for several markers in this region. Linkage to the rest of the X chromosome was excluded (data not shown). Results of the two-point Lod scores for linkage between the NHS gene and Xp22.32–p22.13 markers in all four families are summarized in Table 1. The most significant Lod score was obtained at DXS16 and DXS987 loci ($Z_{max} = 9.06$, $\theta = 0$). Since some of the markers studied (DXS207/DXS1053, DXS1229/DXS365, DXS1052/DXS274) are localized in pairs at the

Table 1 Pairwise Lod scores between NHS and Xp22.32–p22.13 markers. The order of the markers is according to the map location from telomere (*top*) to centromere (*bottom*)

Locus	Lod score at θ =								θ_{max}	Z_{max}
	0.00	0.001	0.01	0.05	0.1	0.2	0.3	0.4		
KAL	–∞	–6.00	–2.08	0.36	1.11	1.33	0.97	0.40	0.17	1.35
DXS85	–∞	–0.79	1.14	2.18	2.32	1.94	1.22	0.43	0.09	2.32
DXS1224	3.39	3.38	3.32	3.06	2.72	2.00	1.23	0.47	0.00	3.39
DXS16	9.06	9.04	8.90	8.27	7.45	5.67	3.71	1.65	0.00	9.06
DXS987	9.06	9.04	8.90	8.27	7.45	5.67	3.71	1.65	0.00	9.06
DXS207	7.85	7.84	7.72	7.16	6.43	4.88	3.19	1.45	0.00	7.85
DXS207/1053	9.36	9.34	9.20	8.55	7.70	5.87	3.86	1.73	0.00	9.36
DXS1053	7.08	7.06	6.94	6.40	5.70	4.20	2.59	0.99	0.00	7.08
DXS43	4.87	4.86	4.78	4.44	4.00	3.07	2.03	0.92	0.00	4.87
DXS418	6.90	6.89	6.78	6.29	5.64	4.24	2.70	1.12	0.00	6.90
DXS999	4.66	4.65	4.58	4.26	3.84	2.97	2.02	0.98	0.00	4.66
DXS7163	7.01	7.00	6.88	6.33	5.61	4.08	2.44	0.90	0.00	7.01
DXS1229	5.57	5.56	5.47	5.04	4.50	3.34	2.09	0.83	0.00	5.57
DXS1229/365	8.28	8.26	8.12	7.47	6.63	4.85	2.94	1.09	0.00	8.28
DXS365	7.98	7.96	7.83	7.22	6.42	4.74	2.95	1.17	0.00	7.98
DXS1052	5.15	5.14	5.05	4.67	4.16	3.07	1.87	0.67	0.00	5.15
DXS1052/274	7.85	7.84	7.72	7.18	6.47	4.95	3.27	1.50	0.00	7.85
DXS274	4.83	4.82	4.74	4.40	3.95	2.99	1.95	0.88	0.00	4.83
DXS1226	–∞	2.20	3.12	3.46	3.31	2.64	1.78	0.81	0.05	3.46
DXS989	4.64	4.63	4.56	4.23	3.80	2.90	1.89	0.82	0.00	4.64
DXS451	–∞	1.24	3.14	4.06	4.05	3.32	2.23	0.98	0.07	4.11
DXS1028	–∞	2.54	4.41	5.23	5.08	4.07	2.65	1.07	0.06	5.24

same position on the X chromosome and have a genetic distance of 0 cM, we used combined haplotypes determined by genotypes from both markers of each pair in the linkage calculations to improve informativity. This yielded the maximum expected Lod score for all four families (Z_{max} = 9.36, θ = 0) at locus DXS207/DXS1053.

Haplotypes defined by the loci listed in the Table 1 were analysed for recombination events. Only three recombinants with markers of the Xp22.32–p22.13 region were observed in three affected males of family 2. The nearest flanking loci showing recombination were DXS85 on the telomeric side (patients III.2 and III.6) and DXS1226 on the centromeric side (patient II.4). Thus, the smallest interval containing the NHS locus was defined by the 18-cM interval bounded by these markers.

Multipoint analysis was performed with the informative markers located in this candidate region. The results of a six-point analysis performed between the disease locus and five markers in the order indicated, taking the recombinant markers and three of the most informative markers at a time, are shown in Fig. 2. Multipoint linkage analysis did not reach a significantly higher Lod score, because these loci were all almost fully informative in the four families. It yielded a peak Lod score of 9.45 when the disease gene was placed in the DXS16–DXS207/1053 interval (θ = 0.05) or between DXS207/1053 and DXS1229/365 (θ = 0.00) and indicated that the most likely location for the NHS gene was between DXS16 and DXS1229/365. However, if we drop 1 Lod unit below the maximum, the support interval spans a 15-cM region, 3 cM/telomeric to DXS16 and 4 cM centromeric to DXS1229/365.

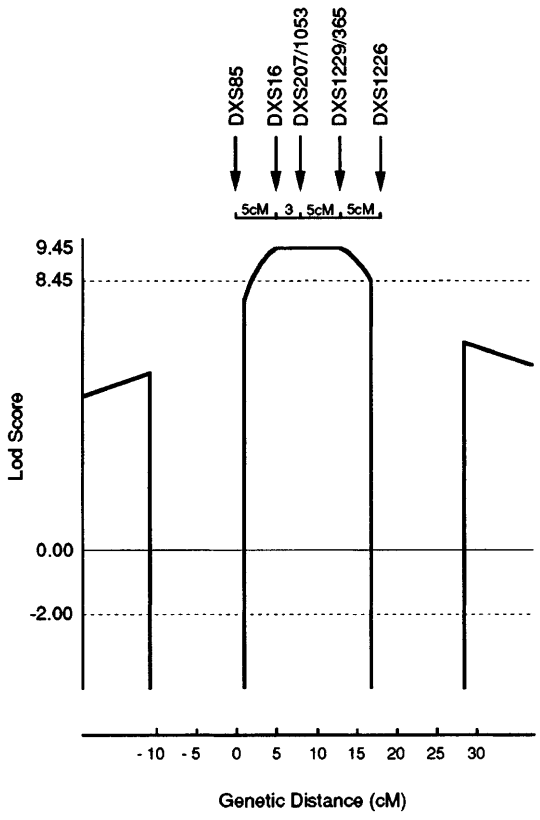
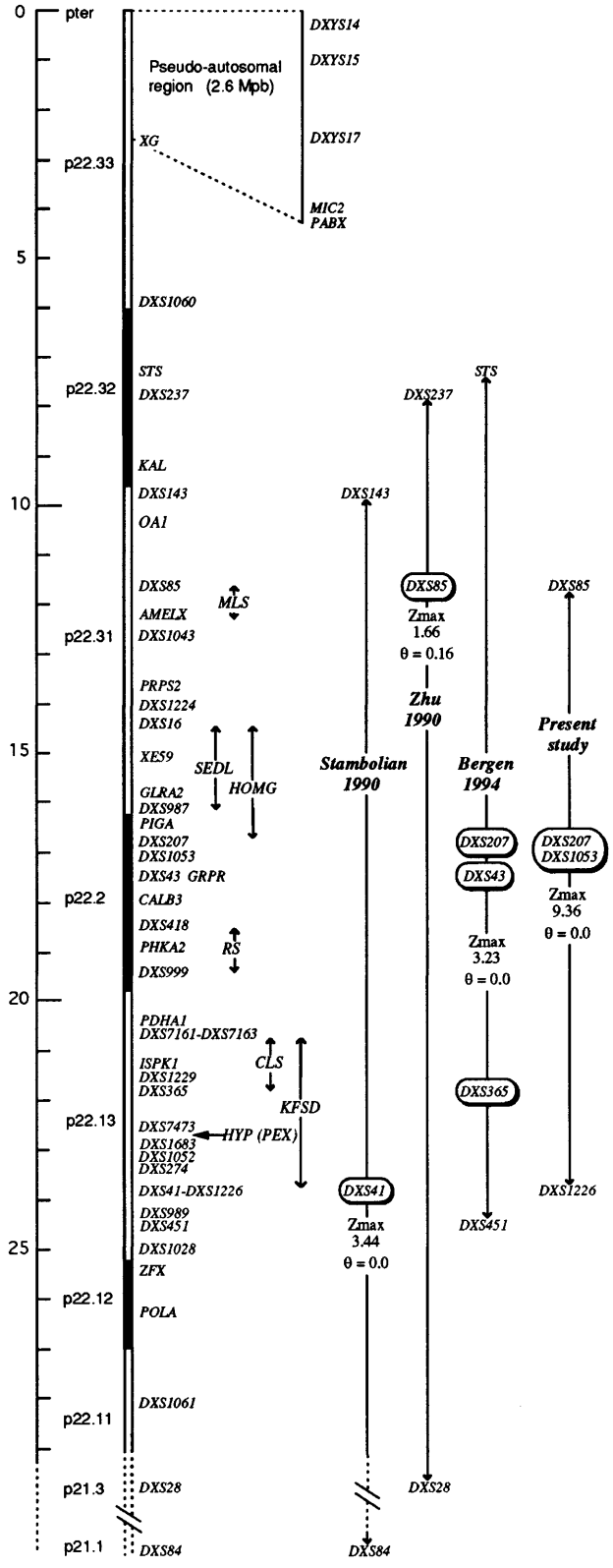


Fig. 2 Multipoint Lod scores of the NHS locus versus Xp22.31–p22.13 markers using the LINKMAP program. The order of the markers is according to the map location from telomere (*left*) to centromere (*right*), DXS85 being arbitrarily set at 0 cM. The curve asymptotically approaches infinity at marker loci at which recombinants occurred and reaches a maximum Lod score of 9.45 at intervals DXS16–DXS207/1053 and DXS207/1053–DXS1229/365

Discussion

In 1990, two teams separately published a linkage analysis in NHS. Stambolian et al. (1990) has studied three families and demonstrated that the NHS gene is located in a very large region extending over more than 30 Mb from DXS143 in Xp22.3 to DXS84 in Xp21.1 and that it is linked to locus DXS41 (two-point Z_{max} of 3.44 at θ = 0 and a multilocus score of 7.07). Zhu et al. (1990) have reported a weak linkage to locus DXS85 (Z_{max} of 1.662 at θ = 0.16) in one large family and a region of localization from Xp22.32 to Xp22.11. More recently, a family has been reported with a tight linkage to several loci of the same region (Z_{max} of 3.23 at θ = 0 with DXS365, DXS43 and DXS207) and recombinants with STS (STS gene) on the telomeric side and DXS451, reducing the region of localization to the centromeric side (Bergen et al. 1994). These combined data place the NHS gene in a region that remains large (Fig. 3), from DXS143 (Xp22.31) to DXS451 (Xp22.13). The present study has confirmed the location of the disease gene in the Xp22.31–p22.13 region, as tight linkage is obtained with several markers that map to the previously defined region and the DXS207-DXS1053 region generates the highest cumulative two-point score. Crossover analysis places the NHS locus in a shorter interval of approximately 12 Mb, from DXS85 to DXS1226, and nearly halves the location interval. Multipoint analysis yields a NHS confidence location interval extending from 3 cM distal to DXS16 to 4 cM proximal to DXS1229/365, with the NHS gene most probably situated between DXS16 and DXS1229/365, although a location in the two flanking intervals within the candidate region cannot be excluded.

All four families studied fulfil the diagnostic criteria of NHS. Three of them are affected by classical NHS. The patients in family 2 have less severe ocular and dental anomalies and all patients from families 1 and 2 suffer from mental handicap, three of them being profoundly retarded with severe autistic symptoms. In this study, the disease gene maps to the Xp22.31–p22.13 region in each family. Genetic heterogeneity of NHS is thus almost certainly excluded, given the results of the previous studies. Another explanation for the variability observed in the clinical picture must therefore be sought. Deletions of variable sizes, presumably involving adjacent disease genes, have been suggested (Warburg 1989). However, this hypothesis is no longer supported by the deletion map of this region. The distal short arm of the X-chromosome shows a very high frequency of chromosomal rearrangements (Ballabio and Andria 1992) but deletion breakpoints are



◀ **Fig. 3** Schematic regional physical map of X chromosome from Xpter to Xp22.11 (after Nelson et al. 1995). *Left* Arbitrary scale approximating the distance in Mb and location of some anonymous markers and identified genes along the X chromosome, which is represented as a *solid line* with the successive bands in *white* and *dark*. The position of unidentified disease genes located in this region is represented on the *vertical line* between the flanking loci. *Right* Regional localization of the NHS gene suggested by the present study compared with previous linkage analyses. The loci where the maximum Lod scores for two-point analysis were reached are *ringed*. Gene symbols: *HYP* X-linked hypophosphatemia with vitamin-D-resistant rickets, *AMELX* amelogenin, *PHKA2* liver alpha subunit of phosphorylase kinase, *PIGA* phosphatidyl inositol glycan class A, *GRPR* gastrin-releasing peptide receptor, *PDHA1* pyruvate dehydrogenase E1 alpha subunit, *GLRA2* glycine receptor alpha2 subunit, *PRPS2* phosphoribosyl pyrophosphate synthetase 2

clustered in two genomic regions, Xp22.3 and Xp21.3, which are extremely deletion prone in contrast to the stretch of DNA between them (Xp22.2–22.1; Schaefer et al. 1993; Ferrero et al. 1995). Since the deletions in male patients never extend proximal to DXS85 and distal to the alpha DNA polymerase (POLA) gene in Xp22.12 and are not associated with clinical features of NHS, it has been suggested that the NHS locus lies within the Xp22.2–p22.1 region (Stambolian et al. 1990). This distal boundary in DXS85 is concordant with the closer telomeric recombination observed in our study (Fig. 3). Breakpoints of X/Y and X/autosomal translocations in females also occur more rarely in this region, defining two wide intervals in a breakpoint-poor region from DXS16 to ZFX in Xp22.12, in which the NHS gene is probably located (Ferrero et al. 1995; Nelson et al. 1995). In our families, none of the sixteen markers studied in the region of 12 Mb between DS85 and DXS1226 (i.e. one marker for every 0.8 Mb) is deleted in affected males, thus excluding very large deletions as the cause of NHS. This finding and the rarity of recombinants in our study and in the other linkage analyses performed in NHS may be attributable to the DNA structure in this region and may have prevented to date the definition of a small chromosomal interval containing the disease gene and therefore positional cloning of the gene. It is thus more likely that the phenotypic variability in NHS is related to allelic mutations in a single gene, presumably located proximal to DXS16 and distal to DXS1226.

No obvious candidate gene for cataract maps in the critical region. Ocular or dental anomalies have been reported in several diseases mapping to chromosome Xp22.31–p22.13 (Fig. 3) but they are different from those of NHS and there is no phenotypic overlap between these conditions and NHS. It is therefore likely that none of these genes is involved in NHS. Because mental impairment is possible in NHS, the localization in the critical region of expressed sequences tags, which are at present derived essentially from brain cDNA libraries, should provide candidate genes. However, it will be necessary to refine the localization by collecting additional families in order to reduce the number of candidate transcripts that have to be studied.

Given the scarcity of the families available for linkage analysis, comparative mapping could lead more rapidly to identification of the NHS gene. It is generally accepted that the mouse mutant *Xcat* is the murine homologue of human NHS; the *Xcat* gene has been mapped to the distal

part of the X chromosome distal to *Hyp* and proximal to *Amel* (Favor and Pretsch 1990; Stambolian et al. 1994). The order of loci in the Xp22.31–p22.13 region in man and the equivalent region in the mouse is relatively conserved, except for the PHKA2 and PIGA genes. The order in man is tel–AMELX–PRPS2–GLRA2–PIGA–GRPR–PHKA2–PDHA1–HYP–cen (Fig. 3), whereas that in mouse is tel–*Amel* (72 cM)–*Prps2* (72 cM)–*Phka2*–*Glra2* (71 cM)–*Grpr* (70 cM)–*Xcat* (68 cM)–*Piga*–*Pdha1* (66 cM)–*Hyp* (65 cM)–cen. This discrepancy might result from the occurrence of a minute chromosomal inversion from mouse to humans in this region, as previously described in the X inactivation centre region, although the localizations of *Piga* and *Phka2* in the mouse are only tentative at the moment. Thus, a comparison between mouse and human maps suggests that the NHS gene could be located between GRPR and PDHA1 in a region of about 3 Mb, in Xp22.2. Furthermore, it establishes that none of these genes can be responsible for NHS, because their murine homologues map to different locations than the mutant *Xcat*. The recombination distances in the mouse consensus map of the X chromosome suggest that the *Xcat* mutation is not the result of a gross rearrangement of sequences but rather of a small alteration (Stambolian et al. 1994). This finding and the small size of the putative critical region for the NHS gene are further arguments for suggesting that NHS results from various molecular defects in a single gene. Cloning of the mouse gene and its subsequent use should facilitate the identification of the human NHS gene.

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