Mutations in *PTPRQ* Are a Cause of Autosomal-Recessive Nonsyndromic Hearing Impairment DFNB84 and Associated with Vestibular Dysfunction

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We identified overlapping homozygous regions within the DFNB84 locus in a nonconsanguineous Dutch family and a consanguineous Moroccan family with sensorineural autosomal-recessive nonsyndromic hearing impairment (arNSHI). The critical region of 3.17 Mb harbored the *PTPRQ* gene and mouse models with homozygous mutations in the orthologous gene display severe hearing loss. We show that the human *PTPRQ* gene was not completely annotated and that additional, alternatively spliced exons are present at the 5′ end of the gene. Different PTPRQ isoforms are encoded with a varying number of fibronectin type 3 (FN3) domains, a transmembrane domain, and a phosphatase domain. Sequence analysis of the *PTPRQ* gene in members of the families revealed a nonsense mutation in the Dutch family and a missense mutation in the Moroccan family. The missense mutation is located in one of the FN3 domains. The nonsense mutation results in a truncated protein with only a small number of FN3 domains and no transmembrane or phosphatase domain. Hearing loss in the patients with *PTPRQ* mutations is likely to be congenital and moderate to profound and most severe in the family with the nonsense mutation. Progression of the hearing loss was observed in both families. The hearing loss is accompanied by vestibular dysfunction in all affected individuals. Although we show that PTPRQ is expressed in many tissues, no symptoms other than deafness were observed in the patients.

Mutations in *GJB2* (MIM *121011) are a frequent cause of autosomal-recessive nonsyndromic hearing impairment (arNSHI, MIM 220700) in nonconsanguineous populations in the US and Europe, especially in the Mediterranean region.[1,2] For other arNSHI genes, the relevance for disease in specific populations is largely unexplored. We aimed to unravel genetic defects underlying arNSHI in Dutch families in which mutations in *GJB2* had been excluded previously. The Dutch population is generally regarded to be a mixed population with only a few relatively genetically isolated populations including that of the former island Urk. However, recent studies on the elucidation of genetic defects in patients with autosomal-recessive retinal degeneration and arNSHI have indicated that the population in the Netherlands is not fully mixed and that subpopulations exist in which disease-causing mutations are present in chromosomal regions that are identical by descent (IBD)[3] (H.K., C.W.R.J.C., H.P.M.K., P.L.M.H., unpublished results).[4,5] We selected 80 familial cases from 38 families and 35 isolated cases with putative arNSHI for homozygosity mapping. There were no indications for nongenetic causes of the hearing impairment in these patients, and *GJB2* was excluded as the causative gene by sequence analysis. The large majority of the patients was of Dutch descent. The study was approved by the local medical ethics committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects or, in case of children, from their parents.

High-resolution SNP genotyping was performed with Affymetrix Genechip Genome-Wide Human Arrays 5.0 or Affymetrix mapping 250K single-nucleotide polymorphism (SNP) arrays on genomic DNA isolated from peripheral blood samples via standard procedures. For both array types, the Genotyping Console software (Affymetrix) was employed for allele calling and calculation of the regions of homozygosity was performed with Genotyping Console software and Partek Genomics Solution Software for the 250K and 5.0 array, respectively. On the long arm of chromosome 12, a homozygous region of 3.17 Mb was shared by all four affected members of families W04-083 and W07-0455 (Figure 1). The parents in family W04-083 are of Moroccan origin and are first cousins. In this family we identified 18 IBD regions that were larger than 1 Mb and shared by the two sibs. The largest homozygous region of 33.32 Mb was located at 12q21.1-q23.3 (flanking SNPs: SNP_A-2246676 and SNP_A-1937576). The two affected subjects in family W07-0455 of Dutch origin shared in total nine IBD regions larger than 1 Mb. Also for this family, the region on chromosome 12q21.31 (3.17 Mb, flanking SNPs: SNP_A-4277907 and SNP_A-1835105) was the largest homozygous region shared by the affected individuals. During the course of the project, it appeared that the critical region on chromosome 12q21.31 was located

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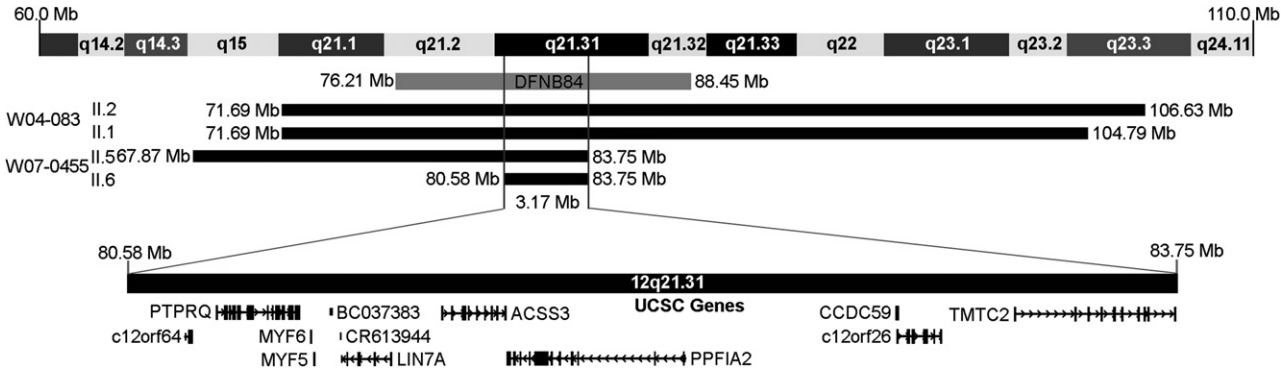

Figure 1. Homozygous Regions in the DFNB84 Locus
Schematic overview of the chromosomal region 12q14.1-q24.11 showing the DFNB84 locus (gray bar) and the homozygous regions (black bars) identified in families W07-0455 and W04-083. The homozygous region of individual II.6 of W07-0455 delimits the region to 3.17 Mb. Mb positions and chromosome bands are according to the UCSC genome browser (GRCh37). The shared homozygous region contains, among others, the *PTPRQ* gene.

in the novel deafness locus DFNB84 (Figure 1), identified in two Palestinian families with arNSHI.[6] The shared 3.17 Mb region encompasses 12 genes (Figure 1) of which *PTPRQ* (MIM *603317) was the most obvious candidate gene because defects of *Ptprq* are associated with deafness in mice.[7]

At the time we identified the candidate interval containing the *PTPRQ* gene, only four exons of *PTPRQ* were annotated in the UCSC Genome Browser (uc001sze.1, NCBI Build 36.1; hg18 annotation tracks, March 2006) and in Uniprot the human protein sequence Q9UMZ3 (Figure 2A) was available. Therefore, we initiated the characterization of the human *PTPRQ* gene. We performed RT-PCR and rapid amplification of cDNA ends (5′- and 3′-RACE, Clontech) in accordance with the manufacturer's protocol via Phusion Taq polymerase (Roche) and Human retina or testis Marathon-Ready (Clontech) cDNA as a template followed by sequence analysis. Primers for RT-PCR were designed based on exons predicted by performing blatp with the amino acid sequence in Q9UMZ3. Primer sequences are provided in Table S1 available online. With RT-PCR we detected transcripts containing all exons encoding Q9UMZ3.

Via 5′RACE experiments with a primer that hybridizes to the second exon of NM_001145026.1, additional exons were identified and indications for splice variants in retina and testis were obtained (Figure 2A, transcript numbers I and II). Seven of these additional exons were predicted in the Genscan entry NT019546.6.1 and others were not annotated previously. With RT-PCR on retina marathon cDNA, we identified two further transcripts, III and IV (Figure 2A), the latter of which was also amplified from testis marathon cDNA. To explore the presence of additional exons at the 5′ end of the gene, we performed 5′-RACE with a primer in the fourth predicted exon of NT_019546.61. This resulted in a cDNA fragment containing two additional exons, exons 1 and 2 (transcript V in Figure 2A). These exons do not contain a significant open reading frame and are therefore considered to be part of the 5′UTR of the *PTPRQ* gene. In total, 58 exons of the *PTPRQ* gene were found to be present in alternatively spliced transcripts. In addition to alternative splicing of exons at the 5′ end of the gene, exon 49 was found to be alternatively spliced in both retina and testis RNA. This exon encodes nine amino acids in the intracellular region of PTPRQ. These amino acids are located N-terminal of the phosphatase domain and are therefore unlikely to directly affect the catalytic properties of the protein. However, it cannot be excluded that the structure of the catalytic domain differs between the two isoforms that lack or contain these nine amino acids and that this alters the catalytic properties of the phosphatase domain.

c12orf64, located upstream of NT_019546.61, encodes an otogelin-like protein. Because otogelin is expressed in inner ear[8] and the protein encoded by *c12orf64* was predicted to consist of extracellular domains only, we investigated whether *c12orf64* may be part of *PTPRQ* by RT-PCR with a forward primer in *c12orf64* and a reverse primer in NT_019546.61. Because no PCR products were obtained, there are so far no indications that *PTPRQ* and *c12orf64* are part of the same gene.

In the rat, two different transmembrane isoforms of PTPRQ are expressed in glomeruli and smooth muscles cells and an intracellular isoform that lacks part of the phosphatase domain. These isoforms result from alternative splicing and the use of an alternative promoter, respectively.[9] We did not further explore whether such isoforms are present in man. The proteins encoded by the alternatively spliced mRNAs indicated in the present study lead to isoforms which differ by the number of FN3 domains (Figure 2B).

To investigate the involvement of *PTPRQ* in the hearing loss in families W04-083 and W07-0455, we performed sequence analysis of the 58 exons and exon-intron boundaries of *PTPRQ* as described.[3] Primer sequences and PCR conditions are provided in Table S1. The nomenclature of

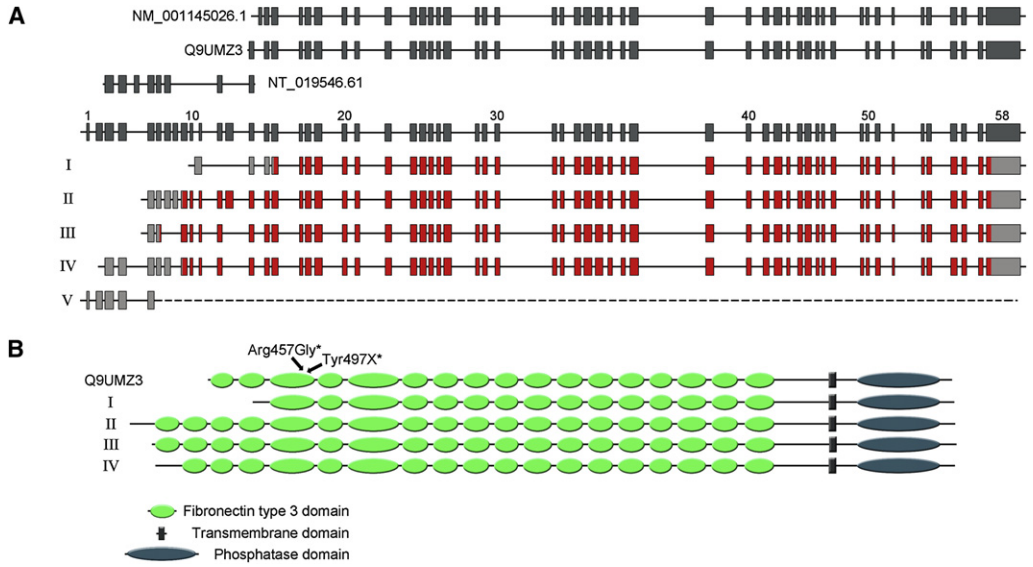

Figure 2. *PTPRQ* Gene Characterization and Schematic Representation of PTPRQ Protein Structure
(A) Schematic overview of the gene organization for *PTPRQ* showing the exon structure of NM_001145026.1 and of the Genscan entry NT019546.61 according to the UCSC genome browser (GRCh37). The exons encoding Q9UMZ3 were determined by performing a Blatp search in the UCSC genome browser with the protein sequence. Splice variants I, II, and V were detected in RACE experiments and numbers III and IV in RT-PCR experiments. The orange colored exons indicate the open reading frame, which was determined with the NCBI ORF finder and only ATG was considered as a start codon. Exon 49 was found to be alternatively spliced.
(B) Predictions of conserved domains of the identified alternatively spliced RNA, determined with the simple modular architecture research tool (SMART). Isoforms differ in the number of FN3 domains and for isoforms II and III, 19 FN3 domains are predicted; for isoform IV 18, for isoform I 15, and for Q9UMZ3 17 FN3 domains. The alternatively spliced exon 49 encodes for amino acids within the phosphatase domain. *The nomenclature of the indicated mutations is based on splice variant III and nomenclature based on the other splice variants is given in Table 1.

the mutations in this section is based on splice variant III, and nomenclature based on the other splice variants is given in Table 1. In individual II.6 of family W07-0455, a homozygous nucleotide substitution, c.1491T>A in exon 19, leads to a premature stop codon at position 497 of the protein (p.Tyr497X; Figure 3A). In individual II.1 of family W04-083, a homozygous missense mutation in exon 19 was found, c.1369A>G, leading to the substitution of a glycine for an arginine at position 457 of the protein (p.Arg457Gly, Figure 3A). The mutations cosegregate with the disease in both families (Figure 3B) and were not found in at least 125 ethnically matched controls via an amplification refractory mutation system (ARMS) approach.

The amino acid substitution p.Arg457Gly was analyzed with polymorphism phenotyping (Polyphen) and sorting intolerant from tolerant (SIFT). Polyphen predicted this change to be probably damaging for protein function, whereas SIFT predicted it to be tolerated. Alignment of PTPRQ protein sequences of different species including mouse, rat, chimpanzee, cow, and zebrafish shows that the arginine is conserved in four of these species but not in zebrafish, which has a leucine in this position. An alignment of part of the proteins is provided in Figure S1. The mutated residue is located in the fifth FN3 domain of splice variant III; these extracellular domains are known to bind ligands such as extracellular proteins and other molecules including collagen and heparin, respectively, and also

Table 1. Nomenclature of *PTPRQ* Mutations for Alternatively Spliced Transcripts and the Corresponding Isoforms

Splice Variant[a]	Size of orf (bps)	Size Protein (# of Amino Acids)	# of FN3 Domains[b]	Mutation W04-083		Mutation W7-0455	
				cDNA	Protein	cDNA	Protein
I	6600	2200	15	c.418A>G	R140G	c.540T>A	T180X
II	7761	2587	19	c.1579A>G	R527G	c.1701T>A	T567X
III	7551	2517	19	c.1369A>G	R457G	c.1491T>A	T497X
IV	7503	2501	18	c.1321A>G	R441G	c.1442T>A	T481X

[a] The number of the transcripts correspond to the numbers in Figure 2A.
[b] The number of FN3 domains was determined with the Simple modular architecture research tool (SMART).

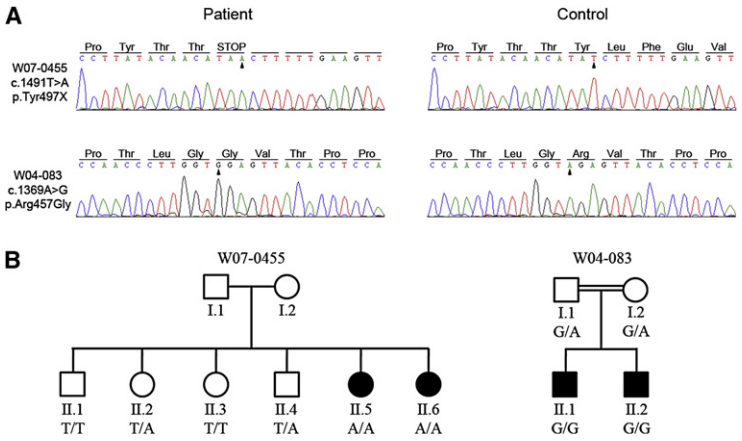

Figure 3. Mutation Analysis of *PTPRQ* in arNSHI Patients

(A) Partial *PTPRQ* sequences are shown for affected members and normal controls. The predicted amino acid changes and the surrounding amino acids are indicated above the sequence. Mutated nucleotides are marked by an arrowhead. As reference, sequence NT_029419.12 was employed.

(B) Pedigrees and genotypes of families with homozygous mutations in *PTPRQ*. The mutations cosegregate with the hearing impairment.

ligands on cells.[10–12] An FN3 domain in the protein tyrosine phosphatase receptor J (PTPRJ) has been shown to be involved in the formation of protein complexes and its localization in the cell.[13] Through the p.Arg457Gly mutation, a big, hydrophilic, and positively charged amino acid, is replaced by a small uncharged residue without a side chain. Therefore, ionic interactions and other possible interactions of the arginine residue in the wild-type PTPRQ such as hydrogen bonds will be lost by the mutation. Alternatively, protein localization may be affected.

The homozygous mutation in a homozygous region indicates that the parents in family W07-0455 have a common ancestor. To estimate the degree of relatedness, we have used a genomic measure of individual autozygosity, F_{roh}, which is strongly correlated with the inbreeding coefficient.[14] A set of individuals whose parents were first cousins had a mean F_{roh} value of 0.108 (between 0.072 and 0.136). Three sibs of Dutch origin from a couple with a common ancestor who lived five generations previous exhibited a mean F_{roh} of 0.018 (between 0.011 and 0.027). The two subjects of family W07-0455 had an F_{roh} of 0.009 and 0.016, which suggests that the common ancestor of their parents lived at least five generations prior to the present day.

Routine clinical examinations did not reveal any abnormalities other than inner ear dysfunction in the participating individuals. Hearing loss is bilateral, symmetric, and sensorineural and probably was congenital in both families. In family W07-0455, first testing of individual II.5 occurred only at 4 years of age (because of World War II) and a hearing loss of 90–95 dB was measured. Hearing loss in individual II.6 of this family was noticed soon after birth but audiograms are available only from older ages (Figures 4A and 4B). Both affected subjects did not develop normal speech spontaneously. Furthermore, progression of hearing loss from severe to profound was reported from 30 years and 45 years onward by individuals II.5 and II.6, respectively. Both affected children in family W04-083 exhibit moderate hearing loss (Figures 4C and 4D) and did not pass the hearing screening at the age of ~10 months. Linear regression analysis of longitudinal series of pure tone audiograms could be performed for individual II.1 and indicates significant progression of the hearing loss only for the left ear with annual threshold deteriorations between 2.4 and 3.4 dB for the frequencies 0.25, 0.5, and 8 kHz. In early childhood, the hearing loss in this family must have been less severe than in family W07-455 as indicated by the fact that speech development was normal in subject II.2 and only mildly impaired in subject II.1, which is probably due to the cooccurrence of recurrent otitis media with effusion in the first 2 years of life of this subject. Hearing aids were used by both children from the age of 3.5 years onward. Normal otoacoustic emissions were measured in patient II.2 at the age of 13 months. Otoscopic examination did not reveal any abnormalities except otitis media in individual II.1 of family W04-083. Electronystagmography in caloric and rotatory testing[15] demonstrated an impaired vestibular function in the patients of both families. No responses were measured for individuals II.5 and II.6 of family W07-0455 at the ages of 57 and 55 years, respectively, and both subjects reported delayed motor development with ability to walk unaided only at 2 years of age. Although this motor development was normal in the affected individuals II.1 and II.2 of family W04-083, severe hyporeflexia was diagnosed by electronystagmography at the ages of 13 years and 7 years, respectively.

The expression pattern of *PTPRQ* was determined by qPCR on cDNA from various fetal and adult human tissues as described,[3] with primers that amplify a fragment encoding the intracellular region of PTPRQ (Table 1 and Figure 5). Transcripts were detected in all but two fetal tissues that were tested and was highest in fetal kidney, followed by fetal lung and fetal cochlea. Transcript levels were below detection level in fetal liver and fetal colon. In all adult tissues that were tested, transcripts were detected with the highest levels in lung and heart. These levels were lower than in fetal cochlea that was included in the same experiment for comparison. Clinical evaluations did not indicate involvement of other organs than inner ear in the disease. Renal functions were found to be normal in laboratory testing of blood and urine for both families.

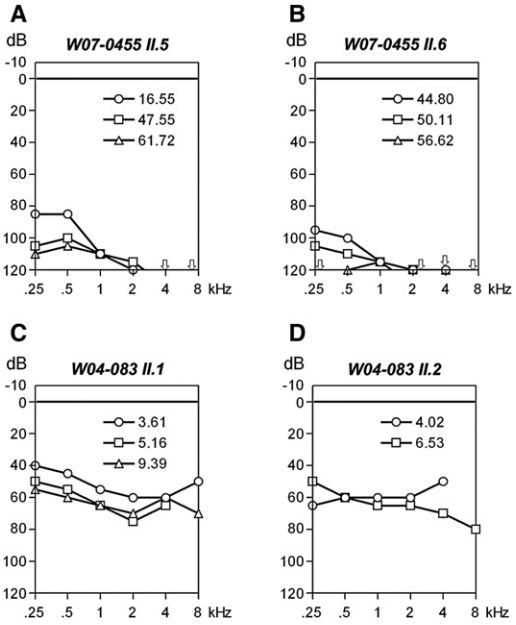

Figure 4. Clinical Characterization of the DFNB84 Families
Audiograms of affected individuals of W07-0455 (A and B) and W04-083 (C and D) at different ages. Only results for the left ear are represented. Pure tone audiometry was performed in a sound-treated room according to current clinical standards.

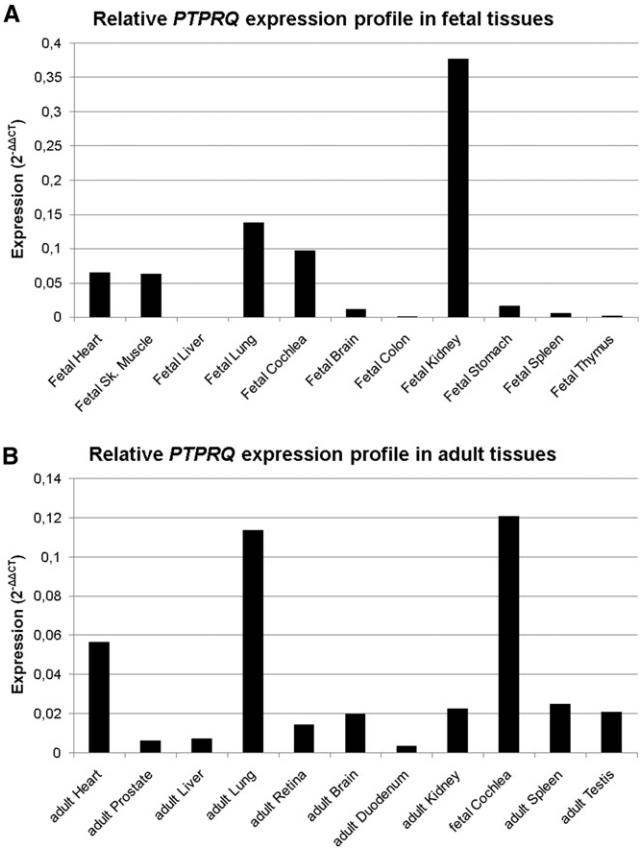

Figure 5. *PTPRQ* Expression Profile
Relative *PTPRQ* mRNA expression as determined by quantitative PCR in fetal (A) and adult (B) tissues. This was performed for adult and fetal tissues in two separate experiments, so fetal cochlea was included in both to be able to compare the expression levels. The relative expression values were determined via the delta delta Ct method. The highest expression levels are seen in fetal kidney, fetal cochlea, fetal and adult lung, and adult heart.

Normal levels of sodium, potassium, chloride, and bicarbonate were found in blood and normal levels of urea and creatinine in urine. Albumin was not detected in urine. No retina abnormalities were observed in recent funduscopy in the patients of family W07-0455. Both patients of this family are hyperopic and in patient II.5 this is severe. However, this is unlikely to be associated with the defects in *PTPRQ*, because the normal hearing father was also severely hyperopic. There are no indications for abnormalities in lung function in both families. The lack of symptoms in organs with relatively high *PTPRQ* expression may point toward redundancy for PTPRQ function. In addition, the relevant PTPRQ isoform in these organs may not be affected by the mutations. In human kidney, however, transcripts encoding the extracellular region of PTPRQ have been identified.[9]

In mouse inner ear, a transmembranous Ptprq isoform with both the extracellular region and the intracellular region[9] is likely to be the predominant isoform because staining patterns with antibodies directed against these regions exhibit similar staining patterns in rodents.[16] This is corroborated by similar phenotypes of mice in which the *PTPRQ* gene has been targeted by deletions in the regions that encode either the transmembrane domain or the phosphatase domain.[7] These mice demonstrate that Ptprq is required for normal maturation of the hair bundles in the basal region of the cochlea. In this part of the cochlea, both inner and outer hair cells exhibit varying degrees of disorganization already in early postnatal stages, whereby the phenotype in inner hair cells precedes that of outer hair cells. In the inner hair cells, stereocilia are missing or fused and in outer hair cells these are severely shortened. In adult mice with a targeted *Ptprq* gene, hair cells have completely degenerated or even the complete organ of Corti is missing.[7] In the apical part of the cochlea of mice homozygous for the deletions, the gross structure of the organ of Corti is normal and no loss of hair cells was seen in this cochlear region or in the vestibular organs although shaft connectors are missing.[7] There was no Preyer reflex to tone bursts up to 105 dB at 20 kHz at 3 months of age in the $Ptprq^{-/-}$ mice, but the hearing loss in these mice has not been characterized further. The mice do not exhibit behavioral abnormalities associated with vestibular dysfunction.[7] This suggests that Ptprq is not essential for vestibular function in mice; however, it is not indicated whether further tests on vestibular function have been performed. In contrast to the apparently normal vestibular function in mice, patients with PTPRQ mutations displayed vestibular dysfunction already in infancy or early childhood. It can not be excluded that the dysfunction of vestibular hair

cells in mice is mild and only detectable upon functional testing. Also, the cochlear defects associated with PTPRQ/Ptprq defects may be more severe in humans than in mice because the complete cochlea seems to be affected in humans, as indicated by hearing loss in all frequencies (Figure 4).

PTPRQ was initially identified as a protein tyrosine phosphatase (PTPase) that exhibits increased expression in a rat model of glomerular nephritis.[17] In further analyses, PTPRQ was found to have low PTPase activity and mainly functions as a phosphatidylinositol phosphatase (PIPase) and PI(4,5)P_2 was efficiently dephosphorylated.[9,18] In hair cells, PI(4,5)P_2 is essential for mechanotransduction and both fast and slow adaptation. PI(4,5)P_2 is concentrated in the distal part of the hair bundle and there is a PIP_2-free zone at the base of the bundle.[19] Because Ptprq was found to be concentrated at the base of the hair bundle with a decaying gradient from base to apex in cochlear hair cells and a subset of vestibular hair cells, it was suggested that Ptprq PIPase activity maintains the PIP_2-free zone at the base of the stereocilia.[7,16,19] Furthermore, it was suggested that the compartmentalization of Ptprq is due to transport of the enzyme toward the base of stereocilia by myosin VI.[16] PTPRQ and Myosin VI are thought to form a complex that is essential for tethering of the membrane to the cytoskeleton in the tapered ankle region of stereocilia.[16]

The truncating mutation in family W07-0455 can be predicted to affect both the formation of shaft connectors and the PIPase activity of PTPRQ. Whether this is also true for the missense mutation detected in family W04-083 is more difficult to predict. In infancy and childhood, the phenotype is less severe than in family W07-0455, which suggests that PTPRQ with the Arg457Gly mutation has residual activity.

Supplemental Data

Supplemental Data include one figure and two tables and can be found with this article online at http://www.cell.com/AJHG.

Acknowledgments

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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/
Polyphen, http://genetics.bwh.harvard.edu/pph/
Simple modular architecture research tool (SMART), http://smart.embl.de/
Sorting Intolerant from Tolerant (SIFT), http://sift.jcvi.org/
UniProt (Universal Protein Resource), http://www.uniprot.org
UCSC Human Genome Database Build hg18, March 2006, http://www.genome.ucsc.edu

Accession Numbers

The GenBank accession number(s) for the sequence(s) obtained from the RACE experiments reported in this paper are GW420685 for PTPRQ transcript I, GW420684 for PTPRQ transcript II, GW574282 for PTPRQ transcript III, GW574283 for PTPRQ transcript IV, and GW420686 for PTPRQ transcript V.

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