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A second kindred linked to DFNA20 (17q25.3) reduces the genetic interval

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Abstract

A family ascertained in the United States displays significant evidence of linkage to 17q25.3 (maximum two-point LOD score 6.32). The non-syndromic autosomal-dominant hearing-loss loci DFNA20 and DFNA26 map to this region. The 3-unit support interval and haplotype for this USA kindred falls within the interval for DFNA20 and DFNA26 and reduces the region to 6.05 cM, according to the deCode genetic map. The same gene is probably responsible for both DFNA20/DFNA26. In addition, the USH1G locus maps to this region and could be an allelic variant of the gene responsible for DFNA20/DFNA26. Clinical data is presented for this kindred, where hearing-impaired family members present with sloping audiograms with mid- and high-frequency hearing loss, which progresses to hearing loss that affects all frequencies. The mean age of onset of hearing impairment is 13.2 years of age (standard deviation: 4.6 years).

Keywords

17q25.3; autosomal-dominant non-syndromic hearing loss (ADNSHL); DFNA20; DFNA26; progressive hearing loss; USH1G

Non-syndromic hearing loss (NSHL) is the most genetically heterogeneous trait known (1). Over 70 loci have been mapped, and a total of 29 genes have been identified (2,3). For autosomal-dominant non-syndromic hearing loss (ADNSHL) alone, a total of 40 loci have been mapped and 16 genes isolated. This extreme genetic heterogeneity suggests that there are many different processes that can malfunction within the inner ear to cause the hearing-loss phenotype (4).

This article presents a family which maps to 17q25.3. The hearing-loss locus that segregates in this kindred was mapped to a region that is contained within the DFNA20 (Mendelian inheritance in man (MIM) 604717) interval (5). DFNA20 maps to a 12-cM region on 17q25, between markers D17S1806 and D17S668. An additional locus, DFNA26, has also been mapped to this region and overlaps with DFNA20 (6). No information is given on the position of DFNA26 besides its cytogenetic location (17q25) and the fact that it overlaps

with DFNA20. For the previously published family which segregates DFNA20, the hearing-impaired members present with bilateral, sloping, progressive, sensorineural hearing loss, first evident at 6000 and 8000 Hz. No clinical information is provided for the two families which segregate the DFNA26 locus. Hearing loss owing to DFNA20 and DFNA26 is probably a result of the same gene, although it is possible that there may be more than one gene responsible for hearing loss in this region.

Patients and methods

Family and clinical diagnosis

The large American family (6) of Scottish–Irish descent presented in this study displays autosomal dominant bilateral hearing loss. Kindred 6 (Fig. 1) was ascertained at The Rockefeller University. Informed consent was obtained from all study participants. A family history was obtained through both questionnaires and oral interview. Audiometric, medical history and DNA samples were obtained from pedigree members in three generations. The hearing of family members was evaluated through pure-tone audiometry (air and bone conduction). Audiograms from several hearing-impaired family members are displayed in Figs 2 and 3. Hearing-impaired family members 35 years of age present with moderate-to-severe to severe hearing loss in the low frequencies, which slopes to profound hearing loss in the mid and high frequencies (II.8, II.10, III.4, III.5, and III.8) (Fig. 2). Individual III.8 obtained a cochlear implant at 35 years of age. Younger hearing-impaired pedigree members at 9, 10 and 11 years of age present with normal hearing in the low frequencies, mild-to-moderate hearing loss in the mid frequencies and moderate-to-severe to severe hearing loss in the high frequencies (IV.1, IV.3, and IV.4) (Fig. 3). The progression of hearing loss over an 8-year period can be seen for individual IV.1 (Fig. 3); from 9–17 years of age her hearing loss progressed from normal hearing in the low frequencies, moderate hearing loss in the mid frequencies and moderately severe hearing loss in the high frequencies, to mild hearing loss in the low frequencies and severe hearing loss in the mid and high frequencies.

Age of onset was determined by the age at which hearing loss was first documented or by the patient's recollection, whichever date was earlier. The hearing loss in this pedigree has onset from 7 to 21 years of age with an average age of onset of 13.15 years (standard deviation: 4.6 years).

Genotyping and linkage analysis

DNA was extracted from 10 ml of blood using standard techniques (7). A genome scan was carried out on 30 DNA samples at the Center for Inherited Disease Research (CIDR), using the Marshfield Screening set 9 (8). A total of 386 fluorescently labelled simple-tandem-repeat (STRP) markers with an average heterozygosity of 0.76 were genotyped. These markers are spaced approximately 10 cM apart and are located on the 22 autosomes and the X and Y chromosomes.

Linkage analysis was carried out under a fully penetrant autosomal-dominant mode of inheritance with no phenocopies. For the majority of autosomal-dominant hearing-loss families there is reduced penetrance at younger ages with complete penetrance after the

period of onset. As individuals with hearing impairment in this kindred had onset as late as 21 years of age, only unaffected individuals older than 25 years of age were included in the analysis. A disease frequency of 0.001 was used in the analysis. The marker-allele frequencies were estimated from the data by means of both observed and reconstructed genotypes of founders within this pedigree. It should be noted that because almost all family members are genotyped, pedigree 6 is very robust to changes in marker-allele frequencies, with varying marker-allele frequencies having little or no effect on the LOD score results. Two-point linkage analysis was carried out on all autosomal markers from the genome scan using MLINK of the FASTLINK computer package (9). For fine mapping, eight additional markers were selected from the Marshfield map (10). These markers (D17S1839, D17S1603, D17S785, D17S937, D17S802, D17S1847, D17S836 and D17S1806) lie between genome scan markers D17S1301 and D17S784. Marker D17S928 is the most telomeric marker on the genetic map. The data were reanalyzed by means of two-point and multipoint linkage analyses. Multipoint analysis was performed using LINKMAP of the FASTLINK computer package (9). SIMWALK2 (11, 12) was used to generate the haplotypes with the highest likelihood (Fig. 1).

Results

The results of the two-point linkage analysis are displayed in Table 1. From the genome scan data a maximum two-point LOD score of 4.24 with marker D17S928 at $\Theta = 0.04$ was obtained. This is the most telomeric marker on chromosome 17. Flanking marker D17S784 produced a maximum LOD score of 2.68 at $\Theta = 0.05$. After genotyping and analyzing the markers genotyped for fine mapping, a maximum two-point LOD score of 6.32 was obtained at $\Theta = 0$ for marker D17S1806. A graph of the results of the multipoint analysis is displayed in Fig. 4. A maximum multipoint LOD score of 5.61 occurred between markers D17S784 at 116.86cM and D17S928cM at 126.46cM. The 3.0-unit support interval for DFNA20 for pedigree 6 is from 116.86cM to 126.46cM (9.6cM), according to the Marshfield map (10). Based upon examination of haplotypes, the interval to which DFNA20 maps is flanked by recombination events in hearing-impaired individuals at markers D17S784 and D17S928 (Fig. 1). The interval between these two markers is 9.60 cM on the Marshfield map and 6.05 cM on the recently published deCode map (13).

Discussion

The original report on DFNA20 maps this locus between markers D17S1806 and D17S668, which is a 12.05-cM region according to the Marshfield map (5). The analysis of kindred 6 made it possible to reduce the genetic interval for DFNA20 to 9.60 cM (Marshfield map), and to a 6.05-cM region according to the recently published deCode genetic map. The deCode map consists of 1257 meioses, compared to the 182 meioses used to construct the Marshfield maps. It is estimated that the deCode genetic map provides approximately five times the average resolution of the Marshfield map (13). On the deCode map marker D17S784 maps to 129.62 cM and marker D17S928 maps to 135.67cM; the interval between these two markers is 6.05 cM. It is not possible to give the length of the genetic interval according to the deCode map for the original DFNA20 linkage report, as marker D17S1806 was not included on the deCode map.

Two additional kindred USA families display linkage to 17q25, and this locus is denoted by the locus name DFNA26 (6). No information was given on the size of the interval or flanking markers for DFNA26, but DFNA26 overlaps with DFNA20 and they are probably not separate loci.

USH1G overlaps with DFNA20 and DFNA26 (14). It is possible that an allelic variation of the same gene is responsible for USH1G and DFNA20/26. There are three examples where different mutations in the same gene are responsible for both Usher syndrome and non-syndromic hearing loss: allelic mutations in the MYO7A (MIM 276903) gene are responsible for DFNB2 (MIM 600060), DFNA11 (MIM 601317) and USH1B (MIM 276903) (15); allelic mutations of the novel cadherin-like gene CDH23 (MIM 605516) are responsible for DFNB12 (601386) and USH1D (MIM 601067) (16); and the USH1C (MIM 605242) gene is responsible for USH1C (MIM 276904) and DFNB18 (MIM 602092) (17).

Numerous genes map to the DFNA20 interval. Of particular interest are genes that are expressed with the inner ear. Cynthia Morton's Human Cochlear cDNA Library and EST Database (<http://hearing.bwh.harvard.edu/cochlearcnallibrary.htm>) and Karen Steel's Table of gene expression in the developing ear (<http://www.ihr.mrc.ac.uk/Hereditary/genetable/index.html>) provide information on potential candidate genes for DFNA20/DFNA26. According to the Human Genome Project - Santa Cruz sequence-based physical map (18), there is only one gene, alpha-1,4-glucosidase (GAA), which is known to be expressed in the cochlea and that falls within the DFNA20 interval. GAA (MIM 606800) is a lysosomal enzyme involved in the degradation of glycogen within cellular vacuoles. GAA was shown via *in situ* hybridization to be expressed in stage 3 of development in the epithelial cells lining the inner ear of the mouse (19). However, this gene, which is responsible for Pompe disease, is not a strong candidate gene for hearing loss. Identification of the gene for DFNA20/DFNA26 should aid in understanding the mechanism of hearing and hearing loss.

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Fig. 1.

Pedigree drawing of the United States Kindred 6, which segregates DFNA20. The sexes of some of the family members have been changed to protect the anonymity of the family. Black symbols represent individuals with hearing impairment as a result of DFNA20. Open symbols represent unaffected individuals. Haplotypes for the most closely linked simple tandem repeats (STRPs) are shown below each symbol. A question mark indicates an unknown allele. The haplotype segregating with the disease allele is shown in rectangles.

Fig. 2. Audiograms for hearing-impaired family members 35 years of age (II.8, II.10, III.4, III.5 and III.8). The IDs correspond to those in Fig. 1. The denoted age is the time when the audiogram was obtained.

Fig. 3. Audiograms for hearing-impaired family members 11 years of age (IV.1, IV.3, and IV.4). The IDs correspond to those in Fig. 1. The denoted age is the time when the audiogram was obtained. Also displayed are the audiograms for individual IV.1 at 9 and 17 years of age.

Fig. 4.

Results from the multipoint linkage analysis. A maximum multipoint LOD score of 5.61 occurred between markers D17S784 and D17S928. The interval that DFNA20 maps to is flanked by recombination events at markers D17S784 and D17S928.

Table 1.

Two-point LODscore results between the DFNA20 locus and chromosome 17 markers

Marker	Marsh. map position ^a	deCode map position ^b	LOD score at the θ value shown below												
			0.0	0.01	0.02	0.03	0.04	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7
D17S1301	100.02	113.59	-∞	0.57	1.1	1.38	1.55	1.67	1.89	1.68	1.15	0.5			
D17S1839	102.46	114.52	-∞	0.25	0.79	1.07	1.25	1.37	1.62	1.45	0.97	0.38			
D17S1603	102.99	115.06	0.11	0.11	0.1	0.1	0.1	0.1	0.09	0.07	0.05	0.03			
D17S785	103.53	115.34	3.42	3.36	3.3	3.24	3.18	3.12	2.8	2.13	1.4	0.61			
D17S937	105.68	118.1	-∞	4.52	4.72	4.79	4.82	4.81	4.57	3.69	2.54	1.15			
D17S802	106.80	120.84	-∞	2.57	2.8	2.9	2.95	2.97	2.89	2.34	1.57	0.64			
D17S1847	111.22	123.75	4.37	4.29	4.21	4.13	4.05	3.97	3.56	2.67	1.69	0.64			
D17S836	112.92	125.04	-∞	4.37	4.57	4.65	4.67	4.66	4.42	3.56	2.43	1.08			
D17S1806	114.41	Not on map	6.32	6.22	6.11	6.01	5.9	5.8	5.25	4.06	2.72	1.22			
D17S784	116.86	129.62	-∞	2.3	2.52	2.62	2.67	2.68	2.59	2.07	1.36	0.53			
D17S928	126.46	135.67	-∞	3.93	4.13	4.21	4.24	4.24	4.04	3.25	2.21	0.97			

^aSex-average Kosambi cM map position for males and females from the Marshfield genetic map.^bSex-average Kosambi cM map position for males and females from the deCode genetic map.

Markers displayed in bold are genome scan markers.