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0002-9297/95/5704-0030$02.00

Am. J. Hum. Genet. 57:965–968, 1995

Nonsyndromic Autosomal Recessive Deafness Is Linked to the DFNB1 Locus in a Large Inbred Bedouin Family from Israel

To the Editor:

Nonsyndromic deafness accounts for ~70% of all genetically determined deafness (Moatti et al. 1990; Gorlin et al. 1995). Several types of nonsyndromic deafness, with a variety of inheritance patterns, have been genetically linked, including dominant, recessive and X-linked forms (Leon et al. 1992; Reardon et al. 1992; Robinson et al. 1992; Chaib et al. 1994; Coucke et al. 1994; Guilford et al. 1994*a*, 1994*b*; Cohen et al. 1995; Friedman et al. 1995). Two of these forms—DFNA3, a dominant form causing moderate to severe hearing loss, predominantly in the high frequencies, and DFNB1, a recessive form causing profound, prelingual, neurosensory deafness affecting all frequencies—have been linked to the same pericentromeric region of chromosome 13 (Chaib et al. 1994; Guilford et al. 1994*b*). This finding is equally compatible with (1) the existence two closely linked deafness genes, (2) different mutations within a single deafness gene, and (3) a single mutation in a single gene that behaves differently in different genetic backgrounds.

We present the linkage analysis of a very large, highly inbred Bedouin family affected with nonsyndromic autosomal recessive deafness. Our analysis indicates that deafness in this family is linked to the DFNB1 locus. In addition to describing the presence of this deafness disorder in a new population, we also present data that narrow the genetic interval of DFNB1. The new DFNB1 interval overlaps that defined for DFNA3. This finding is consistent with the single-gene hypothesis presented by Chaib et al. (1994).

The Bedouin family described in the present study belongs to a tribe founded ~200 years ago by an Arab-Bedouin male who emigrated from Egypt to the southern region of what was then Palestine. He married a local woman and had seven children, five of whom survived to adulthood. Consanguineous marriage has been the rule in the tribe since its third generation. The tribe is presently in its seventh generation and consists of some 3,000 people, all of whom reside in a single geographic area in Israel that is separated from other Bedouin communities. Birth rates within the tribe are high, and polygamy is common.

Within the past three generations, there have been ~80 individuals with congenital deafness. All of these individuals are descendants of two of the five adult sons of the founder. Hearing evaluation of these individuals revealed profound prelingual neurosensory hearing loss with drastically elevated audiometry thresholds at all frequencies (250–8,000 cps). All deaf individuals have an otherwise normal phenotype with the absence of external ear abnormalities, retinopathy, and renal defects. All are of normal intelligence. Some nuclear families in the tribe exhibit pseudodominant segregation of the disease that is due to marriage of deaf persons to hearing carriers of the autosomal recessive gene.

Genotyping was performed with short tandem-repeat polymorphic markers linked to previously reported

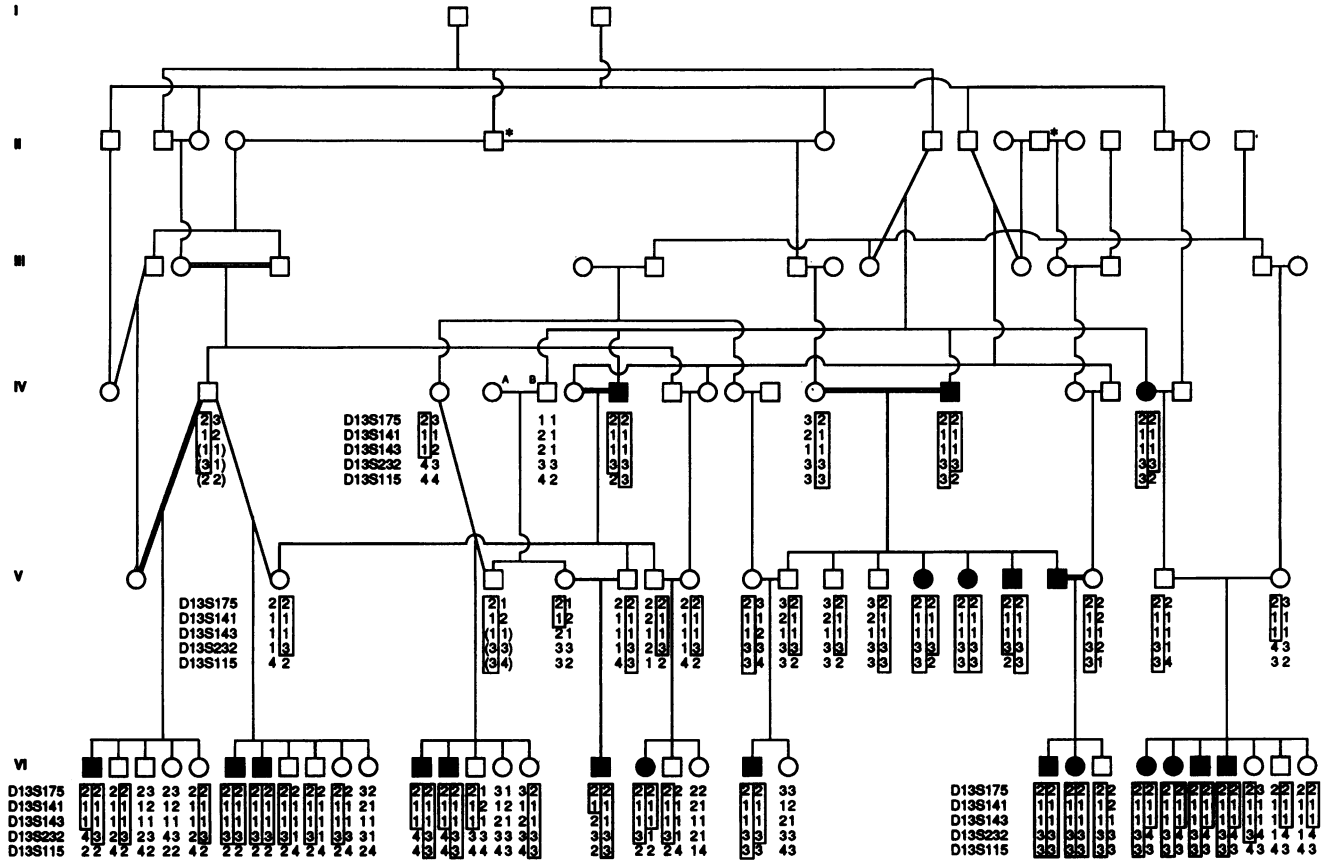

Figure 1 Pedigree of a Bedouin family from Israel that is affected with nonsyndromic autosomal recessive deafness at the DFNB1 locus. Genotypic data for markers D13S175, D13S141, D13S143, D13S232, and D13S115 are shown. Boxes indicate the haplotype associated with DFNB1 in this pedigree. A break between individual B and his parents was made to allow the proper calculation of the LOD score after haplotype analysis indicated that the disease gene was transmitted through his wife, A. The precise relationship of individual A to the rest of the family is not known. Blackened symbols denote deaf individuals; and parentheses denote inferred genotypes. The asterisk (*) indicates a single individual who was shown twice in order to simplify the pedigree drawing.

deafness loci. Linkage was tested using the LOD-score method, and a score ≥ 3.0 was used as the criterion for significance. The pedigree was analyzed as a single family with all but one inbreeding loop intact (fig. 1). A break between individual B and his parents was made, to allow the proper calculation of LOD scores after haplotype analysis indicated that the disease gene was transmitted through the spouse (individual A). The precise relationship of individual A to the rest of the family is not known. Markers with more than four alleles could not be analyzed in the entire family because of the large amount of memory required for such calculations. For these markers, the pedigree was subdivided into three families, with many of the individuals from the first two generations not included. Analysis of all markers was performed by the linkage program Mendel on a Sun workstation.

Linkage was first found on chromosome 13q12, by use of marker D13S175 (maximum LOD score [Z_{max}] 7.06 at a recombination fraction [θ] of .001). After this initial linkage, several other markers in this region were tested, and linkage was found with markers D13S141 ($Z_{max} = 5.29$ at $\hat{\theta} = .001$) and D13S115 ($Z_{max} = 3.35$ at $\hat{\theta} = .075$). Positive LOD scores below the level of significance were found with markers at D13S143 ($Z_{max} = 1.03$ at $\hat{\theta} = .075$) and D13S232 ($Z_{max} = 2.62$ at $\hat{\theta} = .125$). Linkage data are summarized in table 1.

We identified a number of recombination events occurring between the disease locus and the chromosome 13 markers (fig. 1). On the basis of an assumption of a common founder, all affected individuals should share a common homozygous haplotype at the disease locus. Only markers D13S175 and D13S141 are homozygous in all affected individuals, indicating that recombination events have occurred distal to these markers.

To determine the relative location of D13S143, we genotyped 96 CEPH individuals (eight families) with this marker. Two-point linkage analysis between D13S143 and other chromosome 13 markers placed D13S143 telomeric to D13S175. This allowed us to de-

Table 1

Two-Point Lod Scores between NSRD1 and Associated Markers on Chromosome 13

Locus	Lod Score at θ =							Z_{max}	$\hat{\theta}$
	.0	.05	.10	.15	.20	.30	.40		
D13S175	7.06	6.34	5.60	4.85	4.08	2.53	1.07	7.06	.001
D13S141	5.29	4.72	4.14	3.55	2.95	1.78	.71	5.29	.001
D13S143	−∞	1.00	1.02	.93	.79	.49	.21	1.03	.07
D13S232	−∞	1.62	2.51	2.62	2.41	1.60	.69	2.62	.125
D13S115	−∞	3.28	3.30	3.06	2.69	1.79	.85	3.35	.075

fine the genetic interval for DFNB1 as being centromeric to the D13S143 locus, which corresponds to the genetic interval defined for DFNA3.

Using genotyping data from the deafness pedigree as well as the CEPH pedigrees, we constructed the map of the pericentromeric region of chromosome 13, shown in figure 2. This map is consistent with previously generated maps of the region that are found in the literature (Petruckhin et al. 1993; Buetow et al. 1994; Guilford et al. 1994*b*).

It is intriguing that deafness at the DFNB1 locus is shared by isolated families in Tunisia and Israel. Studies of other populations may indicate that nonsyndromic deafness is caused by a mutation at the DFNB1 locus in a significant portion of affected families.

It is likely that genotypic data from distantly related affected individuals in this tribe will allow further narrowing of the disease interval. With this goal in mind, collection of DNA from additional tribe members is underway.

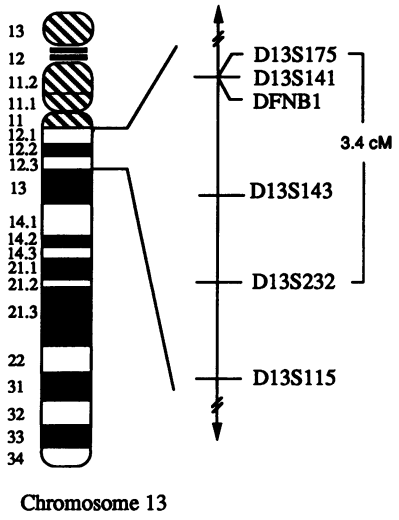

Figure 2 Schematic representation of the pericentromeric region of chromosome 13, showing the relative location of the NSRD1 gene and polymorphic markers.

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Acknowledgments

We gratefully acknowledge the patients and their families for their participation in this study. In addition, we thank Dr. Darryl Nishimura and Anne Kwitek-Black for assistance and helpful discussion. This work was supported by NIH grants HG00457 and P50HG00835 (both to V.C.S.) and by the Roy J. Carver Charitable Trust. E.M.S. is a Research to Prevent Blindness Dolly Green Scholar.

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Am. J. Hum. Genet. 57:968–970, 1995

Refinement of the OPA1 Gene Locus on Chromosome 3q28-q29 to a Region of 2–8 cM, in One Cuban Pedigree with Autosomal Dominant Optic Atrophy Type Kjer

To the Editor:

Kjer type autosomal dominant optic atrophy (Lodberg and Lund 1954; Kjer 1959; Kjer et al. 1983 [MIM 165500; McKusick 1992]) was reported to have a prevalence of 1:50,000 (Lyle 1990) and is therefore the most common form of familial optic atrophy (Eliot et al. 1993). Age at onset and chronic progressive course were used as subclassification criteria by Kjer (1959), Jaeger (1966), and Smith (1972), stating that almost all cases manifested subacutely before 8 years of age. Typically, tritan color defects and small paracentral scotomas are found together with both variable reduction of visual acuity, of approximately 0.3/0.1, and a temporal pallor on fundoscopy. Pathologically the retinal ganglion cells are affected, resulting in a progressive degeneration of the optic nerve (Johnston et al. 1979).

A recent analysis in three Danish families demonstrated the position of a dominant optic atrophy gene within 12 cM on chromosome 3q28-q29 (maximal lod score [Z_{max}] = 10.3), a locus named "OPA1" (Eiberg et al. 1994). We investigated a Cuban six-generation pedigree with 28 members affected by autosomal dominant optic atrophy, for linkage on the OPA1 locus on chromosome 3. Disease manifestation was determined to have occurred before 8 years of age in 17 of 22 patients, while patients IV14, IV20, V4, V14, and V15 (fig. 1) reported subjective complaints only at ages 14, 35, 16, 9, and 10, respectively. Good performances on Ishihara testing were found in patients IV20 and V3, with 16/21 and 15/21 tests, and again in patient V14, with 14/21 Ishihara tests, who was also unusual by being able to count fingers at a distance of 3 m (table 1). Investigation of the clinical details of patient V14 revealed a history of rheumatic fever with tonsillectomy, swellings of large joints, chest pain through pericarditis, endocarditic skin embolisms, and chorea minor. On clinical grounds it was concluded that the visual problems in patient V14 might arise from retinal embolisms, and in the linkage analysis the affection status of this patient was

Table 1

Clinical Details of Affected Individuals of a Cuban Family with Kjer Optic Atrophy

Individual (age [years])	Visual Acuity	Color Vision[a]	Field Defects[b]
III4 (74)	.5 m	0/21	ACS and CR
III6 (69)	centimeters	0/21	ACS and CR
III9 (78)	centimeters	1/21	ACS and CR
IV2 (83)	centimeters	1/21	Impossible
IV5 (46)	centimeters	0/21	ACS and CR
IV8 (54)	centimeters	1/21	ACS and CR
IV9 (44)	.5 m	0/21	ACS and CR
IV12 (49)	2 m	1/21	ACS and CR
IV14 (51)	.5/.3 m	5/21	ACS and CR
IV18 (42)	.3 m	1/21	ACS and CR
IV20 (39)	.2	16/21	RCS and CR
V1 (46)	.5 m	0/21	Impossible
V2 (43)	.5 m	0/21	ACS and CR
V3 (29)	.5	15/21	RCS and CR
V4 (26)	2 m	1/21	RCS and CR
V6 (29)	.05	1/21	ACS and CR
V8 (30)	.05	1/21	ACS and CR
V10 (24)	2 m	1/21	RCS and CR
V13 (20)	1 m	1/21	RCS and CR
V14 (12)	3 m	14/21	ACS and CR
V15 (16)	.5 m	1/21	ACS/RCS and CR
VI1 (9)	.5 m	1/21	ND
VI2 (3)	1 m	1/13	ND

[a] As determined by the Ishihara test.

[b] ACS = absolute central scotoma; CR = concentric reduction; RCS = relative central scotoma; and ND = not determined.