

SHORT REPORT

DFNB39, a recessive form of sensorineural hearing impairment, maps to chromosome 7q11.22–q21.12

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This article describes the identification of a novel locus (DFNB39) responsible for an autosomal recessive form of hearing loss segregating in a Pakistani consanguineous family. The hearing impaired members of this family present with profound prelingual sensorineural hearing impairment and use sign language for communications. Linkage was established to microsatellite markers located on chromosome 7q with a maximum multipoint lod score of 3.8. The region of homozygosity spans a 19 cM region that is bounded by markers D7S3046 and D7S644.

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Introduction

Nonsyndromic hearing loss in humans is the most genetically heterogeneous trait known. To date, over 80 loci have been localized and 30 genes have been identified for nonsyndromic hearing loss.¹ Autosomal recessive nonsyndromic hearing loss (ARNSHL) is the most common form of hereditary hearing impairment and is generally characterized by a sensorineural defect.² Identifying genes involved in hearing impairment and characterizing the proteins they encode will increase our knowledge of the molecular processes involved in the auditory system. In addition, it will improve our understanding of how these processes can become altered and lead to hearing impairment.

Material and methods

Clinical findings

The study was initiated with the prior approval of the Institutional Review Board of Quaid-I-Azam University,

Islamabad, Pakistan. Informed consent was obtained from all subjects who participated in the study. The family (pedigree 4011) described in this article resides in the Punjab province of Pakistan. Owing to strict social customs, the family members rarely marry outside of the family. Pedigree 4011 was constructed on the basis of information obtained from family members. The transmission of hearing impairment is consistent with autosomal recessive inheritance (Figure 1). The onset of hearing impairment is prelingual and most probably congenital. All affected individuals, regardless of age, display the same level of profound hearing impairment, implying that the hearing loss is not progressive. All the affected individuals use sign language for communication. There is no evidence that the hearing impairment in this kindred belongs to a syndrome or that there is gross vestibular involvement.

Linkage analysis

Genomic DNA was extracted from peripheral-blood samples by established procedures.³ DNA samples were obtained from 10 family members, including four individuals who had hearing impairment due to DFNB39. The samples were genotyped using microsatellite markers

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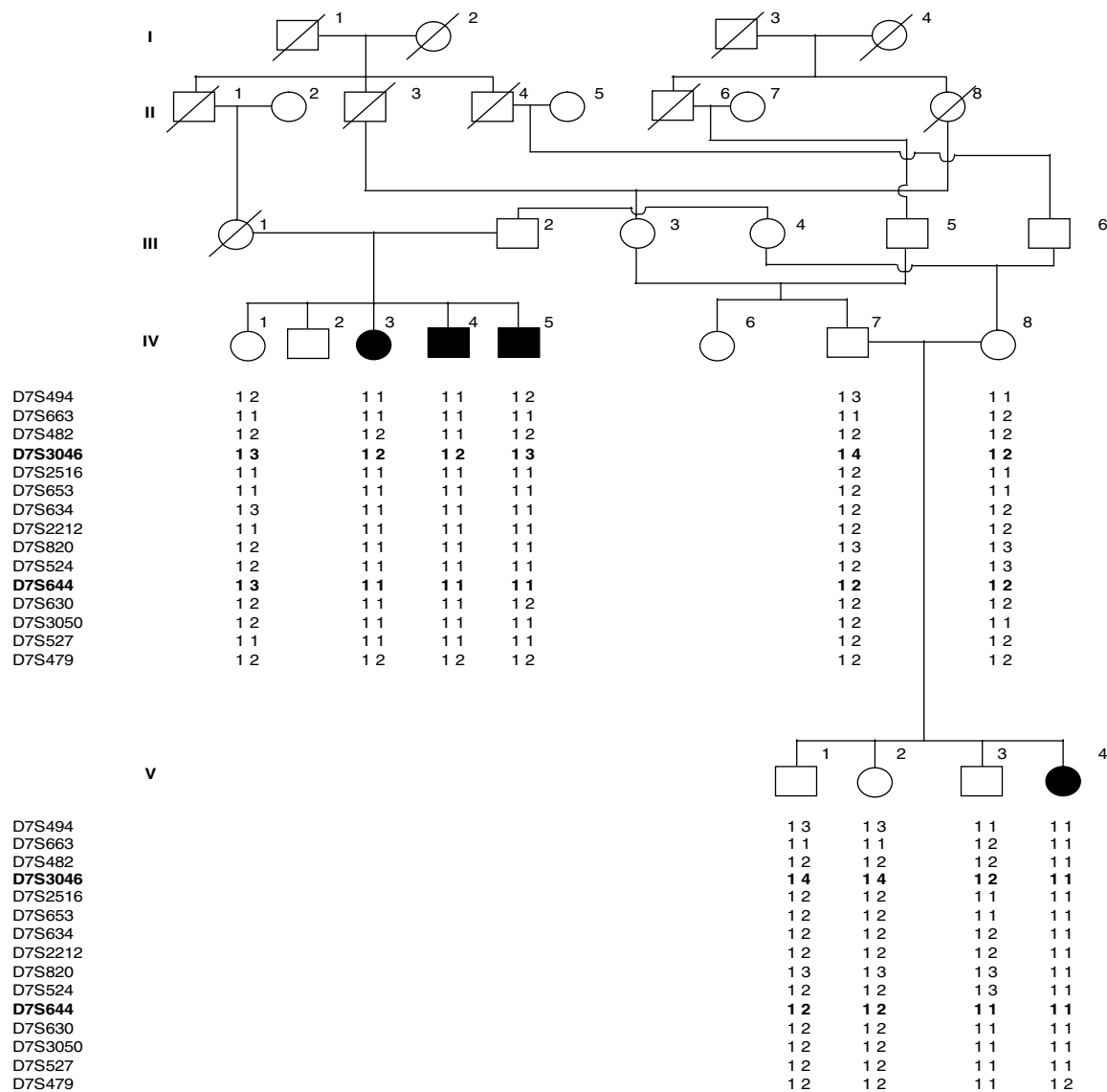


Figure 1 Drawing of pedigree 4011, which segregates DFNB39. The sexes of some of the family members have been changed to protect the anonymity of the family. Black symbols represent individuals with hearing impairment due to DFNB39. Clear symbols represent unaffected individuals. Haplotypes for the most closely linked STRPs are shown below each symbol. The markers D7S3046 and D7S644 that flank the DFNB39 region are shown in bold.

spaced at approximately 10 cM interval in order to localize the ARNSHL locus.

Linkage analysis was carried out under a fully penetrant autosomal recessive model with a disease allele frequency of 0.001. Two-point linkage analysis was carried out using the MLINK program of the FASTLINK computer package.⁴ Multipoint linkage analysis was performed using GENEHUNTER 2.1_r3 beta.⁵ Due to the computational limitations of GENEHUNTER and the size of the family, the pedigree was split into two halves for analysis. Lod scores were calculated for each half and then summed. For

multipoint linkage analysis, marker order and map distances from the deCode genetic map⁶ were used.

Results

After performing linkage analysis for 50 markers, a lod score of 2.7 at $\theta=0$ was observed for marker D7S820. In addition, all affected family members were homozygous for marker D7S820. Fine mapping of the region was carried out by genotyping 17 additional markers in this region

Table 1 Two-point lod score results between the DFNB39 locus and chromosome 7 markers. Also displayed are the genetic and sequence-based physical map distances. Markers displayed in bold flank the region for DFNB39

Marker	deCode map position ^a	Marshfield map position ^b	Physical map position ^c	Lod score at $\theta =$									
				0.0	0.01	0.02	0.03	0.04	0.05	0.1	0.2	0.3	0.4
D7S494	78.49	76.71	56887213	–∞	0.03	0.29	0.42	0.51	0.56	0.65	0.55	0.35	0.16
D7S663	78.96	78.65	65356189	0.56	0.53	0.51	0.49	0.47	0.45	0.36	0.20	0.08	0.02
D7S482	79.22	78.65	65909716	–∞	1.53	–0.99	–0.70	–0.51	–0.37	–0.06	0.03	0.01	0.00
D7S3046	Not on map	78.65	67192609	–∞	–1.10	–0.60	–0.30	–0.10	0.00	0.30	0.30	0.20	0.10
D7S2516	83.51	83.99	69754702	0.79	0.77	0.75	0.73	0.71	0.69	0.59	0.40	0.23	0.09
D7S653	84.6	84.52	70482619	0.79	0.77	0.75	0.73	0.71	0.69	0.59	0.40	0.23	0.09
D7S634	92.49	93.1	78383543	2.70	2.60	2.50	2.50	2.40	2.30	2.00	1.30	0.70	0.30
D7S2212	96.44	95.43	81332041	1.36	1.31	1.27	1.22	1.18	1.13	0.91	0.52	0.23	0.07
D7S820	97.88	98.44	82324655	2.70	2.60	2.50	2.50	2.40	2.30	2.00	1.30	0.70	0.30
D7S524	98.28	97.38	83214534	2.70	2.70	2.60	2.50	2.40	2.40	2.00	1.30	0.70	0.30
D7S644	99.02	97.89	84820201	–∞	0.90	1.10	1.20	1.30	1.30	1.30	0.90	0.60	0.20
D7S630	99.93	98.44	86978841	–∞	–1.45	–0.91	–0.62	–0.43	–0.29	0.02	0.11	0.07	0.03
D7S3050	105.01	105.92	92237735	1.70	1.66	1.62	1.59	1.55	1.51	1.31	0.93	0.56	0.23
D7S527	106.3	108.59	94150287	–∞	–0.37	–0.11	0.02	0.11	0.16	0.26	0.21	0.11	0.05
D7S479	Not on map	109.12	94868067	–∞	–1.90	–1.47	–1.20	–1.01	–0.87	–0.44	–0.13	–0.04	–0.01

^aSex-average Kosambi cM map distance from the deCode genetic map.

^bSex-average Kosambi cM map distance from the Marshfield genetic map.

^cSequence-based physical map distance in bases according to the Human Genome Project – Santa Cruz.

(Table 1). Three of these markers (D7S1433, D7S611 and D7S627) were not informative for linkage and are not included in Table 1. Although none of the additional 14 markers that were genotyped exhibited a significant lod score, markers D7S524 and D7S634 also produced maximum lod scores of 2.7 at $\theta=0$. It was observed that there was an inconsistency in the position of marker D7S820 between the Marshfield genetic map⁷ and both the deCode genetic map⁶ and the Human Genome Project – Santa Cruz sequenced-based physical map⁸ order (Table 1). In order to confirm that the position of marker D7S820 on the Marshfield map was potentially incorrect, Centre d'Etude du Polymorphisme Humain (CEPH) genotype data were analyzed using MAP-O-MAT.⁹ The support for the position of marker D7S820 on the Marshfield genetic map was low, therefore for the multipoint analysis the deCode genetic map distances and marker order were used. Those markers that were not included on the deCode genetic map were not included in the multipoint analysis (see Table 1).

Multipoint linkage analysis yielded a significant lod score of 3.8 at marker D7S2122. Three affected individuals (IV-3, IV-4, IV-5) are heterozygous for marker D7S3046 and individual (V-3) who is not hearing impaired is homozygous at D7S644 (Figure 1). Thus, the region of homozygosity is 19.2 cM according to the Marshfield genetic map,⁷ flanked by markers D7S3046 and D7S644. This region encompasses 17.6 Mb.⁸ Marker D7S3046 is not included on the deCode map, the next centromeric marker is D7S482. According to the deCode genetic map, both the

region of homozygosity and the three-unit support interval is 19.8 cM and is flanked by markers D7S482 and D7S644.

Discussion

Four other loci for hearing loss DFNB4 (7q31.1), DFNB13 (7q34–36), DFNB14 (7q31) and DFNB17 (7q31) have already been mapped on the long arm of chromosome 7.¹ For these three loci only the SLC26A4 gene has been identified for the DFNB4. Mutations within the SLC26A4 gene are also responsible for the Pendred syndrome¹⁰. DFNB39, which is centromeric to these loci, does not overlap with any of these loci, thus indicating the involvement of a novel gene responsible for hearing loss in kindred 4011. Further work is currently being carried out to identify the gene that is responsible for DFNB39.

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