A new locus for non-syndromal, autosomal recessive, sensorineural hearing loss (DFNB16) maps to human chromosome 15q21-q22

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Abstract

Non-syndromal, recessive deafness (NSRD) is the most common form of inherited deafness or hearing impairment in humans. NSRD is genetically heterogeneous and it has been estimated that as many as 35 different loci may be involved. We report the mapping of a novel locus for autosomal recessive, non-syndromal deafness (DFNB16) in three consanguineous families originating from Pakistan and the Middle East. Using multipoint analysis (HOMOZ/MAPMAKER) a maximum combined lod score of 6.5 was obtained for the interval D15S1039-D15S123. Recombination events and haplotype analysis define a 12-14 cM critical region between the markers D15S1039 and D15S155 on chromosome 15q15-q21.

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Severe or profound congenital sensorineural deafness affects between 1/1000 and 1/2000 live births.[1] Epidemiological studies suggest that there is a hereditary cause in 20-60% of cases, an acquired cause in 20-40%, and an unknown cause in the remaining 20-40%. Of the inherited cases, 59-85% are autosomal recessive and 33% are autosomal dominant, with X linked and mitochondrial inheritance accounting for the remainder. Autosomal recessive forms of deafness, thought to arise almost exclusively from cochlear defects, are the most severe forms and account for nearly all profound congenital deafness. Segregation studies have implicated the involvement of at least five common genes and possibly as many as 35 genes in total.[2] To date, 13 autosomal recessive loci (DFNB1-13) have been mapped using inbred families or population isolates.[3–14] We describe a novel locus for NSRD mapping to chromosome 15q15-q21 in families originating from Pakistan, Palestine, and Syria.

We screened 29 Pakistani families and 12 Middle Eastern families for linkage to known autosomal recessive (DFNB1-9) and autosomal dominant, non-syndromic deafness loci (DFNA1-8) using microsatellite markers flanking each locus.[2] Initial results indicated that three families had genotypes consistent with linkage to the DNA markers D15S123 and D15S132. These markers had been reported to define a putative dominant, non-syndromal deafness locus in an Austrian family, DFNA8.[15] However, further analysis indicated that the family in fact showed linkage to chromosome 11q.[16] Accordingly, DFNA8 was reassigned to chromosome 11q.[2] To test the validity of our initial results, we analysed five additional microsatellite DNA markers spanning a 30 cM region of chromosome 15q21-q22: D15S994, D15S1039, D15S155, D15S997, and D15S125. DNA marker genotypes for each pedigree are shown in fig 1. Two point linkage analysis was performed for each marker using LIPED and the combined values are shown in table 1. Multipoint analysis was performed for each family using the HOMOZ/MAPMAKER[17] programs and the maximum combined lod score is shown in fig 2. In classical linkage analysis, the minimal critical region can only be determined using recombination events by looking for obligatory crossovers within the marker haplotypes. In autozygosity mapping, the boundaries of the minimal critical region are defined by the loss of homozygosity of the markers (smallest region of homozygosity) in affected subjects. The smallest region of homozygosity in our families is seen in family 3 between markers D15S132 and D15S155, a region of approximately 12-14 cM. No common haplotype was observed between the two families from Palestine and Syria. However, higher density mapping of the newly defined critical region may show an ancestral haplotype.

Non-syndromal deafness most commonly occurs sporadically, that is, as an isolated case within a family. It is not usually possible to discriminate reliably in such a family between an acquired or genetic cause purely on clinical or audiological grounds such as age of onset, severity of hearing impairment, or shape of the audiogram. The chance of recurrence of deafness in subsequent offspring in this situation is

Table 1 Combined two point lod scores for families 1–3

DNA marker	Recombination fraction (θ)					
	0	0.05	0.1	0.2	0.3	0.4
D15S994	−6.69	0.573	1.041	1.078	0.743	0.314
D15S132	1.859	2.766	2.614	2.011	1.277	0.534
D15S1039	−3.46	2.055	2.124	1.686	1.046	0.415
D15S123	4.238	3.756	3.269	2.604	1.352	0.519
D15S1028	3.635	3.221	2.805	1.982	1.198	0.5
D15S155	−26.5	−3.99	−2.72	−0.83	−0.29	−0.086
D15S997	−31.1	−3.81	−2.22	−0.87	−0.31	−0.07
D15S125	−8.66	−1.53	−1.17	−0.33	−0.14	−0.06

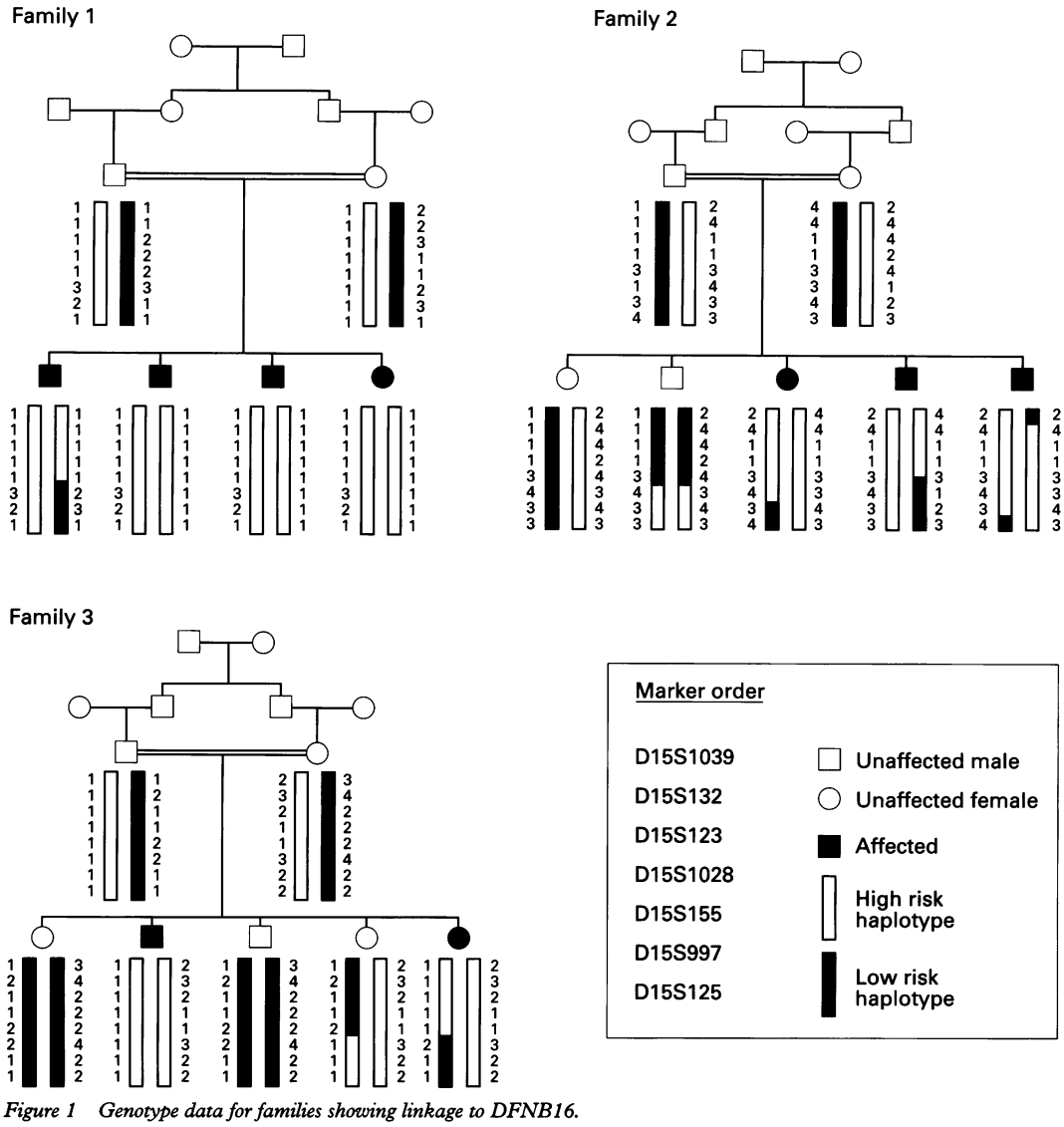

Figure 1 Genotype data for families showing linkage to DFNB16.

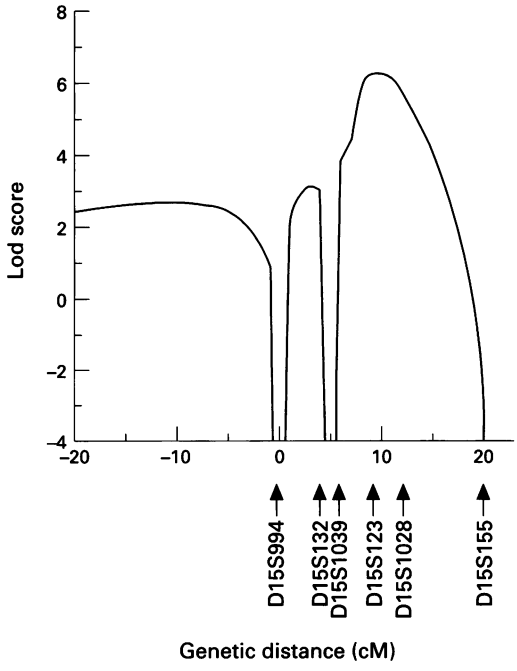

Figure 2 Graph showing maximum combined multipoint lod score.

based on empirical figures, that is, the observed recurrence of deafness in such families. Estimates of the relative contribution of individual DFNB loci to non-syndromal deafness within different populations are limited. A study of markers linked to DFNB1 in 19 consanguineous New Zealand families of western European origin has shown cosegregation of the same alleles in affected subjects consistent with approximately one half of the families segregating DFNB1.[18] A separate study estimated that 60% of families of Mediterranean origin are linked to DFNB1.[19] However, studies of 26 families of southern Indian origin failed to detect any DFNB1 linkage.[4] In our own study, one of 29 families originating from Pakistan and two of 12 families from the Middle East are linked to DFNB16. Clearly, only when all the genes responsible for non-syndromal deafness have been identified and mutation analysis performed will it be possible to gain a true estimate of the relative contribution of DFNB loci in different ethnic populations. The identification of the genes responsible for NSRD will also allow more accurate genetic counselling.

Recently it has been shown that Usher syndrome IB is caused by mutations in the

myosin VIIa gene.[20] Myosin VIIa belongs to the unconventional myosin group of proteins and is localised to the hair cells of the cochlear and the pigmented cells of the retina. In mice, unconventional myosins fall into six groups and at least 16 different genes have been mapped.[21] The map locations of five of these genes have been identified in humans including two, myosin IC and myosin VA/VB, which map to chromosome 15q21-q22.[21] As such, these represent plausible candidate genes for the DFNB16 locus.

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