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Mutation in the *COCH* gene is associated with superior semicircular canal dehiscence

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To the Editor:

The prevalence of significant hearing loss (≥ 25 db HL) is 15-20% in young adults and rises to approximately 50% in individuals 80 years of age or older [Morton 1991]. Autosomal dominant nonsyndromic hearing loss (ADSNHL) accounts for approximately 15% of inherited hearing loss. To date, 22 genes have been implicated as causative for ADSNHL, and a further 30 loci mapped to autosomal chromosomal regions [Van Camp and Smith 2007].

ADSNHL at the DFNA9 locus is unusual amongst ADSNHL forms of deafness in that it is also associated with vestibular dysfunction. This type of hearing loss is caused by mutations in the *COCH* gene (chromosome 14q12), which encodes cochlin, a protein that consists of a signal peptide, an LCCL module, and two von Willebrand factor A (vWFA) domains (Table I) [de Kok et al., 1999]. Cochlin is the most highly expressed protein in the human and mouse inner ear, but its precise function remains unclear [Dessens et al., 2004; Robertson et al., 2006]. A possible role in either structural integrity or antimicrobial activity is predicted by its protein structure [Liepinsh et al., 2001] and immunohistochemistry of a temporal bone from a person with DFNA9-related deafness showing abundant aggregation of homogeneous acellular eosinophilic deposits with loss of cellularity in the cochlea and the vestibular labyrinth [Robertson et al., 2006].

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Most DFNA9-causing mutations are located within the LCCL domain, which is predicted to be involved in protein folding or a host-defense function (Table I) [Trexler et al., 2000]. The p.P51S variant that affects the LCCL module is the most frequently observed mutation in DFNA9 families [Bischoff et al., 2005; de Kok et al., 1999; Fransen et al., 2001; Fransen et al., 1999; Lemaire et al., 2003]. The identification of a large number of DFNA9 families carrying this variant has facilitated a detailed longitudinal analysis of the audiometric and vestibular impairment in 74 mutation carriers, which has shown that vestibular failure precedes and progresses more rapidly than hearing impairment [Bischoff et al., 2005].

In this study (approved by the University of Iowa Institutional Review Board), we recruited American subjects with ADNSHL and obtained DNA samples and audiograms. Audiograms were formatted for audioprofile analysis, which was conducted using the AudioGene v2.0 system [Hildebrand et al., 2008]. This system predicts the likely underlying genetic cause of hearing loss based on a number of different phenotypic parameters, including auditory thresholds, and rate of decrease in hearing relative to age and frequency. AudioGene v2.0 was trained with audiometric data from families with known deafness-causing mutations in *KCNQ4* (DFNA2), *DFNA5* (DFNA5), *WFS1* (DFNA6/14/38), *TECTA* (DFNA8/12), *COCH* (DFNA9) and *COL11A2* (DFNA13).

To validate AudioGene v2.0 as a clinical and research tool, we studied a cohort of 77 families segregating presumed ADSNHL represented by audiograms from 160 individuals. Individuals from seven families were identified by AudioGene v2.0 as having a DFNA9 profile, and in six families, mutation screening of the *COCH* gene was completed (genomic DNA was unavailable for screening in one family). While no mutations were identified in five families, one family was found to segregate the p.P51S mutation (positive predictive value, ~16.7%) (Figs 1, 2). To our knowledge, this family is the first outside Western Europe to be reported with this mutation. However by comparing highly heterozygous short tandem repeat polymorphisms (STRPs) tightly linked to the *COCH* gene, we could show that this family is related to five previously reported Belgian p.P51S families [Fransen et al., 2001] (data not shown), providing further evidence of a founder effect in the Benelux region of Western Europe.

The clinical presentation of all p.P51S families is very similar (Table I) [de Kok et al., 1999; Fransen et al., 2001; Fransen et al., 1999; Lemaire et al., 2003]. The hearing loss initially preferentially affects high frequencies (down-sloping) and progresses to become profound across all frequencies at a rate of ~1.8 dB annually [Bom et al., 1999]. In a few exceptional cases, however, hearing at low frequencies declines much more rapidly, at greater than 24 dB annually [Bom et al., 1999]. In the American family, the self-reported age-of-onset of hearing loss ranged from 20 to 60 years. The hearing loss was progressive, with a general trend of initial moderate-to-severe high frequency (> 2000 Hz) hearing loss (HFSNHL) that became profound (Fig.3). In younger persons, the audioprofile was down-sloping, preserving hearing in the low and mid frequencies; with advancing age, low and mid frequency loss developed and the audioprofile flattened. Individuals IV:5 and IV:6 represent phenocopies.

All hearing impaired persons in this family excluding IV:5 and IV:6 also had vestibular impairment characterized by intermittent unsteadiness, particularly in the dark, and sporadic periods of dizziness. In addition, one person was diagnosed with Meniere's-like symptoms and another with autoimmune inner ear disease requiring treatment with a diuretic and a low-salt diet. This variety of complaints is similar to that reported in other p.P51S families [Bischoff et al., 2005]. In general, p.P51S mutation carriers over 40 years of age usually have prominent vestibular symptoms however these complaints only emerge from the medical history if a targeted vestibular history is obtained.

Computed tomography (CT) scanning on a number of family members revealed intact ossicles, cochleae and semicircular canals with the exception of individual V:1. This person presented at age 31 in October, 2006, for an audiogram because of the family history of hearing loss. He has no complaints and by audiometry had 10 dB thresholds bilaterally through 2 kHz, a drop to 25 dB between 3-6 kHz, and normal hearing again at 8 kHz (Fig. 4A). In February, 2008, he returned with a complaint of left aural fullness and persistent otalgia (6-9 months) and underwent temporal bone CT, which revealed bilateral superior semicircular canal dehiscence (SSCD) (Fig.4B).

SSCD is a rare disorder. Originally described by Minor and colleagues, it is characterized by the absence of bone overlying the superior semicircular canal, which creates a third labyrinthine window (with the oval and round windows) [Minor 2000; Minor 2005]. The consequence is the loss of acoustic energy and abnormal stimulation of the vestibular system; the clinical manifestations include Valsalva- and exercise-induced vertigo, sound-induced vertigo (Tullio phenomenon), and variable conductive hearing loss [Cox et al., 2003; Mikulec et al., 2004; Minor et al., 2003]. Diagnosis requires high resolution temporal bone CT [Belden et al., 2003; Hirvonen et al., 2003].

The genetics of SSCD have not been studied, and our finding of a *COCH* mutation in a single patient with SSCD is noteworthy since both DFNA9-related deafness and SSCD are rare. Although it seems unlikely that SSCD is directly related to the well-documented type of vestibular impairment that is part of the DFNA9 phenotype, SSCD may be present in other DFNA9 patients. We therefore recommend high resolution temporal bone CT in patients with DFNA9-related deafness and screening of *COCH* in sporadic or familial cases of SSCD. This diagnostic algorithm is important because SSCD and its associated symptoms can be partially or fully corrected with surgery [Carey et al., 2007; Limb et al., 2006; Mikulec et al., 2005; Wilkinson et al., 2008].

A remarkable finding in the process of identifying DFNA9/*COCH* as the underlying cause of deafness in this American family was not only that a dedicated computer program, AudioGene v2.0, hinted at this possibility, but that this occurred in the course of a screening procedure for DFNA2 families [Hildebrand et al., 2008]. It is reassuring to find that AudioGene v2.0 can distinguish between the audioprofiles of genetically different types of ADNSHL, especially when both DFNA2 and DFNA9 show remarkably similar high frequency hearing loss with steeply downsloping thresholds.

Admittedly, in the case of p.P51S mutation carriers genetic screening should be preferentially directed to DFNA9 and DFNA11, on the basis of the vestibular impairment findings. However, it is realistic to acknowledge the possibility that vestibular symptoms can go unnoticed. Furthermore, with other DFNA9/*COCH* mutations vestibular failure can be less prominent. It is not invariably penetrant and/or occurs at a more advanced age [Kemperman et al., 2005; Pauw et al., 2007a].

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Abbreviations

ADSNHL	autosomal dominant sensorineural hearing loss
COCH	cochlin gene

CT	computed tomography
HFSNHL	high frequency sensorineural hearing loss
SSCD	superior semicircular canal dehiscence

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Figure 1.

Pedigree of the five-generation American family with nonsyndromic autosomal dominant HFSNHL, vestibular dysfunction and SSCD. Genotypes for nucleotide c.151 in the *COCH* gene are shown for those individuals included in the genetic analysis. Individuals IV:5 and IV:6 were reported to have hearing loss, however they are likely to represent phenocopies. Diagonal line deceased.

Figure 2.

The causative mutation in the *COCH* gene in the American family. The mutation is a heterozygous C-to-T base change in exon 3 (c.151C→T) that results in substitution of a proline residue for a serine residue at position 51 (p.P51S).

Figure 3.

Audiograms of representative affected family members at various ages. Affected individuals initially exhibit high frequency (> 2000 Hz) mild-to-moderate SNHL (HFSNHL) that progresses to become severe-to-profound before flattening out later in life.

V:1 31y

Figure 4.

Audiometry and temporal bone CT of individual V:1. **A** Audiogram recorded at 31 years of age showing slightly elevated hearing thresholds at high frequencies. **B** Coronal high-resolution CT scan of the temporal bones showing bilateral superior semicircular canal dehiscence (SSCD).

Table 1

DFNA9-causing mutations in the *COCH* gene

Family	Mutation	Domain	Type	Progressive	Frequency Loss	Vestibular symptoms	Age of onset	Reference
1 USA	p.V66G	LCCL	SNHL	Yes	Initially high Progresses to all	Present in one third	2 nd -3 rd decade	[Robertson et al., 1998]
1 USA	p.G88E	LCCL	SNHL	Yes	Initially high Progresses to all	Present in some	5 th decade	[Robertson et al., 1998]
1 USA	p.W117R	LCCL	SNHL	Yes	Initially high Progresses to all	Present in some	5 th decade	[Robertson et al., 1998]
1 Belgian 2 Dutch	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	4 th -6 th decade	[Fransen et al., 1999]
4 Dutch	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	4 th -7 th decade	[de Kok et al., 1999]
8 Belgian	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in most	4 th -7 th decade	[Fransen et al., 2001]
1 Australian	p.I109N	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	2 nd -3 rd decade	[Kammarinos et al., 2001]
1 Belgian	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in most	4 th -5 th decade	[Lemaire et al., 2003]
1 Japanese	p.A119T	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	5 th decade	[Usami et al., 2003]
1 Hungarian	p.V104del	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	4 th decade	[Nagy et al., 2004]
1 Dutch	p.G88E	LCCL	SNHL	Yes	Initially high Progresses to all	Present in some	5 th -7 th decade	[Kemperman et al., 2005]
1 Dutch	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	4 th -7 th decade	[Bischoff et al., 2005]
1 USA	p.C542F	vWFA2	SNHL	Yes	Initially high Progresses to all	Present in some	2 nd -3 rd decade	[Street et al., 2005]
1 Dutch	p.G87W	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	5 th -7 th decade	[Collin et al., 2006]
1 Dutch	p.I109T	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	5 th decade	[Pauw et al., 2007b]
2 Chinese	p.M512T p.C542Y	vWFA2	SNHL	Yes	Initially high Progresses to all	Present in some	2 nd -5 th decade	[Yuan et al., 2008]
1 USA	p.P51S	LCCL	SNHL	Yes	Initially high Progresses to all	Present in all	4 th -7 th decade	This study