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Address for correspondence and reprints: Dr. Daniel Grinberg, Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Av. Diagonal 645, 08071 Barcelona, Spain. E-mail: danielr@porthos.bio.ub.es

0002-9297/99/6404-0040$02.00

Am. J. Hum. Genet. 64:1238–1241, 1999

Deafness Locus DFNB16 Is Located on Chromosome 15q13-q21 within a 5-cM Interval Flanked by Markers D15S994 and D15S132

To the Editor:

Inherited human deafness has an incidence of ~1/2,000 births (Cohen and Gorlin 1995). The hearing impairment can be associated with other clinical features as part of a distinct syndrome, but in most cases (70%) it is the sole clinical sign (Bergstrom et al. 1971). Autosomal recessive transmission accounts for ⩽85% of nonsyndromic sensorineural deafness (Cohen and Gorlin 1995). Nonsyndromic autosomal recessive deafness is clinically homogeneous; in most cases, the hearing loss has a prelingual onset, involves all the frequencies, is severe or profound, and is nonprogressive (Van Camp et al. 1997). However, as expected from the structural and functional complexity of the inner ear, sensorineural deafness exhibits a very high genetic heterogeneity. Nineteen loci for autosomal recessive hearing loss have been mapped, to date (Hereditary Hearing Loss home page). One of these loci, DFNB16, was mapped to chromosome 15q21-22 by linkage studies of three consanguineous families from Pakistan, Palestine, and Syria (Campbell et al. 1997). Analysis of recombinant haplotypes indicated that the locus was in a 20-cM interval delimited by markers D15S994 and D15S155. Acting on the results of homozygosity data, Campbell et al. (1997) narrowed the location of DFNB16 to the 15-cM distal part of the interval, between markers D15S1039 and D15S155. The pedigree and haplotype analysis of family S040 (fig. 1) provides evidence against the last conclusion. Our work locates DFNB16 to the proximal 5-cM part of the interval, between D15S1044 and D15S132.

Informed consent was obtained from all the individuals included in the study. All the family members underwent a clinical examination. Environmental factors were eliminated as the cause of deafness in all affected family members. There were no features suggestive of ophthalmologic, skin, or renal syndromic anomalies. Conductive hearing loss was ruled out by otoscopic examination, tympanometry with acoustic reflex testing, and use of the tuning fork test. Pure-tone audiometry was performed to test for air conduction (frequencies of

125–8,000 Hz) and bone conduction (frequencies of 250–8,000 Hz). The hearing loss is bilateral and sensorineural in the six affected patients. Onset of hearing loss was in early childhood and was nonprogressive (the ages of deaf individuals are 35–60 years, and there are records of audiometry tests performed during their childhood). A characteristic audiogram is shown in figure 2. The hearing impairment involves all the frequencies and is moderate in the range of 125–1,000 Hz but is severe in the higher frequencies. Findings from vestibular function testing were normal, and there were no symptoms of tinnitus. This phenotype could not be compared with those of the other families with DFNB16, because their clinical data have not been reported (Campbell et al. 1997).

To map the deafness locus, we extracted DNA from blood samples from all members of the family and genotyped it for a set of microsatellite markers located close to the deafness loci already known (two markers per locus; Hereditary Hearing Loss home page). PCR was performed as described elsewhere (del Castillo et al. 1996), but one of the primers was labeled with a fluorescent dye (TET, 6-FAM, or HEX), and amplified alleles were resolved by capillary electrophoresis in an ABI Prism 310 Genetic Analyzer (Perkin-Elmer). We performed linkage analysis using the LINKAGE 5.1 software package (Lathrop et al. 1985), setting the frequency of the deafness gene to .0001 and considering marker-allele frequencies to be equal to each other. Two-point LOD scores were calculated with MLINK and ILINK programs (LINKAGE). Extensive alterations of the disease-gene frequency, or of the allele frequencies of microsatellite markers, did not significantly change the LOD scores.

Table 1

Two-Point LOD Scores between Marker Loci from 15q21 and the DFNB16 Locus

	Recombination Fraction at θ =								
Marker	.00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D15S102	−∞	−.84	−.19	.05	.17	.14	.05	.18	.218
D15S1044	−∞	1.82	2.25	2.20	1.77	1.14	.44	2.26	.063
D15S129	2.38	2.34	2.17	1.95	1.48	.96	.38	2.38	.000
D15S994	3.88	3.82	3.53	3.16	2.37	1.50	.57	3.88	.000
D15S514	3.88	3.82	3.53	3.16	2.37	1.50	.57	3.88	.000
D15S780	3.88	3.82	3.53	3.16	2.37	1.50	.57	3.88	.000
D15S222	2.38	2.34	2.17	1.95	1.48	.96	.38	2.38	.000
D15S132	−∞	1.82	2.25	2.20	1.77	1.14	.44	2.26	.063
D15S1039	−∞	1.82	2.25	2.20	1.76	1.13	.42	2.26	.063
D15S123	−∞	.12	1.26	1.52	1.40	.96	.38	1.54	.122

Evidence of linkage to markers D15S1028 and D15S982, in the 15q21 region near the DFNB16 locus, was found (all the other deafness loci were excluded). Genotyping the family for additional markers of this

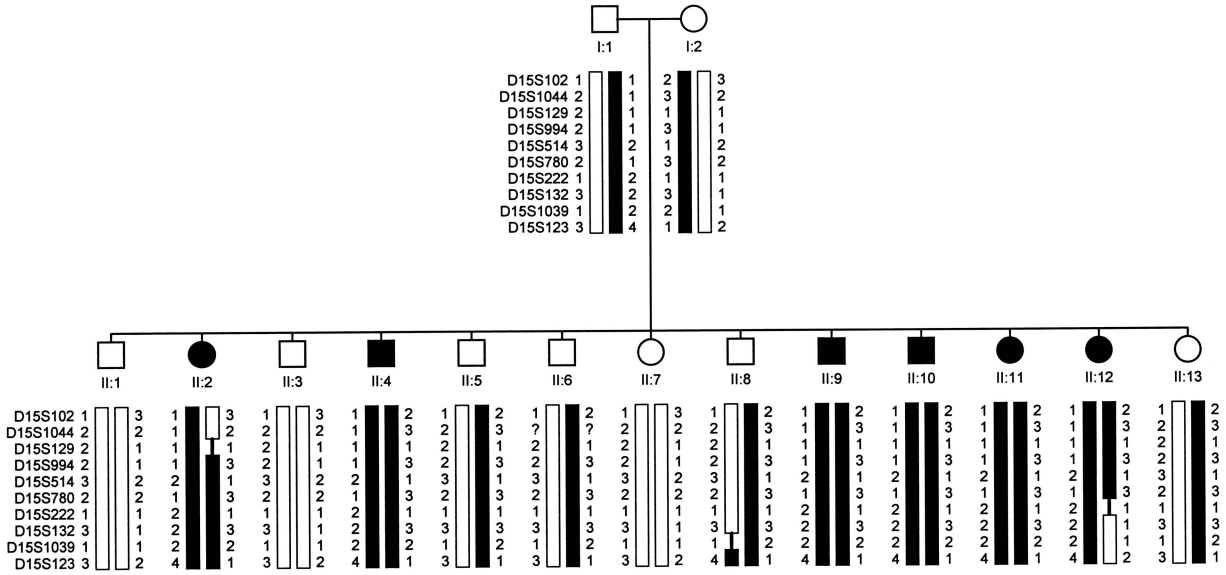

Figure 1 Pedigree and haplotype analysis of family S040. The order of the markers was set by integrating genetic and physical data from previous studies (Fougerousse et al. 1994; Allamand et al. 1995; Dib et al. 1996; Robinson et al. 1997). However, the relative order of markers D15S1044 and D15S129, as well as that of markers D15S994 and D15S514, are arbitrary and remain to be established (note that this does not affect the conclusions of this study). The D15S155 marker mentioned in the text is distal to D15S123 (Campbell et al. 1997). Blackened symbols represent affected individuals. Haplotypes are represented by bars, with the haplotype associated with deafness blackened to show the recombinations. A thin line between two bar segments indicates that the marker was not informative for mapping the breakpoint.

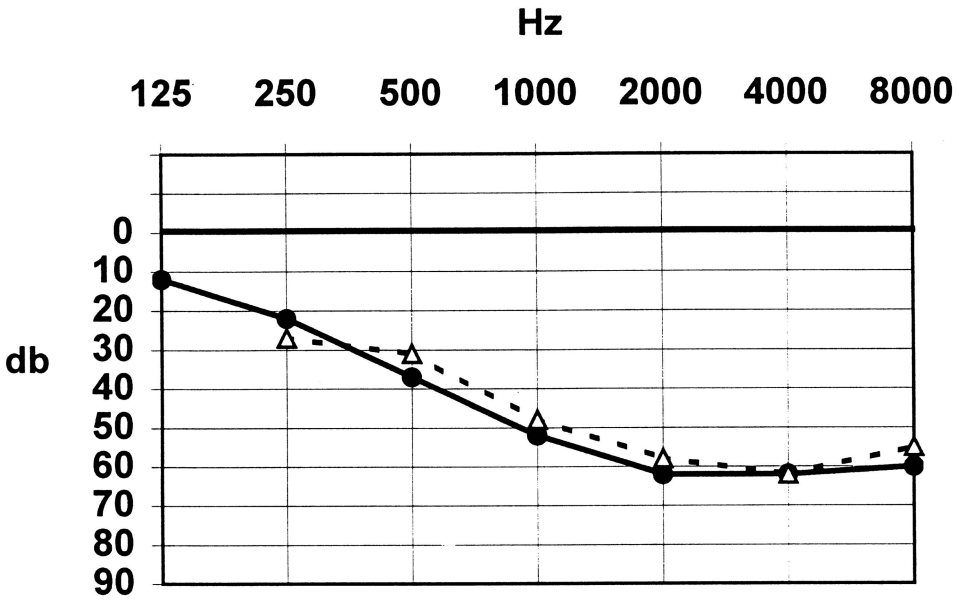

Figure 2 Audiogram of patient II-2. Audiograms of other affected individuals in the family were not significantly different. Hearing loss is bilateral, with a very similar pattern for both ears. For clarity, only results for the right ear are presented. Dots denote air conduction, triangles denote bone conduction.

region confirmed the linkage. A maximum LOD score (Z_{max}) of 3.88 at a recombination fraction (θ) of .000 was obtained for markers D15S994, D15S514, and D15S780 (table 1). The position of the disease locus was narrowed by haplotype analysis. Three recombinant chromosomes were identified (fig. 1). Two of them defined the limits for the interval that must contain the disease locus. In patient II-2, the recombination event, between D15S1044 and D15S994, located the disease telomeric to marker D15S1044. In patient II-12, the recombination took place between D15S780 and D15S132, mapping the disease locus centromeric to marker D15S132.

These mapping data are fully consistent with those obtained by Campbell and colleagues from the study of two of their families, which defined the 20-cM interval between D15S994 and D15S155. Data to narrow this interval were provided by autozygosity mapping performed on a third family (Campbell et al 1997). However, the homozygosity region in this family was relatively small (only two markers, D15S123 and D15S1028, very close together, were in homozygosity in two affected individuals of that family) (Campbell et al. 1997). If data from this third family are taken into account, the interval established by Campbell and colleagues and the interval defined in our report would not be overlapping, and we would have defined a novel locus for autosomal recessive hearing loss. However, because the evidence for linkage of the third family is weak, we find it is more likely that there is only one deafness locus in the region, DFNB16. On the basis of this assumption, and integrating all the available data, DFNB16 would be within a genetic interval of 5 cM, between D15S994 (centromeric limit) and D15S132 (telomeric limit).

The DFNB16 critical interval corresponds to a region that was investigated thoroughly during the search for a gene responsible for a recessive form of limb-girdle muscular dystrophy (*LGMD2A*). As a consequence, a YAC contig and a transcriptional map of the region, containing $\geqslant$5 known genes and 12 anonymous cDNAs, are available (Fougerousse et al. 1994; Chiannilkulchai et al. 1995). Given the functional diversity of the genes and proteins involved in inherited deafness, no positional candidate gene can be excluded a priori. Comparative mapping is not of help, unfortunately, because no mouse mutations causing hearing impairment map to the region homologous to human 15q13-q21. Testing the expression of positional candidates in the inner ear should help to identify the gene responsible for autosomal recessive hearing impairment at DFNB16.

Acknowledgments

We thank the members of family S040 for their kind cooperation. We are also grateful to Prof. Jacques S. Beckmann for his kind gift of primers and YAC strains. This work was supported by grants from the European Community (PL 951324) and the Fondo de Investigaciones Sanitarias de la

Seguridad Social (no. 96/1556; Ministerio de Sanidad y Consumo, Spain).

MANUELA VILLAMAR, IGNACIO DEL CASTILLO, NOELIA VALLE, LOURDES ROMERO, AND FELIPE MORENO
Unidad de Genética Molecular, Hospital Ramón y Cajal, Madrid

Electronic-Database Information

URL for data in this article is as follows:

Hereditary Hearing Loss home page, http://dnalab-www.uia.ac.be/dnalab/hhh (for loci and markers)

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Address for correspondence and reprints: Dr. Felipe Moreno, Unidad de Genética Molecular Hospital Ramón y Cajal, Carretera de Colmenar Km 9, 28034 Madrid, Spain. E-mail: felipe.moreno@hrc.es

0002-9297/99/6404-0041$02.00

Am. J. Hum. Genet. 64:1241–1243, 1999

Prevalence of Bloom Syndrome Heterozygotes among Ashkenazi Jews

To the Editor:

Bloom syndrome (MIM 210900) is a condition of intrauterine and postnatal growth failure, facial erythema, immunodeficiency, and early malignancies (German 1995). Death from malignancy typically occurs in the second or third decade (German 1997). At the cellular level, mutations in both alleles of the Bloom syndrome gene (*BLM*) lead to chromosomal breakage, an excess number of somatic mutations, and an observed increase in the frequency of sister chromatid exchange in cultured cells (German et al. 1996). Among 28 of 29 Ashkenazi Jewish individuals, a single, noncomplementing mutation has been observed (Ellis et al. 1995). This was shown to be a deletion of 6 bp, followed by insertion of 7 bp, leading to a frameshift with premature termination of the encoded gene product (Ellis et al. 1995). The finding of linkage disequilibrium of this mutation with neighboring DNA markers demonstrated that this unusual mutation had a single genetic origin in the Ashkenazi Jewish population ~400–500 years ago (Ellis et al. 1994). A 1977 survey of Israeli patients with Bloom syndrome suggested that 1 in 110 Ashkenazi Jews was a heterozygote for a mutated *BLM* gene (German et al. 1977).

A number of autosomal recessive conditions are known to occur with increased frequency among Ashkenazi Jews, including Tay-Sachs disease, cystic fibrosis, Gaucher disease, Canavan disease, Fanconi anemia complementation group C, Niemann-Pick disease, familial dysautonomia, and Bloom syndrome (Motulsky 1995). Early success of Tay-Sachs carrier-screening programs has led to increased interest in screening for other prevalent disorders, and as the genetic basis for these conditions is identified, the new information is used to develop carrier-screening tests (Eng et al. 1997; Kronn et al. 1998). The recent identification of the gene for Bloom syndrome provided an opportunity to determine the frequency of heterozygotes in the Ashkenazi Jewish pop-