# SHORT COMMUNICATION

# A Gene for Recessive Nonsyndromic Sensorineural Deafness (*DFNB18*) Maps to the Chromosomal Region 11p14–p15.1 Containing the Usher Syndrome Type 1C Gene

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**Autosomal recessive nonsyndromic sensorineural deafness segregating in a large consanguineous Indian family was mapped to chromosome 11p14–p15.1 defining a new locus, *DFNB18*. A maximum lod score of 4.4 at $\Theta = 0$ was obtained for the polymorphic microsatellite marker *D11S1888*. Haplotype analysis localizes this gene between markers *D11S1307* and *D11S2368*, which is approximately 1.6 cM and encompasses the region of Usher syndrome type 1C (*USH1C*). We postulate that *DFNB18* and *USH1C* are allelic variants of the same gene.** 

Nearly 1 in every 1000 infants is affected with clinically significant hearing impairment, and of these cases, approximately 75% are genetically determined (6, 8, 11). Greater than 70% of these genetically determined cases are nonsyndromic and are expressed in the absence of other clinical features. Individuals with nonsyndromic sensorineural deafness inherit this disorder as a simple Mendelian trait, with as many as 75% showing an autosomal recessive pattern of inheritance. Of the remainder, almost 20% have autosomal dominant inheritance and 2–3% have an X-linked recessive pattern. In other instances, maternally inherited types of deafness have been directly linked to mutations within the mitochondrial genome (10).

The family used for linkage analysis is from the Maharashtra state located in southwestern India. Affected individuals in the family demonstrated profound, prelingual, nonsyndromic sensorineural deafness. Vestibular function and visual function were normal on clinical examination of all individuals. The presence of congenital infections was ruled out by taking detailed histories from family members. After linkage to the *USH1C* region of chromosome 11 was confirmed, individuals III-1 and III-6 were clinically reevaluated. In the two affected individuals, ages 18 and 19, electronystagmography (ENG) was normal with absence of nystagmus and normal caloric responses. The electroretinogram (ERG) demonstrated no electrophysiological evidence of retinal involvement with normal photopic and scotopic responses.

Large consanguineous families have been effectively studied to map loci responsible for recessive nonsyndromic hereditary hearing impairment (9). Published loci causing recessive nonsyndromic hereditary deafness were excluded by the typing of 2–9 polymorphic microsatellite markers at regions for the known loci *DFNB1-12*, *B15*, and *B16*. Pairwise and multipoint lod scores (4-point) were calculated using FASTLINK version 5.1 (2, 3), assuming a fully penetrant, recessive mutant allele and equal recombination for males and females. The genetic locations for recessive deafness can be found at the Hereditary Hearing Loss Home Page (http://dnalab-www.uia.ac.be/dnalab/hhh/). A genome-wide search was conducted using fluorescent markers (Linkage Mapping Set User's Manual, P/N 904999, available from PE Applied Biosystems, Foster City, CA), and linkage was observed with marker *D11S902*. Linkage was confirmed with several markers including *D11S1888*, which sustained a lod score of 4.4 – 4.5 at $\Theta = 0$ as the mutant allele frequency was varied from 0.01 to 0.0001. The allele frequencies of marker *D11S1888* were calculated on the basis of genotyping 50 chromosomes of 25 unrelated individuals from the same ethnic and geographical area. An examination of the haplotypes from affected individuals places the *DFNB18* locus between markers

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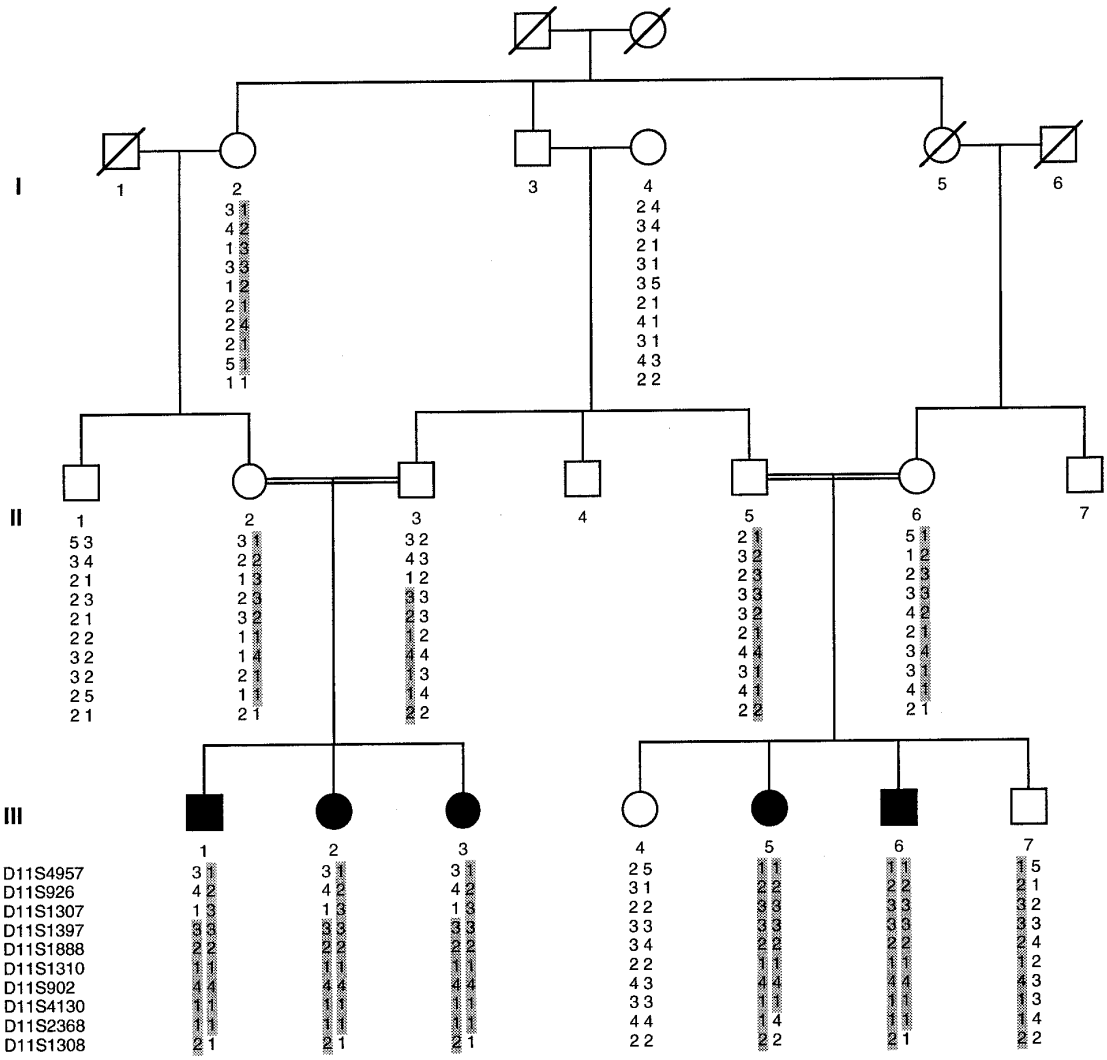


**FIG. 1.** Pedigree and haplotype data for the family S-11/12 segregating nonsyndromic deafness. Genotypes of markers *D11S4957*–7.9 cM–*D11S926*–0.5 cM–*D11S1307*–0.5 cM–*D11S1397*–0 cM–*D11S1888*–0 cM–*D11S1310*–0 cM–*D11S902*–0 cM–*D11S4130*–1.1 cM–*D11S2368*–2.2 cM–*D11S1308*. *DFNB18* maps to an approximately 1.6-cM interval between markers *D11S1307* and *D11S2368*. The disease chromosomes are shaded.

*D11S1307* and *D11S2368* (Fig. 1). *D11S1307* shows recombination with the disease locus in individuals III-1, III-2, and III-3; *D11S2368* shows recombination in individual III-5. The distance between these two markers is approximately 1.6 cM (http://www.marshmed.org/genetics/).

The *USH1C* maps to chromosome 11p14–p15.1 between markers *D11S902* and *D11S1888* (1). In a recent study on *USH1C* patients of Acadian extraction, all affected individuals shared one common allele at *D11S921*, two alleles at *D11S902*, and three alleles at *D11S1310* (7). Shows *et al.* (12) ordered the three markers mentioned in a PAC contig through this region of chromosome 11 [tel–*D11S1890*–*D11S921*–*D11S902*–MYOD1–(KCNC1–*D11S1888*)–*D11S1310*–cen]. The three markers *D11S921*, *D11S902*, and *D11S1310* are contained within the linkage region of *DFNB18* as seen in Fig. 1. We therefore postulate that *DFNB18* and *USH1C* are allelic variants of the same gene.

Usher syndrome type 1 (*USH1*, MIM 276904) is a heterogeneous disorder of at least six different loci [*USH1A*–*USH1F*, Hereditary Hearing Loss Home Page (http://dnalab-www.uia.ac.be/dnalab/hhh/)]. These are genetically distinct loci, yet affected individuals are clinically indistinguishable. Patients with *USH1* have congenital, profound, sensorineural deafness with auditory thresholds typically 100 dB, show markedly reduced activity of vestibular function (13), and become visually impaired with progressive pigmentary retinopathy during their second decade of life. In the family described herein, the progressive pigmentary retinopathy of the *USH1* phenotype was excluded by clinical history, physical examination, ERG, and ENG.

*DFNB18* (nonsyndromic deafness) and *USH1C* (syndromic deafness) map to the same interval. There is precedence for such an observation. *DFNB2* maps to

the *USH1B* interval. Recently, two different mutations in the unconventional myosin VIIA (*MYO7A*) were described as being responsible for nonsyndromic deafness in such families (4, 15). Additionally, a large family with dominant nonsyndromic deafness defining the *DFNA11* locus (also linked to the *USH1B* linkage region) has a 3-amino-acid deletion in the *MYO7A* gene (5, 14). These newly described mutations are not found among the 20 known mutations responsible for *USH1B*. This variable manifestation in phenotype can be explained by allelic heterogeneity or by the influence of genetic background.

Once candidate genes in this region are identified, mutation analysis in our *DFNB18* family and in the Acadian population segregating for *USH1C* can be performed. When such a gene is cloned, it may be possible to arrive at a better understanding of the mechanism and developmental molecular pathology of human autosomal recessive sensorineural deafness. We postulate that there is a single gene in this region of chromosome 11p causing either *DFNB18* or *USH1C*, depending upon the allele, genetic background, or both.

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