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A Gene for Autosomal Dominant Nonsyndromic Hearing Loss (DFNA12) Maps to Chromosome 11q22-24

Kristien Verhoeven,[1] Guy Van Camp,[1] Paul J. Govaerts,[3] Wendy Balemans,[1] Isabelle Schatteman,[1] Margriet Verstreken,[1] Lut Van Laer,[1] Richard J. H. Smith,[4] Matthew R. Brown,[4] Paul H. Van de Heyning,[2] Thomas Somers,[3] F. Erwin Offeciers,[3] and Patrick J. Willems[1]

Departments of [1]Medical Genetics and [2]Otolaryngology, University of Antwerp, and [3]University Department of Otolaryngology, St-Augustinus Hospital, Antwerp; and [4]Department of Otolaryngology, University of Iowa Hospitals and Clinics, Iowa City

Summary

We performed linkage analysis in a Belgian family with autosomal dominant midfrequency hearing loss, which has a prelingual onset and a nonprogressive course in most patients. We found LOD scores >6 with markers on chromosome 11q. Analysis of key recombinants maps this deafness gene (DFNA12) to a 36-cM interval on chromosome 11q22-24, between markers D11S4120 and D11S912. The critical regions for the recessive deafness locus DFNB2 and the dominant locus DFNA11, which were previously localized to the long arm of chromosome 11, do not overlap with the candidate interval of DFNA12.

Introduction

Nonsyndromic hearing loss is a very common sensory disability. It can be classified in two groups: prelingual and postlingual. Prelingual hearing loss occurs at a frequency of 1/1,000 births and has a monogenic origin in ~50% of cases (Morton 1991). Prelingual hereditary hearing loss has a recessive mode of inheritance in 75% of cases and a dominant inheritance pattern in 20%–25% (Cohen and Gorlin 1995). However, prelingual hearing loss makes up only a small part of the hearing loss in the total population, because postlingual hearing loss is much more frequent. At the age of 65 years, nearly 10% of the western population has a significant hearing loss, and this figure rises to ~50% at the age of 80 years (Morton 1991). In most cases, postlingual hearing loss is probably a multifactorial disease caused by an interaction of environmental and genetic factors. However, there are families with purely genetically determined postlingual hearing loss. With few exceptions, these families have an autosomal dominant mode of inheritance (Cohen and Gorlin 1995). These families present an ideal opportunity to identify the genes responsible for postlingual hearing impairment, by linkage analysis and positional cloning.

At present, 4 loci for X-linked hearing loss, 11 loci for autosomal dominant hearing loss, and 11 loci for autosomal recessive hearing loss have been reported. A review of the gene localizations for nonsyndromic hereditary hearing loss can be found on the Hereditary Hearing Loss homepage (Van Camp and Smith 1996). These 26 loci clearly illustrate the genetic heterogeneity of hearing loss. Linkage to regions on the X chromosome has been found in families with X-linked profound prelingual hearing loss and in families with mixed conductive and sensorineural hearing loss. The dominant families for which linkage has been found originate from a great number of countries, and most of them show a postlingual, progressive hearing loss. However, both a French family (DFNA3) (Chaib et al. 1994) and an Austrian family (DFNA8) (Kirschhofer et al. 1995) have a moderate to severe stable hearing loss with prelingual onset. The recessive families, on the contrary, are all consanguineous and originate from ethnic isolates. The hearing loss in these recessive families is always characterized by a prelingual onset and a profound and stationary disease pattern, with the exception of DFNB8 (Veske et al. 1996). The hearing loss in this family is postlingual and progressive, although the onset is early, and progress is rapid compared to most dominant families.

Until now only two genes for hereditary nonsyndromic hearing loss have been identified. Mutations in the POU3F4 gene are responsible for X-linked mixed hearing loss with stapes fixation (DFN3) (de Kok et al. 1995), and a mutation in the myosin VIIA gene on chromosome 11q13.5 is responsible for DFNB2 (C. Petit, personal communication). Previously, mutations in the myosin VIIA gene had already been shown to be responsible for Usher syndrome type1B, a recessively inherited combination of prelingual deafness and progressive retinitis pigmentosa (Weil et al. 1996). In the

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Address for correspondence and reprints: Dr. Guy Van Camp, Department of Medical Genetics, University of Antwerp, Universiteitsplein 1, B-2610, Antwerp, Belgium. E-mail: gvcamp@uia.ac.be

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present study, we mapped a new gene for autosomal dominant hearing loss to chromosome 11q, telomeric to the previously localized DFNB2 and DFNA11 genes.

Material and Methods

Clinical Diagnosis

A family pedigree was constructed at the Saint Augustinus Hospital, and audiograms and blood samples from the family members were obtained after informed consent was granted. We performed pure-tone audiometry on all family members with air conduction at 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz and with bone conduction at 500, 1,000, 2,000, and 4,000 Hz. Family members were considered to be affected if they had a bilateral sensorineural hearing loss at the mid- and high frequencies below the 95th percentile of an age- and sex-dependent control curve of the general population (International Organization for Standardzation 1984). Information on deceased members of the pedigree obtained from relatives indicated that three individuals in the older generation had manifested hearing loss. Family members were considered to be unaffected if their hearing thresholds (at most frequencies) were better than the 20-dB hearing level (HL) or above the 50th percentile (International Organization for Standardization 1984). Patients with a hearing loss suspected to be caused by other than genetic causes, patients with an audiogram atypical for this family, and patients with threshold values between the 50th and 95th percentile were given an uncertain affection status and were excluded from the genetic analysis.

Genetic Analysis

Genomic DNA was extracted from blood samples by standard techniques. Microsatellite markers were amplified using PCR and separated on polyacrylamide gels (Hughes 1993). All markers used are listed in the most recent Généthon map (Dib et al. 1996).

Linkage Analysis

Linkage analysis was carried out using the LINKAGE 5.1 program package (Lathrop and Lalouel 1984) and the FASTLINK computer program (Cottingham et al. 1993). MLINK two-point linkage analysis was performed between the disease gene and each marker. The deafness was coded as a fully penetrant autosomal dominant trait with a gene frequency of .0001. Equal recombination frequencies between males and females were assumed. For each marker, the number of alleles in the LOD-score calculations was set at the observed number of alleles in the pedigree (N), and allele frequencies were set equal at $1/N$. Changes in the allele frequencies resulted in only minor alterations of the two-point LOD scores and did not alter the conclusions of the study.

Results

Family Pedigree

In this family, bilateral sensorineural hearing loss is transmitted in an autosomal dominant way. Fourteen tested family members between the ages of 6 and 85 years were considered to be affected. Nine tested family members were considered to be unaffected, and nine family members were excluded from the linkage studies because of an uncertain affection status. Examination of the audiograms of the 14 affected individuals showed a mild to moderately severe hearing loss (21–80 dB best ear HL), mainly in the middle frequencies (500–2,000 Hz). There was no correlation between the severity of hearing loss and age. No hearing loss was found exceeding a Fletcher index of 73 dB HL. The history and records of most of the patients suggested a prelingual onset (at birth or in the first years of life) with no progression over the subsequent decades.

Seven affected family members had complaints of tinnitus. There were no family members with a history of dizziness or vertigo. Because no further abnormalities were found, the deafness was classified as nonsyndromic.

Linkage Analysis

Linkage to known deafness loci, DFNA1-DFNA10 and DFNB1-DFNB9, was investigated in our family with the markers listed on the Hereditary Hearing loss homepage (Van Camp and Smith 1996). Negative LOD scores were obtained for each of these chromosomal regions, with the exception of DFNB2 on chromosome 11q. Suggestive LOD scores of ~2.0 were obtained for DFNB2 with D11S937 and D11S911. Therefore, additional markers spanning the DFNB2 region were analyzed. Figure 1 shows the relative position of these markers on the Généthon map (Dib et al. 1996). Two-point LOD scores >6 were obtained with several markers 20–40 cM telomeric to DFNB2. The LOD scores for linkage of the deafness locus in our family with the 11q markers are given in table 1.

The most likely 11q haplotype was constructed for the family represented in figure 2. In all affected family members, the linked haplotype was found. Three key recombinants were identified. In patient IV-2, a recombination is present between D11S912 and D11S4151, mapping DFNA12 centromeric to marker D11S912. This localization is confirmed by a recombination between the same markers in individual III-1. Another important recombinational event is present in individual III-8 between D11S4120 and D11S1778, mapping DFNA12 telomeric to D11S4120. His two affected daughters (IV-9 and IV-10) have inherited this recombinant chromosome, confirming the localization of DFNA12 telomeric to D11S4120. Combining the information from these recombinants indicates that the criti-

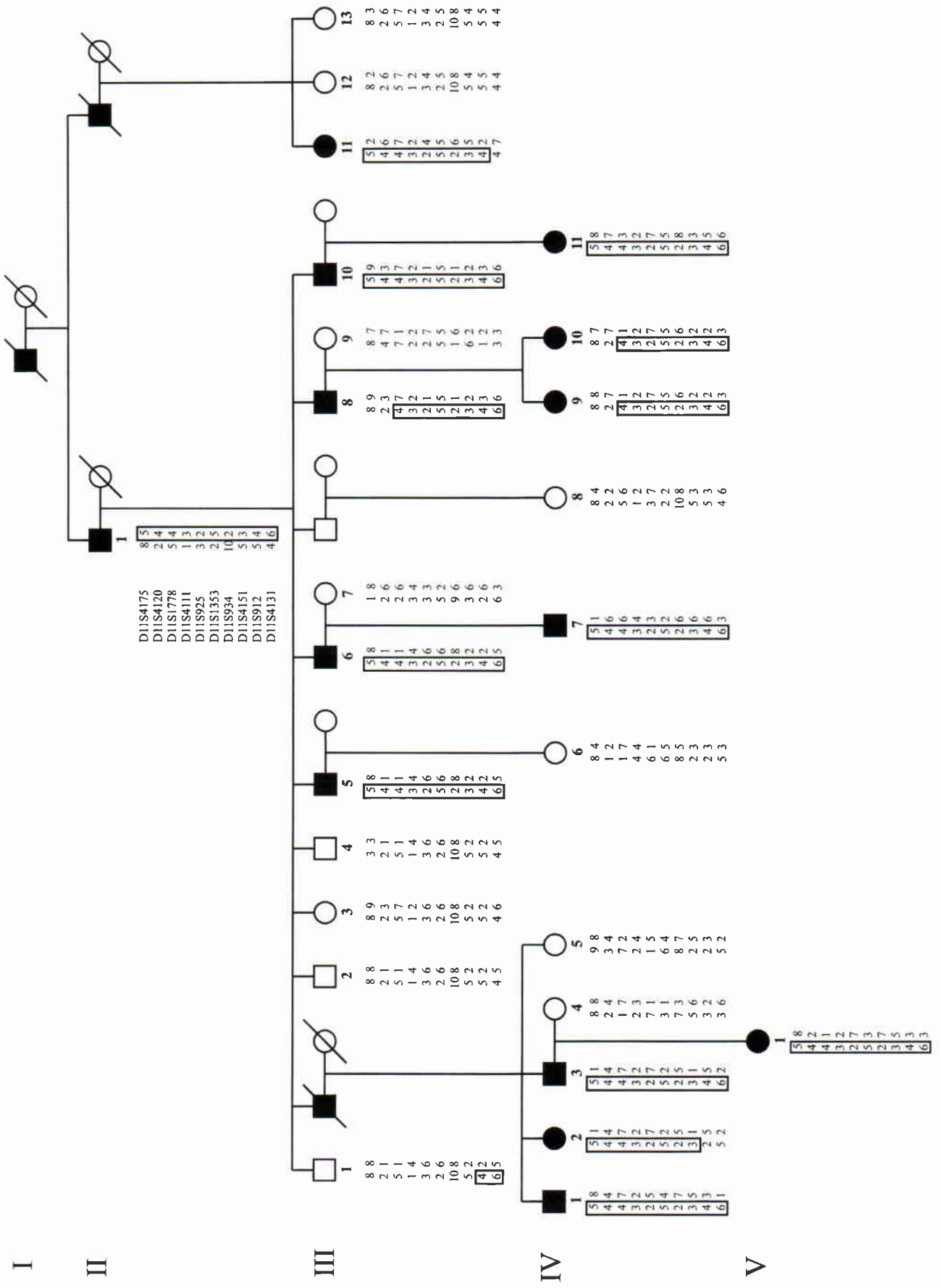

Figure 2 Pedigree of the Belgian family with autosomal dominant hearing loss, showing the most likely haplotypes for the chromosome 11 markers. Only family members of whom DNA was analyzed are numbered. The haplotype linked to DFNA12 is boxed.

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