Published in final edited form as:

Clin Genet. 2010 April ; 77(4): 395–398. doi:10.1111/j.1399-0004.2009.01338.x.

A novel mutation adjacent to the *Bth* mouse mutation in the *TMC1* gene makes this mouse an excellent model of human deafness at the DFNA36 locus

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To the Editor

Inherited hearing impairment is a highly heterogeneous genetic trait. To date, 22 and 27 genes have been associated with autosomal dominant and recessive non-syndromic hearing loss, respectively (ADNSHL, ARNSHL) (1). Mutations in seven of these genes – *GJB2*, *GJB3*, *GJB6*, *MYO6*, *MYO7A*, *COL11A2* and *TMC1* – cause both ADNSHL and ARNSHL.

TMC1 belongs to a large *TMC* (Trans Membrane Channel-like) gene family. Its eight members encode transmembrane proteins with intracellular amino- and carboxyl- termini and multiple transmembrane domains. In the inner ear, murine *Tmc1* is expressed in outer and inner hair cells after P3. *Tmc1* deficiency in the recessive deafness mouse mutant *dn* leads to complete deafness and hair cell degeneration, while the *Tmc1* p.M412K missense mutation in the semi-dominant *Bth* mutant causes progressive hearing loss and hair cell degeneration in heterozygotes and early-onset deafness in homozygotes (2,3). These data suggest that *Tmc1* is necessary for maturation and survival of hair cells in the murine cochlea (4).

Twenty-two recessive mutations of *TMC1* are associated with ARNSHL at the DFNB7/11 locus in 39 families worldwide (2,5–10), however only two dominant mutations have been reported. These two mutations - p.D572N and p.D572H - affect the same amino acid (2,11, 12) and were found in three unrelated North American families with progressive ADNSHL at the DFNA36 locus.

We have identified a novel dominant mutation, p.G417R, and a novel recessive mutation, p.N50KfsX26, in *TMC1* in a large Iranian DFNA36 family (Family L1754) and a consanguineous Iranian DFNB7/11 family (Family L787), respectively (Fig 1A). These families were ascertained through the Research Centre of Ear, Nose, Throat and Head and Neck Surgery, Iran University of Medical Sciences, Tehran, Iran, as part of a study approved by the Human Research Institutional Review Boards at the participating institutions. Written informed consent was obtained from all study subjects.

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Consistent with the phenotypes of the DFNA36 and DFNB7/11 families as previously reported, hearing impairment in Family L1754 is rapidly progressive, starting in the higher frequencies and ultimately affecting all frequencies, while hearing impairment in Family L787 is congenital and profound (Fig 2). Haplotype analysis in both families was consistent with linkage to DFNA36 (LOD score >6.02) and DFNB7/11 (LOD score >2.5 – the maximum possible for this family), and sequence analysis of *TMC1* revealed a p.G417R (c.1249G>A) mutation in Family L1754 and a p.N50KfsX26 (c.150delT) mutation leading to a premature stop in Family L787. Neither mutation was seen in 500 control chromosomes.

As in many other genes involved in both dominant and recessive non-syndromic hearing loss, the dominant mutations of *TMC1* mostly likely cause disease by a dominant-negative or gain-of-function mechanism rather than haploinsufficiency. Studying of the pathogenic roles of these specific mutations, therefore, may provide us important insights into the function of *TMC1* and its interacting proteins. It is noteworthy that our report is the first to document a dominant mutation of *TMC1* from a region other than North America. The p.G417R mutation in Family L1754 is the second amino acid position of *TMC1* associated with ADNSHL (Fig 1B). The adjacent amino acid, p.M418, is orthologous to murine p.M412, which is replaced by lysine in the *Bth* mouse mutant (Fig 1C). Both p.G417 and p.M418 lie within a predicted transmembrane (13) and the substitution of these hydrophobic amino acids with highly charged, hydrophilic amino acids is likely to lead to abnormal protein folding or abnormal protein-protein interactions. Consistent with the positional proximity and substitution similarity of p.G417R and p.M412K mutations, the phenotypes in both Family L1754 and the *Bth* mouse are characterized by rapidly progressive hearing loss. We hypothesize that these two mutations therefore share pathogenic mechanisms making the *Bth* mouse an excellent animal model to study *TMC1* p.G417R-associated ADNSHL.

Acknowledgments

This project was supported in part by: The Science and Technology Commission of Shanghai Municipality, China (09DJ1400604 to TY); The National Institutes of Health-National Institute on Deafness and Other Communication Disorders (Grants DC02842 and DC03544 to RJHS); and The Iranian National Science Foundation (Grants 85073/23 and 85033/10 to HN). RJHS is the Sterba Hearing Research Professor, University of Iowa College of Medicine.

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Figure 1.

Family L1754 carrying the G417R mutation in *TMC1* segregates ADNSHL at the DFNA36 locus. (A) Pedigree and haplotype segregation of STRP markers D9S1817, D9S273, D9S175, D9S167 and D9S283 (top to bottom). Note the recombination event in the paternal chromosome inherited by IV-16. (B) Sequencing result showing the heterozygous p.G417R mutation in affected individuals. (C) Amino acids p.G417 and p.M418 (bolded) of TMC1 are conserved across species: 1 Homo sapiens, 2 Pan troglodytes, 3 Canis familiaris, 4 Bos taurus, 5 Equus caballus, 6 Mus musculus, 7 Monodelphis domestica, 8 Gallus gallus, 9 Taeniopygia guttata, 10 Danio rerio and 11 human TMC2). The predicted transmembrane domain is boxed.

Figure 2.
Audiograms from all affected persons shown in Figure 1A (○, right ear; x, left ear; arrows, no response).