LETTERS

An Autosomal Recessive Nonsyndromic Form of Sensorineural Hearing Loss Maps to 3p-*DFNB6*

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Autosomal recessive nonsyndromic hearing loss (ARNSHL) is the most common form of congenitally acquired inherited hearing impairment. Although numerous loci are believed to exist, only five have been identified. Using a pooled genomic DNA screening strategy, we have identified a sixth locus, *DFNB6*, on 3p in the interval bounded by *D3S1619* and *D3S1766*.

Autosomal recessive nonsyndromic hearing loss (ARNSHL) is the most common type of inherited hearing impairment (Bergstrom et al. 1971). Although almost exclusively monogenic, it is highly heterogeneous with some estimates of the number of gene loci exceeding 100 (Chung and Brown 1970). Only five loci have been identified (Guilford et al. 1994a,b; Baldwin et al. 1995; Friedman et al. 1995; Fukushima et al. 1995), however, as affected families cannot be pooled and single nonconsanguineous families rarely are informative enough to obtain linkage. Recently, we proposed simultaneous analysis of multiplex sibships of consanguineous unions as a mapping strategy to exploit the heterogeneity of ARNSHL for gene localization (Fukushima et al. 1995). The hearing-impaired progeny of a consanguineous union are expected to share a region of many centimorgans (cM) around the disease locus that is homozygous by descent—other genomic regions also are homozygous by descent but vary from one child to next. For this strategy to be successful, highly informative polymorphic

markers must be used to minimize the false-positive rate (estimated at 5%; Fukushima et al. 1995), and powerful algorithms and software must be available to perform linkage calculations within reasonable time periods (Kruglyak et al. 1995).

RESULTS

Single alleles were demonstrated in two of nine families using *D3S1767*. Two other markers tightly linked to *D3S1767* (*D3S1619* and *D3S1289*) did not show allelic homozygosity in one of these families. In the remaining family, homozygosity by descent was demonstrated in the parents over an interval of 19–22 cM. From the affected progeny, the location of *DFNB6* was mapped to the 14- to 20-cM interval bounded by *D3S1619* and *D3S1766* ($\bar{Z} = 3.3$; Fig. 1).

DISCUSSION

This region is the site of several genes that could be essential for normal auditory function, including zinc finger protein 35 (Calabro et al. 1995), β -catenin (CTNNB1; Bailey et al. 1995), guanine

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on regions of high GC content (Antonarakis 1994). When allelic homozygosity was demonstrated with a particular marker, parents and nonaffected siblings were genotyped and haplotypes were reconstructed by typing other polymorphic markers in the region. If results suggested homozygosity by descent, more markers were typed to determine the size of the homozygous interval. Allele sizes were assigned in reference to an M13mp18 sequencing ladder, and genomic DNA from CEPH individual 1347-O2 with known alleles for each marker was typed with all DNA samples.

LOD scores were calculated using the MAPMAKER/HOMOZ computer package (Kruglyak et al. 1995), setting the frequency of each ARNSHL gene at 0.005 (Morton 1991) and coding the disease as fully penetrant. To guard against inflated LOD scores, the frequency of all homozygous alleles was determined by screening 35 unrelated individuals from the same geographic region and cultural background. A sensitivity analysis also was calculated by imposing a lower band of 10% on allele frequencies.

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