

Autosomal Dominant Progressive Sensorineural Hearing Loss Due to a Novel Mutation in the *KCNQ4* Gene

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Objective: To identify the genetic etiology in a family with autosomal dominant progressive sensorineural hearing loss.

Design: Prospective molecular genetic research study.

Setting: Academic genetic research laboratory.

Participants: Seventeen members of a family with dominant progressive nonsyndromic sensorineural hearing loss: 9 affected, 6 unaffected, and 2 spouses.

Interventions: Clinical data from questionnaires, interviews, serial audiograms, and medical records; genetic data from genome-wide linkage analysis and candidate gene mutation analysis.

Main Outcome Measures: Symptoms, age at onset, serial audiometric data, and the presence or absence of a deafness-associated mutation.

Results: Affected individuals in this family presented with autosomal dominant nonsyndromic high-frequency pro-

gressive sensorineural hearing loss, with age at onset ranging from 1 to 21 years. Genome-wide linkage analysis of single-nucleotide polymorphisms yielded evidence of linkage to an 18.9-Mb region on chromosome 1p34-p36, with a multipoint logarithm of odds score of 3.6. This interval contains a known deafness gene, *KCNQ4*, which underlies *DNFA2* deafness. Sequencing of the 14 coding exons and intron-exon junctions of *KCNQ4* revealed a novel heterozygous missense mutation, c.859G>C, p.Gly287Arg. The mutation disrupts the highly conserved GYG motif (glycine-tyrosine-glycine) of the phosphate-binding loop, hypothesized to be critical in maintaining pore structure and function. All 274 controls were negative for the mutation.

Conclusions: Autosomal dominant high-frequency hearing loss is genetically heterogeneous, and linkage analysis is an efficient means of identifying the etiology in larger families. Deafness in this family is caused by a novel mutation in *KCNQ4*.

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IN RECENT YEARS, MORE THAN 50 genes responsible for hearing impairment have been identified.¹ Whereas *GJB2* mutations are the most common cause of recessive nonsyndromic deafness in the US population, dominant nonsyndromic deafness may result from mutations in a variety of genes, none of which predominate in the population. Although various clinical algorithms have been proposed, developing an efficient and cost-effective means to diagnose the genetic etiology of dominant deafness remains a challenge.

The *DFNA2* (deafness, nonsyndromic, autosomal dominant 2) locus was originally mapped to chromosome 1p in 2 families with progressive high-frequency sensorineural hearing loss (SNHL).² Ultimately,

a potassium channel gene, *KCNQ4* (OMIM NM_0047000), was identified as the responsible gene.^{3,4} We used genetic linkage analysis and candidate gene screening to identify the genetic cause of deafness in a family with dominant progressive high-frequency SNHL.

METHODS

This research was approved by the University of Michigan and the Baylor College of Medicine and Affiliated Hospitals institutional review boards, and informed consent was obtained from all the participants. A family (family 63) of European descent segregating high-frequency SNHL was ascertained through contact with the principal investigator (M.M.L.) (**Figure 1**). Participants completed

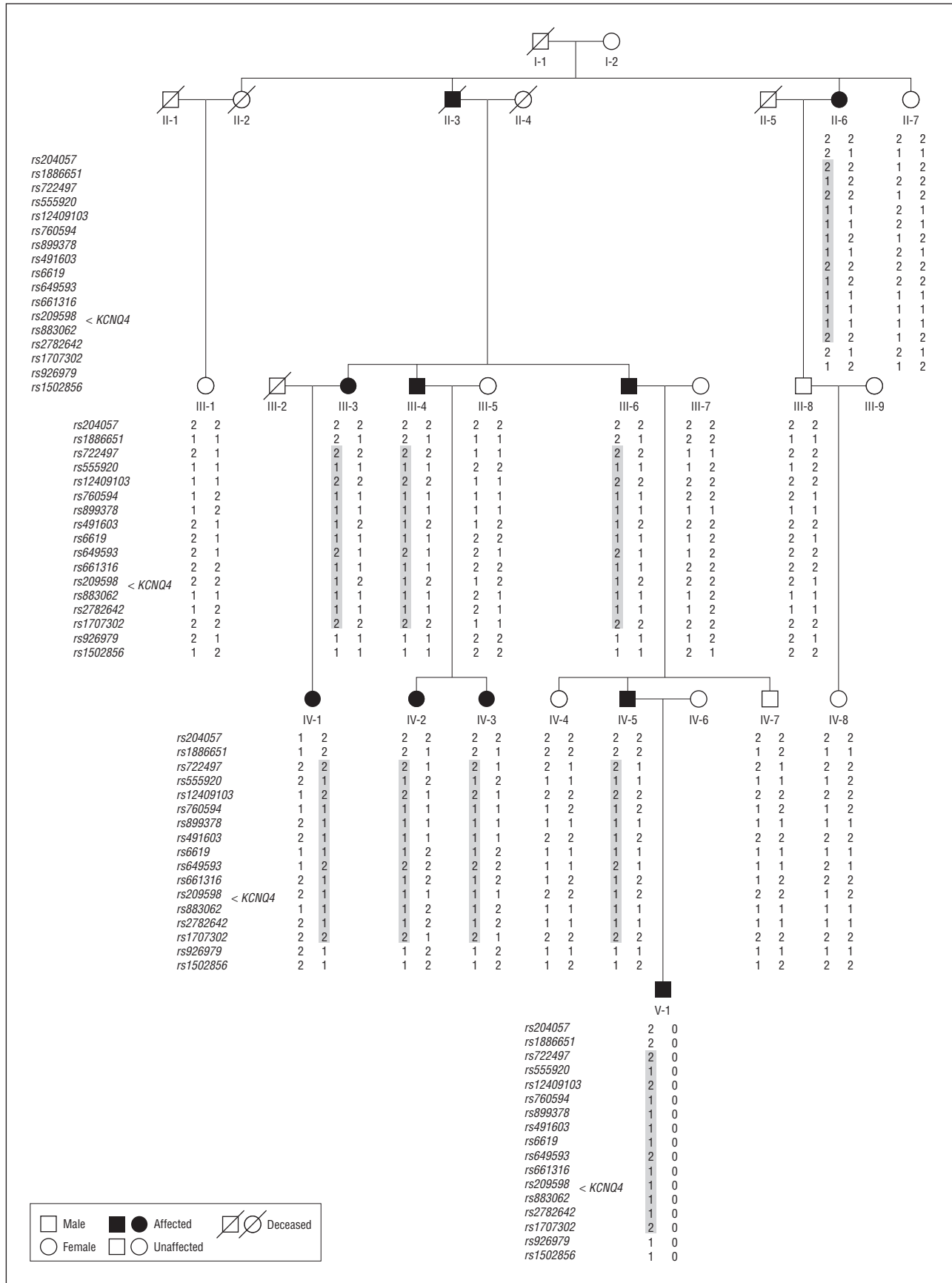


Figure 1. Pedigree of family 63 segregating progressive high-frequency sensorineural hearing loss. Single-nucleotide polymorphisms are listed to the left of the individual's genotype. The haplotype segregating with deafness is highlighted with a gray box. The interval is defined by recombination events at *rs1886651* (centromeric) and *rs926979* (telomeric). *KCNQ4* maps between *rs209598* and *rs883062*.

Table 1. Polymerase Chain Reaction Primers Used for Amplification of *KCNQ4* Exons

Primer Name	5'-3' Sequence	Type	Exon Targeted
KCNQ4x1f	GGAAGAGCAGCCCGAGT	Forward	1
KCNQ4x1r	GATCAGAAACCGGGCTTAGG	Reverse	1
KCNQ4x2f	CCAGGGAATCCAATTCTGA	Forward	2
KCNQ4x2r	TTGCATAGAGGCAGGAGGTC	Reverse	2
KCNQ4x3f	CCCTAACCCAGGACTCTTG	Forward	3
KCNQ4x3r	GATTGGGAGTAAAGGCGTCA	Reverse	3
KCNQ4x4f	GAGACCCGCACAGATTCAG	Forward	4
KCNQ4x4r	AGACAGCCCTCTGACCTC	Reverse	4
KCNQ4x5f	CCTTTATCCCTTCCCGTGT	Forward	5
KCNQ4x5r	TGAGTCAGGAGTACGATGG	Reverse	5
KCNQ4x6f	CCTGTACCCCAACAAGC	Forward	6
KCNQ4x6r	CAAATGTGTGACAGGGGTGA	Reverse	6
KCNQ4x7f	GACACCCTTGACGCCTCTTA	Forward	7
KCNQ4x7r	AGCACACAGGGTTGACACAC	Reverse	7
KCNQ4x8f	CCAAGGACTGGGTTCTTTCA	Forward	8
KCNQ4x8r	TCTCAGCCACTTGTCCCTCAA	Reverse	8
KCNQ4x9f	TCCACCCTGTCTATTCTGG	Forward	9
KCNQ4x9r	GGCAGGCTGTGAGAGGATG	Reverse	9
KCNQ4x10f	AGTCAGCTTTGTCCCACTC	Forward	10
KCNQ4x10r	AGACGCCAGCCAGATCTTT	Reverse	10
KCNQ4x11f	CTGGTGGTTTGGCATAAAG	Forward	11
KCNQ4x11r	GGCTGGTCTCAAACCTCTGA	Reverse	11
KCNQ4x12f	TGGACAAGGGGATAGCAAAG	Forward	12
KCNQ4x12r	GGCCTCAGACTTCATTGAGG	Reverse	12
KCNQ4x13f	TTCTCCTTCATCAGGCAACC	Forward	13
KCNQ4x13r	GCATCCTCCCATGTCAC	Reverse	13
KCNQ4x14f	CTAGCCAAGCTCCACCTTTC	Forward	14
KCNQ4x14r	CATAGGGCCTTGATGGAGTG	Reverse	14

questionnaires, underwent audiologic testing, and provided saliva or peripheral venous blood samples. Historical clinical and audiometric data were obtained as available. DNA was isolated from blood using the Genra Puregene Cell Kit (Qiagen, Valencia, California) and from saliva using the Oragene DNA Kit (DNA Genotek, Kanata, Ontario, Canada) according to the manufacturers' instructions.

GENOTYPING AND LINKAGE ANALYSIS

A whole-genome scan was performed at the Center for Inherited Disease Research using the Illumina HumanLinkage-12 panel (Illumina Inc, San Diego, California), which contains 6090 single-nucleotide polymorphism (SNP) marker loci, for all 16 pedigree members from whom a DNA sample was available. Genotype data were screened for mendelian incompatibilities using PedCheck,⁵ and MERLIN (Multipoint Engine for Rapid Likelihood Inference)⁶ was used to assess the data for the occurrence of double recombination events over short genetic distances, which are most likely due to genotyping error. MLINK of the FASTLINK software package⁷ was used to perform 2-point linkage analysis, and Allegro1.2c⁸ was used for multipoint linkage analysis. An autosomal dominant mode of inheritance with complete penetrance and a disease allele frequency of 0.001 were used in the analysis. Marker allele frequencies were based on HapMap⁹ for the CEU (Centre d'Etude de Polymorphisme Humain) population. (CEU is a control population consisting of 180 Utah residents with Northern and Western European ancestry.) For the multipoint analysis, genetic map distances were based on the Build 36 version of the Rutgers combined linkage-physical map of the human genome.¹⁰ For SNP loci that were not included on the Rutgers map, the sequence-based physical map (Build 36)

Table 2. Audiologic Findings for Affected Members of Family 63

Individual	Age When Tested, y	Audiometric Pattern of Hearing Loss ^a
II-6	89	Severe to profound SNHL
III-3	39	Moderate to profound SNHL
III-4	36	Mild sloping to moderately severe SNHL
III-4	44	Moderate sloping to severe SNHL
III-4	51	Moderate sloping to severe-profound SNHL
III-6	49	Moderate to 4000-Hz sloping to profound SNHL
IV-1	7	Mild sloping to moderately severe SNHL
IV-2	1.5	Borderline normal sloping to mild SNHL in the better-hearing ear
IV-2	4	Mild SNHL
IV-2	15	Mild sloping to 4000-Hz sloping to moderately severe SNHL
IV-3	4	Borderline normal sloping to mild SNHL
IV-3	5	Mild to moderate SNHL
IV-3	10	Mild to moderate SNHL
IV-3	18	Mild to moderately severe SNHL
IV-5	7	Mild sloping to moderate SNHL
IV-5	12	Mild sloping to moderate SNHL
IV-5	24	Mild sloping to moderately severe SNHL
V-1	3	Moderate SNHL

Abbreviation: SNHL, sensorineural hearing loss.

^aHearing loss is bilateral unless otherwise specified.

was used as a reference to determine the physical positions of SNP marker loci, and then interpolation was used to determine the genetic map distance. Haplotype reconstruction was performed using SimWalk2.^{11,12}

SEQUENCING OF CANDIDATE GENES

Candidate genes mapping to the linkage region were screened by sequencing of all exons and intron-exon boundaries. Primer sets for polymerase chain reaction were designed using Primer3 Software¹³ (Table 1). Polymerase chain reaction was performed using the FailSafe PCR Kit according to the manufacturer's instructions (Epicentre Biotechnologies, Madison, Wisconsin) with a 50- μ L reaction volume, 200-ng template DNA, and 0.2- μ M primer, with 32 cycles at 58°C annealing temperature and 1 minute 30 seconds of extension time. The polymerase chain reaction product was purified using Qiaquick columns (Qiagen) and was sequenced by the University of Michigan DNA Sequencing Core.

ANALYSIS OF VARIANTS

Sequence data were compared with the reference sequence (NM_004700) for *KCNQ4*, and variations were recorded. Novel variants were assayed in a panel of 275 controls (550 control chromosomes), of which 185 were from the Caucasian-American Panel and 90 were from the Polymorphism Discovery Resource (Coriell Cell Repositories, Camden, New Jersey), containing 24 European Americans, 24 African Americans, 24 Asian Americans, 12 Mexican Americans, and 6 Native Americans, according to the same protocols listed previously herein.

To assess the affect of amino acid substitutions, wild-type amino acid sequence was compared with mutant sequence using the SIFT (Sorting Intolerant from Tolerant) program.¹⁴ A SIFT score of 0.05 or lower is predicted to be deleterious, and a score higher than 0.05 predicts a tolerated substitution.

Table 3. LOD Scores for the *DFNA2* Locus Region^a

Marker Name	Physical Positions ^b	Genetic Positions ^c	MPT LOD ^d	2-Point LOD, Recombination Fraction						
				0.00	0.01	0.05	0.10	0.20	0.30	0.40
<i>rs213006</i>	21,551,187	46.050	1.25	0.34	0.34	0.33	0.32	0.26	0.18	0.10
<i>rs6426746</i>	22,501,644	47.280	−∞	−∞	1.20	0.53	0.27	0.06	0.02	0.03
<i>rs742230</i>	25,124,011	51.220	−∞	−∞	0.90	0.25	0.01	0.15	0.16	0.11
<i>rs6564</i>	28,085,562	54.000	0.05	1.60	1.56	1.39	1.17	0.72	0.28	0.01
<i>rs1886651^{e,f}</i>	29,579,999	55.000	−∞	−∞	0.15	0.35	0.40	0.19	0.07	0.12
<i>rs555920</i>	30,832,451	57.011	2.91	−0.09	0.03	0.13	0.21	0.21	0.13	0.04
<i>rs12409103</i>	31,747,269	59.610	3.27	0.35	0.34	0.28	0.22	0.12	0.05	0.01
<i>rs760594</i>	33,231,390	60.510	3.34	0.47	0.46	0.41	0.35	0.23	0.11	0.03
<i>rs899378</i>	34,287,917	61.420	3.41	0.45	0.44	0.39	0.33	0.21	0.11	0.03
<i>rs491603</i>	36,304,903	64.310	3.57	1.88	1.85	1.73	1.56	1.18	0.76	0.33
<i>rs6619</i>	37,803,283	66.140	3.56	0.45	0.44	0.39	0.33	0.21	0.11	0.03
<i>rs649593</i>	37,980,150	66.770	3.55	0.95	0.94	0.89	0.81	0.65	0.45	0.23
<i>rs661316</i>	39,403,884	69.700	3.54	1.47	1.44	1.30	1.12	0.75	0.39	0.10
<i>rs209598^g</i>	40,635,418	71.570	3.52	1.51	1.48	1.36	1.22	0.91	0.60	0.28
<i>rs883062^g</i>	42,382,454	72.840	3.48	−0.07	0.07	0.05	0.04	0.02	0.01	0.00
<i>rs2782642</i>	43,658,908	74.310	3.43	−0.04	0.04	0.03	0.02	0.01	0.00	0.00
<i>rs1707302</i>	46,373,504	75.400	3.40	0.48	0.46	0.42	0.36	0.24	0.12	0.03
<i>rs926979^e</i>	48,458,022	77.800	1.68	−0.12	0.11	0.06	0.02	0.01	0.02	0.01
<i>rs1502856</i>	50,644,434	78.260	1.52	0.50	0.49	0.44	0.37	0.24	0.12	0.03
<i>rs1242330^f</i>	53,169,430	79.250	13.11	−∞	0.90	0.28	0.08	0.04	0.04	0.01

Abbreviations: LOD, logarithm of odds; MPT, multipoint.

^aAll the data are given for theta values of 0.0 to 0.4.

^bPhysical map positions from Build 36 of the human reference sequence.

^cGenetic map positions from the Rutgers combined linkage-physical map of the human genome, Build 36.

^dScores obtained using Allegro1.2c.

^eThese markers flank the haplotype.

^fThese markers delimit the 3-unit support interval.

^gThe gene *KCNQ4* is located between the marker loci *rs209598* and *rs883062*.

RESULTS

CLINICAL DATA

Of 17 participants, 9 were affected with hearing loss, 6 were unaffected, and 2 were spouses. Age at onset ranged from 1 to 21 years. Affected family members had sloping SNHL, with low-frequency thresholds less affected than high-frequency thresholds. In general, hearing was symmetrical. Hearing loss was noted to typically progress with age, with mild to moderate hearing loss identified early in life progressing to severe-profound loss by the seventh decade of life (**Table 2**). Several family members successfully used hearing aids; none were cochlear implant recipients. The phenotype in the family members affected with hearing loss was consistent with *DFNA2* deafness.¹⁵

GENETIC ANALYSIS

Results of the genome-wide SNP genotyping analysis showed significant evidence of linkage to chromosome 1p34-p36. The maximum 2-point logarithm of odds (LOD) score of 1.8 and the maximum multipoint LOD score of 3.6 both occurred at marker *rs491603* (chromosome 1; 36.3 Mb) (**Table 3**). Haplotype analysis revealed recombination events that define an 18.9-Mb interval between *rs1886651* (chromosome 1; 29.6 Mb) and *rs926979* (chromosome 1; 48.5 Mb), containing the *KCNQ4* gene (Figure 1). This region corresponds closely to the 3-unit

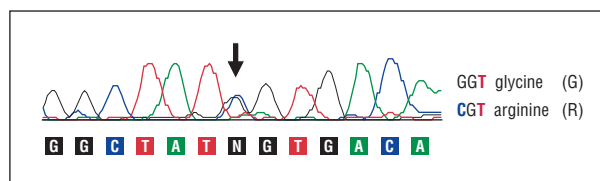


Figure 2. Sequencing chromatogram of *KCNQ4* exon 6 in a representative affected individual demonstrating the heterozygous c.859G>C base substitution (arrow) that results in a p.Gly287Arg amino acid substitution.

support interval, which is slightly larger and extends from *rs491603* to *rs1242330* (chromosome 1; 53.2 Mb).

A heterozygous point mutation in exon 6 of *KCNQ4*, c.859G>C, was detected by sequencing DNA in affected family members (**Figure 2**). The c.859G>C nucleotide substitution results in a p.Gly287Arg amino acid substitution in the phosphate-binding loop (P-loop) region of *KCNQ4*. This mutation was not found in 275 controls (550 control chromosomes). SIFT analysis of the Gly287Arg amino acid substitution predicted a deleterious effect on protein function, with a score of 0.00.

COMMENT

The *KCNQ4* gene encodes a tetrameric voltage-gated potassium protein with 6 transmembrane domains; the N and C termini of the protein are on the intracellular side of the membrane, and the fourth transmembrane domain is the voltage sensor portion of the protein. The fifth and sixth transmembrane domains of the

protein form the pore region of the protein, with the peptides between these domains constituting the P-loop. In the complete protein tetramer, 4 of these P-loops form the selectivity filter of the protein.¹⁶ More than 15 mutations in *KCNQ4* have been previously reported in association with *DFNA2* deafness, including missense, frameshift, nonsense, and splicing mutations.¹⁷ Most mutations occur in the channel pore (P-loop) region.¹⁸ Surface channel expression studies in *Xenopus* oocytes suggest that missense mutations in the P-loop of *KCNQ4* reduce potassium currents in a dominant negative manner.^{3,19} A dominant negative effect is also seen with mutations in the P-loop of a related gene, *KCNQ1*, which affect potassium currents and cause cardiac arrhythmias in long QT syndrome.²⁰ This evidence supports the hypothesis that the conserved sequences of the P-loop region are critical to pore structure, function, and targeting.

More than 50 genes have been identified in which mutations cause nonsyndromic hereditary hearing impairment, but clinical genetic testing is not widely available in the United States for most of these genes. For certain types of hearing loss, there is 1 predominant gene in which mutations are commonly found, such as *WFS1* mutations and autosomal dominant low-frequency SNHL.²¹ Forms of hearing loss associated with temporal bone anomalies are also associated with a limited number of genes.²² However, for dominant high-frequency SNHL, mutations may occur in any of many possible genes. Affected individuals in family 63 have mild low-frequency and moderate high-frequency SNHL early in life, progressing to moderate low-frequency and severe-profound high-frequency SNHL later in life, consistent with the phenotype of *DFNA2* deafness associated with *KCNQ4* mutations.^{2,23} For families with dominant nonsyndromic SNHL following this pattern, clinical genetic testing for *KCNQ4* is reasonable to consider (for laboratory listings, see <http://www.genetests.org>).

High-throughput technologies, such as resequencing microarrays, have been developed to analyze multiple genes mutated in SNHL.²⁴ However, these “gene chips” may be expensive, and genes such as *KCNQ4* may be excluded. In addition, without a priori evidence of linkage to a particular chromosome, it is difficult to classify variants of unknown significance.

For families that are large enough to provide sufficient statistical power, genetic linkage analysis remains an efficient means of identifying deafness genes. New methods using SNP markers have greatly decreased the cost and time of whole-genome genotyping analyses. For dominant high-frequency hearing loss, phenocopies, such as individuals with hearing loss due to aging or noise exposure, are common, which may reduce the power to detect linkage. Although family 63 (with 9 affected individuals) may be at the borderline level of power to detect linkage for a dominant trait, we detected linkage with a significant multipoint LOD score of 3.6. The linkage region identified in family 63 also includes another reported hearing loss gene, *GJB3*.²⁵ However, because the evidence implicating *GJB3* mutations as a cause of dominant nonsyndromic

deafness is unclear,¹⁷ *GJB3* was not examined for mutations in this family.

In conclusion, we describe a novel mutation in *KCNQ4* segregating in a family with autosomal dominant high-frequency SNHL. Linkage analysis may still have a role to play in facilitating identification of the molecular etiology of deafness in patients in the future.

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a rare cause of failed parathyroidectomy that should be considered before reoperation. Patients with persistent hyperparathyroidism who have negative findings on sestamibi scans may benefit from widening or customization of scanned fields as directed by selective venous sampling.

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Author Contributions: Mr Nguyen and Dr Yeh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Abemayor and Yeh. *Analysis and interpretation of data:* Nguyen, Lau, Abemayor, and Yeh. *Drafting of the manuscript:* Nguyen, Abemayor, and Yeh. *Critical revision of the manuscript for important intellectual content:* Lau, Abemayor, and Yeh. *Administrative, technical, and material support:* Nguyen. *Study supervision:* Lau, Abemayor, and Yeh. **Financial Disclosure:** None reported.

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Correction

Omission of Grant Number. In the article titled "Autosomal Dominant Progressive Sensorineural Hearing Loss Due to a Novel Mutation in the *KCNQ4* Gene," by Arnett et al, published in the January issue of the *Archives* (2011; 137[1]:54-59), a funding source was omitted. The acknowledgment on page 58 should have read as follows:

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