Report

Mutations of *MYO6* Are Associated with Recessive Deafness, DFNB37

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Cosegregation of profound, congenital deafness with markers on chromosome 6q13 in three Pakistani families defines a new recessive deafness locus, *DFNB37*. Haplotype analyses reveal a 6-cM linkage region, flanked by markers D6S1282 and D6S1031, that includes the gene encoding unconventional myosin VI. In families with recessively inherited deafness, DFNB37, our sequence analyses of *MYO6* reveal a frameshift mutation (36-37insT), a nonsense mutation (R1166X), and a missense mutation (E216V). These mutations, along with a previously published missense allele linked to autosomal dominant progressive hearing loss (DFNA22), provide an allelic spectrum that probes the relationship between myosin VI dysfunction and the resulting phenotype.

Autosomal recessive deafness is a genetically heterogeneous neurosensory disorder for which 54 distinct loci have been published and 32 genes have been identified (Petit et al. 2001; Griffith and Friedman 2002). Most autosomal recessive deafness is clinically indistinguishable, so genetic loci are most often identified by linkage studies using large, usually consanguineous pedigrees (Friedman et al. 2000). We ascertained a large Pakistani family, PKDF10 (fig. 1), with six individuals who have bilateral, profound, sensorineural, congenital hearing loss segregating as an autosomal recessive disorder. In addition to deafness, vestibular dysfunction and mild facial dysmorphology also occur in this family. One hearing-impaired individual (IV:19; table 1) has retinitis pigmentosa (RP) along with a vestibular abnormality. The latter two signs, when co-occuring with deafness, constitute Usher syndrome, which is also genetically heterogeneous (Hereditary Hearing Loss Homepage). However, the other clinical phenotypes were mild and did not occur in all deaf individuals (table 1).

A new autosomal recessive deafness locus, *DFNB37*, was defined in family PKDF10, by virtue of exclusion of linkage of the deafness phenotype to markers linked to known DFNB loci. A genomewide scan using the Weber 9 marker panel revealed cosegregation with markers at 6q13 (LOD score [Z] 7.10 for D6S1589, at a recombination fraction [θ] of 0; see table 2). Haplotype analysis defined a proximal recombination at marker D6S1282 (82.59 cM) in affected individual IV:17 and a distal recombination in individual IV:15, who has normal hearing and is homozygous for marker D6S460 (89.63 cM) (fig. 1). Markers in the *DFNB37* interval were used to screen 250 Pakistani and 100 Indian families segregating recessive deafness. Two additional families with *DFNB37* linkage were identified, PKDF71 and PKSR14 (fig. 1; table 2). Affected individuals from family PKDF71 have profound sensorineural hearing loss, and the affected individual from family PKSR14 has severe-to-profound hearing loss. There were no obvious clinically relevant traits segregating in the families, other than deafness. Haplotype analysis of affected individual IV:10 from family PKDF71 defined a distal recombination breakpoint, reducing the linkage region for *DFNB37* to ~6 cM, bounded by markers D6S1282 (82.59 cM) and D6S1031 (88.63 cM) (fig.
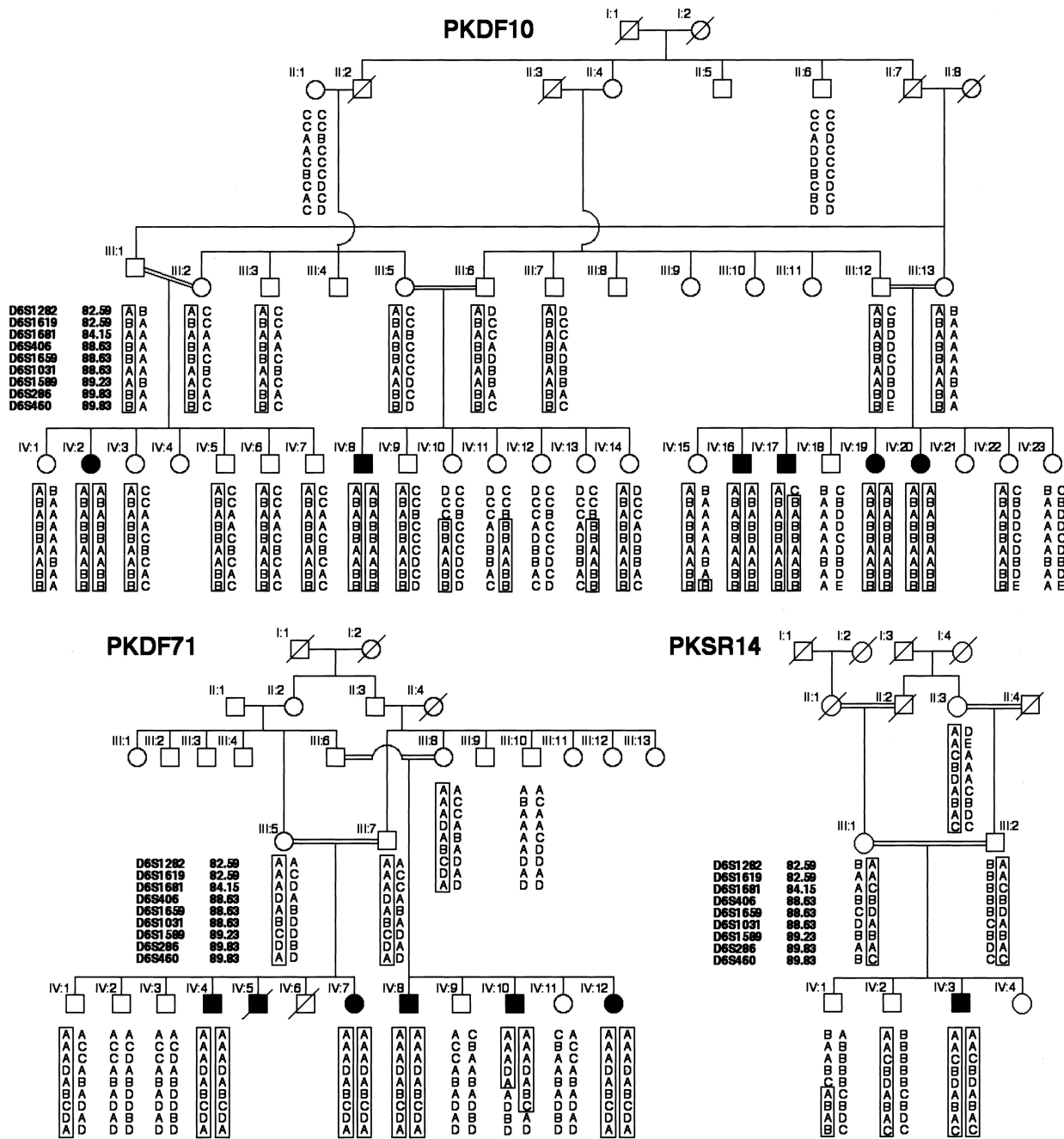
Figure 1 Haplotypes of markers showing linkage to *DFNB37* at 6q13 for three families segregating profound, sensorineural, recessive hearing loss. Affected individual IV:17 in family PKDF10 provided the proximal recombination breakpoint at marker D6S1282 (82.59 cM). The distal recombination is provided by affected individual IV:10 of family PKDF71 at marker D6S1031 (88.63 cM). National Institutes of Health (OH93-N-016) and National Centre of Excellence in Molecular Biology (CEMB) institutional review board approval and written informed consent were obtained from all participating subjects. DNA was extracted from either peripheral blood samples or buccal swabs and was amplified using fluorescent-labeled primers for STR markers linked to reported nonsyndromic recessive deafness (DFNB) loci. Amplimers were visualized by gel electrophoresis on ABI 377 DNA sequencers, and genotypes were determined using Genescan and Genotyper software (Applied Biosystems). The genetic linkage distances are from the Center for Medical Genetics Web server.

Table 1

Clinical Description of PKDF10

Subject[a]	Age (years)	Hearing Phenotype	Vestibular Phenotype		Eye Phenotype		Other Findings
			Age at Ambulation	ENG Results	Fundoscopy Results	ERG Results	
IV:16	20	Profound hearing loss	6 years	Abnormal	Congenital stationary night blindness	Normal	Retinal pigment epithelial changes; flat feet and prominence of the talus due to lack of arches in the feet; atrophy of the muscles around the Achilles tendon; minor facial dysmorphic features
IV:17	9	Profound hearing loss	14 mo	NA	No abnormality detected	Normal	History of hysteric fits from the age of 1 mo; flat feet and prominence of talus due to lack of arches in the feet; minor facial dysmorphic features; lordotic posture but no muscular weakness
IV:19	10	Profound hearing loss	15 mo	NA	RP	RP	Alternating squint; difficulties in tandem gait
IV:20	16	Profound hearing loss	18 mo	NA	No abnormality detected	Normal	History of hysteric fits from the age of 1 mo; alternating squint
IV:8	13	Profound hearing loss	18 mo	NA	No abnormality detected	Normal	Alternating squint; flat feet and prominence of talus due to lack of arches in the feet
IV:2	18	Profound hearing loss	30 mo	Abnormal	No abnormality detected	NA	
IV:23	17	Normal	3 years	NA	No abnormality detected	NA	Weakness in the right leg
IV:22	11	Normal	15 mo	NA	No abnormality detected	NA	
IV:18	24	Normal	18 mo	NA	No abnormality detected	NA	

NOTE.—ENG = electronystagmography; ERG = electroretinography; NA = not available. All examinations were performed by local physicians in Pakistan, and the neurological examinations were videotaped. All results were reviewed by the clinicians at the National Institutes of Health who are also coauthors of the present article (A.J.G., R.C.C., and A.G.).

[a] All subjects had normal reflexes and ambulated normally during the examination.

Table 2

Two-Point LOD Scores (at $\theta = 0$)

	LOD Score in Family[a]		
Marker	PKDF10	PKDF71	PKSR14
D6S1282	$-\infty$	1.47	1.08
D6S1619	4.84	4.03	.98
D6S1681	3.16	3.01	.92
D6S406	6.44	4.22	.38
D6S1659	6.53	3.90	1.23
D6S1031	4.67	2.05	1.02
D6S1589	6.99	2.27	.18
D6S286	6.44	1.63	.34
D6S460	5.35	1.35	.41

[a] LOD scores were calculated using parameters described elsewhere (Ahmed et al. 2001; Bork et al. 2001).

1). This interval includes *MYO6* (GenBank accession number AB002387), which encodes unconventional myosin VI.

We screened for mutations in *MYO6* by sequencing the 1 noncoding and 32 coding exons in the affected individuals from families PKDF10, PKDF71, and PKSR14. All exons were amplified by PCR from genomic DNA in a 20-μl reaction volume. Primers were designed to flank all of the exon-intron boundaries (see appendix A, table A1). PCR amplification, sequencing reactions, and mutational analyses were performed as described elsewhere (Ahmed et al. 2001). In all affected individuals of family PKDF10, we found a homozygous single-base-pair insertion (36-37insT) in the second exon of *MYO6* (fig. 2). This insertion is predicted to cause a frameshift and premature translation termination after the first 12 amino acids of myosin VI. In family PKDF71, affected individuals are homozygous for a transition mutation, 3496C→T
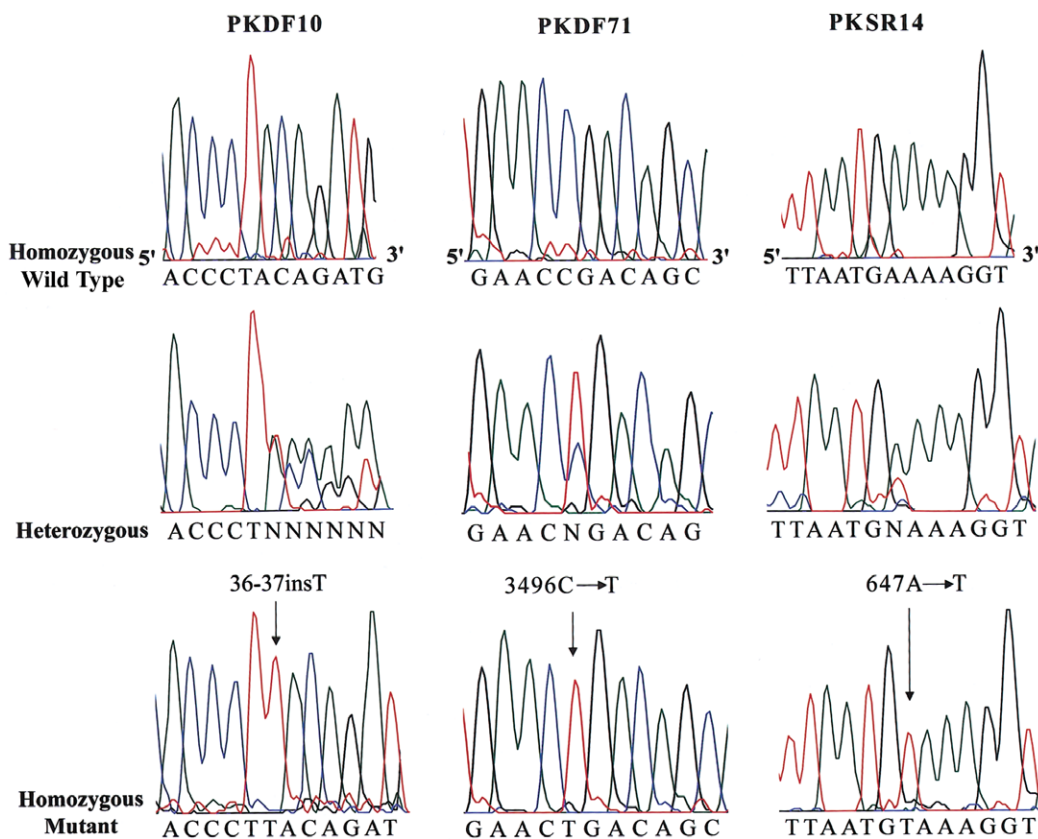

Figure 2 *MYO6* mutations segregating in three Pakistani families. *Left,* Electropherograms of amplimers from genomic DNA templates, illustrating homozygosity for a single-base-pair insertion mutation in an affected individual, heterozygosity in an obligate carrier, and homozygosity for the wild-type allele in an unaffected individual from family PKDF10. An arrow indicates the site of the 36-37insT in the second exon. *Center,* Electropherograms illustrating genotypes of a homozygous wild-type allele, a 3496C→T heterozygote, and a person homozygous for 3496C→T of family PKDF71. *Right,* Electropherograms are shown for transversion mutation 647A→T, a carrier, and the wild-type allele of family PKSR14. All the mutations described here are numbered from start codon ATG (GenBank accession number AB002387).
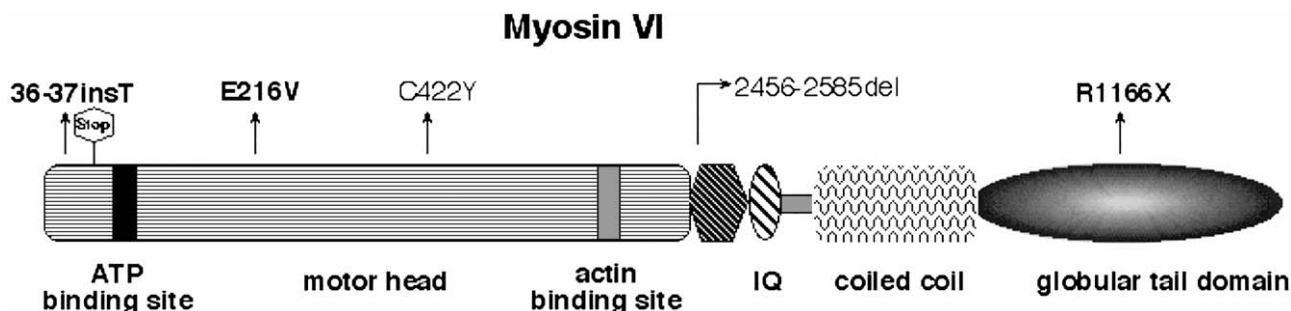
Myosin VI

Figure 3 A drawing of myosin VI, showing the locations of the mutations causing deafness in humans and mice. The three mutant alleles reported in this study are shown in bold letters, whereas C442Y and 2456-2585del are from the studies by Melchionda et al. (2001) and Avraham et al. (1995), respectively. Shown also is the predicted stop codon after twelve out-of-frame amino acids due to 36-37insT.

(fig. 2), resulting in a nonsense codon (R1166X) in exon 32, which encodes part of the globular domain of the tail region (fig. 3). These two mutations were not found in 100 ethnically matched control DNA samples from Pakistan.

The single affected individual in family PKSR14 is homozygous for a missense mutation (E216V) in the motor domain of myosin VI caused by a transversion mutation, 647A→T (fig. 2). The E216V mutation substitutes a valine (nonpolar) for glutamate (polar, negatively charged). This glutamate residue is conserved in myosin VI proteins from human, mouse, chicken, pig, striped bass, and sea urchin (fig. 4). In *Caenorhabditis elegans* myosin VI, there is an aspartate residue (also polar, negatively charged) at this position, but *Drosophila melanogaster* myosin VI has a nonpolar amino acid (alanine) at this position. The 647A→T transversion segregating in family PKSR14 was not found among 270

normal representative DNA samples (540 chromosomes) from the same ethnic group or from the 81 DNA samples (162 chromosomes) of a Human Diversity panel (Coriell Cell Repositories).

Myosins are motor proteins that hydrolyze ATP and translocate along actin filaments (Sellers 1999; Berg et al. 2001). Mutations of myosins IIA, IIIA, VIIA, and XVA are associated with hearing loss in humans (Gibson et al. 1995; Weil et al. 1995; Liu et al. 1997a, 1997b; Probst et al. 1998; Wang et al. 1998; Lalwani et al. 2000; Liburd et al. 2001; Walsh et al. 2002). Unlike these other actin-based motors, myosin VI moves toward the minus end of F-actin filaments (Wells et al. 1999; Nishikawa et al. 2002). Myosin VI is involved in many processes, including membrane trafficking, recycling, cell movement, and endocytosis (Mermall and Miller 1995; Bohrmann 1997; Mermall et al. 1998; Buss et al. 2001; Morris et al. 2002). In the inner and outer hair cells of the
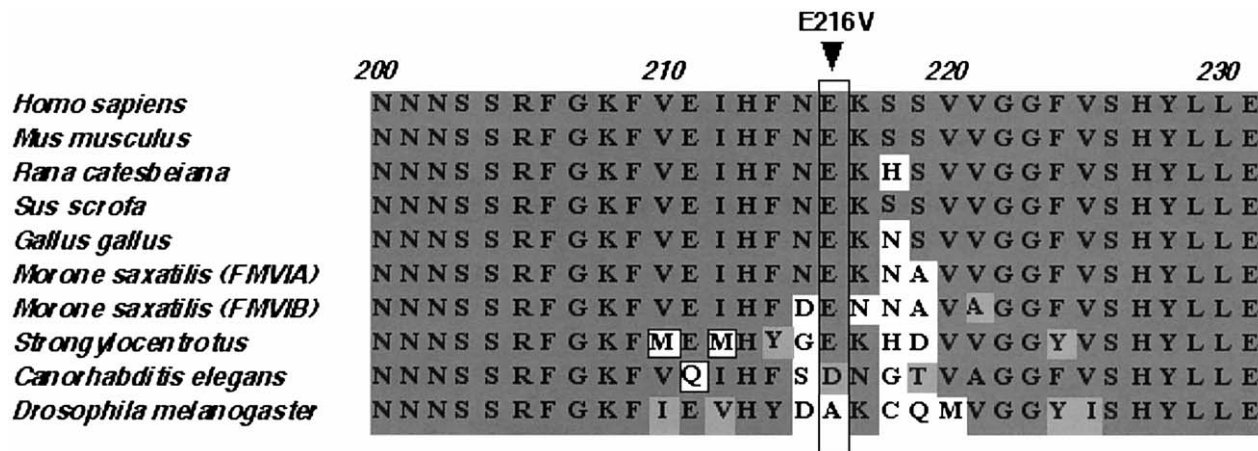

Figure 4 Alignment of a portion of myosin VI proteins from various species, showing conservation of the glutamate residue at position 216 in the motor domain among seven myosin VI proteins from *Homo sapiens, Mus musculus, Rana catesbeiana, Sus scrofa, Gallus gallus, Morone saxatilis,* and *Strongylocentrotus.* The conserved amino acids are shown with dark gray background, similar amino acids are shown with a light gray background, and the nonconserved amino acids are shown with a white background.

organ of Corti, myosin VI is highly expressed at the base of stereocilia rootlets and in the pericuticular necklace (Avraham et al. 1997; Hasson et al. 1997; Self et al. 1999).

Myosin VI is abundantly expressed in the retina (Breckler et al. 2000), and it has been speculated that mutations of *MYO6* might cause RP (Ahituv et al. 2000). Interestingly, one hearing-impaired individual (IV:19, age 10 years; table 1) among the families with DFNB37 was found to have RP. No ocular abnormalities were detected in the older deaf individuals, and electroretinography results were normal among the other eight affected individuals (aged 9–21 years) from the three families with DFNB37. We cannot rule out the possibility of an atypical Usher syndrome in family PKDF10, since most of the affected individuals are too young to exhibit the ocular phenotype or there could be a modifier altering the effect of a null mutation in retina. In addition to deafness in family PKDF10, vestibular dysfunction and mild facial dysmorphology also occur, but not in all of the deaf individuals (table 1). Late ambulation, which may or may not be related to a vestibular dysfunction, was also found in individual IV:23 (table 1), who has normal hearing and is a noncarrier of the *MYO6* mutant allele. The small sample size makes it difficult to determine whether there is reduced penetrance for these and other clinical findings that can be attributed to a null mutation of *MYO6*.

Two recessive putative null mutations of mouse *Myo6* are responsible for deafness and vestibular dysfunction in *Snell's waltzer* mice (Avraham et al. 1995), and a missense allele (C422Y) of MYO6 cosegregates with nonsyndromic, dominantly inherited, progressive hearing loss in a single family that defined the *DFNA22* locus

(MIM 606346) (Melchionda et al. 2001). The predicted structural motifs and the known, postulated mutant alleles of myosin VI that are associated with hearing loss are shown in figure 3. Since the *DFNB37* alleles appear to be functional null alleles and since the heterozygous carriers of *DFNB37* mutations of *MYO6* have normal hearing, the putative *DFNA22* mutation likely acts via a dominant-negative or gain-of-function mechanism. There is a possibility that two missense substitutions (C422Y and E216V) found in *MYO6* may have nothing to do with hearing loss and may be in linkage disequilibrium with actual mutations. Biophysical measurements, such as a motility assay with these substitutions in the motor domain of *MYO6,* may help to address the pathogenic potential, if any exists. Nevertheless, two of the *DFNB37* alleles (36-37insT and R1166X) reported herein constitute convincing genetic evidence that disablement of *MYO6* causes recessively inherited deafness in humans.

Appendix A

Table A1

MYO6 Intronic Primer Pairs Flanking Known Exons

	Primer (5′→3′)		Product Length (bp)
Exon	Forward	Reverse	
1	aac aag aac tcc cgg ctt gt	cat cca tca cct gct tct cc	589
2	ggc aga tgt gtt tgt tag ttg g	cct agg gca cat acc tct gat t	452
3	tat gca acc aat taa gcc ctt c	ttc tga acc cgc aca gtg tat	253
4	agg atg agt caa agt gat tca ga	tct att caa gag gct cag atc aa	291
5	gga ctg att tgg gag tct tag tt	cca aga ggt ata cag ttt ctc caa	391
6	tga ttt ctt taa gag taa gtg gtc ct	aga atg agg tgg aac agt gg	364
7	tga tga tct agg ttt cag ttt tat atg	aag aga gtc ttt tgc atc tct ga	258
8	tgg aga tat acc atg cat att ttg	tcc tgc aac cat cta aag taa ca	303
9	aac ctc ttt gat aga caa atg gta tt	aag tat tag gct tga tgg caa tta t	651
10	tct tca tgg ttg gca cta ttt g	gtt aga act ctt act tgg gct cta aaa	279
11	agt gca tta att gac ctg gtg t	cat tct tca ttt ggg aga ttc a	423

(*continued*)

Table A1 (continued)

Exon	Primer (5′→3′) Forward	Reverse	Product Length (bp)
12	aag cct tgc cta tta tat ggt ttt t	cca agc tca ggt ttt aaa cag aa	352
13	tgt gcc tat tct cac atg acc t	cat caa gta aaa tga gtt aca aag gag	394
14	gcc att att aca att aca ttt tat cct	ctt ccg tta tac acc atc cat c	293
15	gtt cag aaa cag tgc aaa att ca	gca cag aaa aag cac taa aca ca	218
16	tga tca gtc ctt gaa atc tgt ga	tgc acc ttt tta ata atg tct cgt	286
17	tga aaa gtg tga aaa ttt cct gt	aat aac cac gtg aaa taa tta ata acc	320
18	gga gaa aac cat ttc atg ttg a	ggg tct gct ctt gaa ctt cac t	585
19	cac tgt gta ctt tgg ctt ttt ga	tgc cat gtc tgg aga atg tta c	442
20	tgc ttt gaa agt tgc agg tat t	tgc act gta aaa taa tca aga taa tgg	289
21	ttt tgg act tcc gaa cag tga t	caa agc ttt aaa caa agc ctg aa	295
22	tat aaa tgc cac cca aat tga a	tgt tgt tag tga cca tat aat tca aga	289
23	ttg aca tgt gac cat ttt cag ac	caa cac tcc aca aac cat ctt g	313
24	ttg agc att act ttg tga aaa tga	gaa aac ctg agt atc caa act gc	286
25	gaa gtg aaa tac cct gtt tag ca	ttt gaa aaa cta agg acg ttt tct	346
26	ttt tgc tgt att tgc ata ttg ga	aaa atc gat tga acc cga gag	575
27	ctt ctg aag gat tct tta ttt tct gtt	cca tgt ccg gct aat ttg tt	328
28	aag ggg agt gat caa gta aac aa	tca ttc act tga gta tga aag tcg	398
29	aac aca aat ttg cac aat cca g	cca atg aga aaa cta ctc cca aa	176
30	tgt gtt acg gct aga ttt gtt ga	cat gta aca ggt tct ggt cca a	308
31	gca tgc ttt ctt gcc tct tta g	cat aac tat gtg gga tcc tct gg	450
32	aaa aat ctc ctt atg cga cag aat	tgg gac att tta ccc atg tct t	314
33	act ttt cag tca cca cct cga t	cca ctg aaa att gta gca aaa ca	238
34	tta cta tta ggg acc ttt ctt ctt ttt	ccc tca acc ctg aaa tgt aat a	446
35a	aat agg tat ttc agg cat aca act g	tag tct tct ggc aaa gga tga g	568
35b	cat cct ttg cca gaa gac tac c	gaa aca act tgg aca aga ttc tga	619
35c	ggc ata gtg gct aaa ctg gac t	caa aca cta gtc agc tgg gaa a	554

Note.—Primers were designed through use of the Primer3 Web-Based Server.

Electronic-Database Information

The accession number and URLs for data presented herein are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/
Hereditary Hearing Loss Homepage, http://www.uia.ac.be/dnalab/hhh/
GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *MYO6* [accession number AB002387])
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for DFNA22)
Primer3 Web-Based Server, http://www.genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi

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