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Hearing loss and *PRPS1* mutations: Wide spectrum of phenotypes and potential therapy

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Abstract

Objective—The purpose of this review was to evaluate the current literature on phosphoribosylpyrophosphate synthetase 1 (*PRPS1*)-related diseases and their consequences on hearing function.

Design—A literature search of peer-reviewed, published journal articles was conducted in online bibliographic databases.

Study sample—Three databases for medical research were included in this review.

Results—Mutations in *PRPS1* are associated with a spectrum of non-syndromic to syndromic hearing loss. Hearing loss in male patients with *PRPS1* mutations is bilateral, moderate to profound, and can be prelingual or postlingual, progressive or non-progressive. Audiogram shapes associated with *PRPS1* deafness are usually residual and flat. Female carriers can have unilateral or bilateral hearing impairment. Gain of function mutations in *PRPS1* cause a superactivity of the PRS-I protein whereas the loss-of-function mutations result in X-linked nonsyndromic sensorineural deafness type 2 (DFN2), or in syndromic deafness including Arts syndrome and X-linked Charcot-Marie-Tooth disease-5 (CMTX5).

Conclusions—Lower residual activity in PRS-I leads to a more severe clinical manifestation. Clinical and molecular findings suggest that the four *PRPS1* disorders discovered to date belong to the same disease spectrum. Dietary supplementation with S-adenosylmethionine (SAM) appeared to alleviate the symptoms of Arts syndrome patients, suggesting that SAM could compensate for PRS-I deficiency.

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Keywords

PRPS1; sex-linked; mutation; genetic deafness; phenotypic variation; hearing impairment

X-linked deafness accounts for about 5% of all congenital hearing impairment (Reardon, 1990), which implies that it affects roughly one in every 50 000 newborn males. Hearing loss is common in many X-linked syndromes and is generally classified by the overall syndrome that leads to hearing impairment, such as Arts syndrome and CMTX5. In contrast, only a limited number of sex-linked loci and only the *POU3F4* and *PRPS1* genes have been shown to be involved in non-syndromic hearing impairment.

Defects in phosphoribosylpyrophosphate (PRPP) synthetase 1 (*PRPS1*) (MIM 311850) are the cause of both nonsyndromic and syndromic forms of hearing loss: X-linked nonsyndromic sensorineural deafness (DFN2) (MIM 304500) (Liu et al, 2010), Charcot-Marie-Tooth disease-5 (CMTX5, or Rosenberg-Chutorian syndrome) (MIM 311070) (Kim et al, 2007; Rosenberg & Chutorian, 1967), Arts syndrome (MIM 301835) (Arts et al, 1993; de Brouwer, 2007), and PRS-I superactivity (MIM 300661) (Sperling et al, 1972). These latter three syndromes have deafness as one of the features. Human PRPS genes encode three very similar and highly conserved isoforms: PRPS1, PRPS2, and PRPS3 (PRPS1L1). PRPS1 is the major isoform of the human phosphoribosyl pyrophosphate (PRPP) synthetase gene family and code for PRS-I. PRPS1 and PRPS2 are mapped on opposite arms of the X chromosome with the PRPS1 locus at Xq22-q24 and the PRPS2 locus at Xp22.2-P22.3. Both X-linked PRPS cDNAs share ~ 80% nucleotide sequence identity throughout their 954 bp translated regions. They have 95.3% amino-acid homology at the protein level (Becker et al, 1990) and are widely expressed (Taira et al, 1989). PRPS3 is located on human chromosome 7 and is restricted to the testes (Taira et al, 1989).

To date, a total of 15 mutations have been reported in only the *PRPS1* gene; four have been identified as causing DFN2, two in Arts syndrome and CMTX5 and seven in PRS-I superactivity. In this review, we focused on the spectrum of non-syndromic and syndromic hearing loss associated with *PRPS1* mutations. We present auditory data of patients carrying deafness-causing mutations of *PRPS1* and summarize the predicted effect of the mutations on protein structure and function. Advances in the treatment of *PRPS1*-linked diseases is also reviewed, providing yet another example of how mutation in a single gene can lead to both syndromic and non syndromic deafness

Role of PRS-I in purine metabolism pathway and inner-ear function

PRS-I plays a central role in both the *de novo* synthesis and the salvage pathways of purine as well as in pyrimidine biosynthesis. Purine *de novo* biosynthesis is a complex, energy-expensive pathway. It begins with formation of PRPP by PRS-I and leads to the first fully formed nucleotide, inosine 5'-monophosphate (IMP). IMP can then be converted into either AMP or GMP. The levels of PRPP are thought to play a crucial role in regulating the rate of purine nucleotide synthesis (Barankiewicz & Henderson, 1977; Benke & Dittman, 1977). PRPP is also used for salvaging purines by adenine phosphoribosyl transferase (APRT) and hypoxanthine guanine phosphoribosyl transferase (HGPRT). PRPP is also essential for the

synthesis of pyrimidines, where it is added to the first fully formed pyrimidine base (orotic acid), forming orotate monophosphate (OMP), which is subsequently decarboxylated to UMP, the precursor of all other pyrimidine nucleotides. Finally, PRPP is also a key player in the pyridine nucleotide synthesis, where it is transferred onto the precursors, nicotinate and nicotinamide by nicotinate phosphoribosyl transferase (NAPRT) and nicotinamide phosphoribosyl transferase (NAMPT), respectively, for formation of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) (Preiss & Handler, 1958; Kanehisa & Goto, 2000). NAD and its derivative NADP are essential cofactors for both energy metabolism and signal transduction as is also seen with the dual functional nucleotides, ATP and GTP. Thus, defects in *PRPS1* have tremendous implications in a number of vital cellular processes, such as nucleic acid synthesis, cellular metabolism, and signaling (de Brouwer et al, 2010).

PRPS1 transcription is tightly regulated by microRNA-376. The *PRPS1* gene, which contains target sites for the edited version of miR-376 within its 3'UTR, is repressed in a tissue-specific manner (Kawahara et al, 2007). Only unedited mature miR-376 transcripts are detected in the liver whereas the edited version of miRNAs are expressed in select tissues including the cerebral cortex, heart, and kidney. Mutations in the miR-376 binding sites of the *PRPS1* gene or in miR-376 itself could therefore, in theory, result in imbalances in nucleotide metabolism. Thus, tissue-specific control of PRS-I activity through the editing of miR-376 appears to be one of the mechanisms that ensure tight regulation of metabolic pathways, and this may explain why mutations in the *PRPS1* gene can give rise to clinically distinct disorders.

PRS-I is expressed in many tissues (Taira et al, 1989) including human fetal cochlea (A Human Cochlear EST Database; http://www.brighamandwomens.org/bwh_hearing/). *In situ* hybridization analysis of Prs-I in the murine cochlea showed it to be expressed in both vestibular and cochlear hair cells in developing and early postnatal mice (Liu et al, 2010). At embryonic day 18.5 (E18.5), Prs-I expression is observed in utricular and crista hair cells as well as in cochlear hair cells, Claudius cells, and the greater epithelial ridge (GER), but not in other cochlear supporting cells. By postnatal day 6 (P6), expression of Prs-I could be detected in the spiral ganglion cells in addition to hair cells in the organ of Corti and Claudius cells, although expression in the GER is reduced. Thus, the temporal distribution pattern of Prs-I suggests a role in development and maintenance of the inner ear. Detectable distortion product otoacoustic emissions (DPOAEs) were absent in affected males and female carriers tested in the Chinese DFN2 family with the c.193G> A (D65N) mutation in *PRPS1*, which suggests that lesions in hair cells are the likely source of the hearing loss in DFN2 (Liu et al, 2010). There were no signs of auditory neuropathy involving either the spiral ganglion cells or their axons, nor was there any visual dysfunction due to optic neuropathy. Therefore, defects in sensory hair cells appear to be the cause of deafness observed in DFN2 patients.

Wide phenotypic spectrum of *PRPS1* mutations

Mutations in *PRPS1* can lead to a broad spectrum of phenotypes including syndromic and non-syndromic hearing loss. These comprise CMTX5, Arts syndrome, PRS-I superactivity,

and nonsyndromic sensorineural deafness (DFN2). Sensorineural hearing loss is a clinical feature of CMTX5 and Arts syndrome but only present in the severe form of the PRS-I superactivity. Prevalence of *PRPS1* mutations in the general population has not been estimated.

On the basis of the results obtained from *in silico* molecular modeling, mutations that have less effect on the PRS-I structure, are predicted to lead to a milder phenotype. The four missense mutations (p.D65N, p.A87T, p.I290T, and p.G306R) identified in the four DFN2 families, result in a loss of PRS-I activity, as has been suggested by *in silico* structural analysis and been demonstrated by *in vitro* enzymatic assays in erythrocytes and cultured fibroblasts from patients (Liu et al, 2010). None of the mutations causing DFN2 are expected to exert a drastic structural impact on the PRS-I protein, which may explain why the phenotype is limited to nonsyndromic hearing loss. Molecular modeling showed that the p.D65N (DFN2), p.E43D, p.M115T (CMTX5), and p.Q133P, p.L152P (Arts syndrome) mutations are likely to affect the ATP-binding pocket (de Brouwer et al, 2010). However, the analysis predicted that the effect of the D65N mutation is much less severe, compared with the Q133P mutation (de Brouwer et al, 2007), which has more severe consequence than the M115T mutation (Kim et al, 2007). Furthermore, the level of PRS-I activity observed in patients with *PRPS1* mutations, seems to correlate with the severity of the phenotype. Arts syndrome is characterized by mental retardation, early-onset hypotonia, ataxia, delayed motor development, hearing loss, and optic atrophy. There was no detectable PRS-I activity in erythrocytes from affected males with Arts syndrome and the enzyme activity was reduced 13-fold in comparison to that in fibroblasts from controls (de Brouwer et al, 2007). Patients with CMTX5 have hearing loss, visual impairment, and peripheral neuropathy. The PRS-I activity in fibroblasts from affected males was down to 38% of normal activity compared with that of unaffected family members and unrelated healthy controls (Kim et al, 2007; Table 1). Hearing loss is found as an isolated feature in DFN2 patients. The PRS-I activity in erythrocytes and cultured fibroblasts from affected males was decreased to 55%–56% of normal activity compared to that of normal male family members and unrelated control subjects (Table 1). Moreover, inter- and intrafamilial phenotypic variability of disease expression have been reported for PRS-I superactivity and Arts syndrome (Arts et al, 1993; Becker, 2001). There are a number of possible explanations for this phenotypic variation. Firstly, there may be functional redundancy and compensation of the three PRS isoforms, encoded by *PRPS1*, *PRPS2*, and *PRPS1L1*, which should regulate a desirable level of PRPP production. However, PRS-II expression levels were not found to be elevated in fibroblasts from patients with Arts syndrome to compensate for PRS-I deficiency (de Brouwer et al, 2010). Secondly, variations in genes encoding regulators of PRS-I synthesis, such as miR-376 may contribute to the clinical variability. However, no sequence variants in miR-376 have been detected in the original Arts syndrome kindred (de Brouwer et al, 2010). Thirdly, attenuation of the clinical manifestation may be a consequence of differences in the rate-limiting enzyme, PRPP amidotransferase (PPAT) expression levels between individuals. Finally, there may be modifier loci contributing to the inter- and intrafamilial variability in the phenotypic expression. Moreover, defects in PRS-I activity could theoretically have effect on the enzymatic conversions catalyzed by phosphoribosyltransferase enzymes using PRPP as substrate. Thus, it came as no surprise

that numerous symptoms that are present in patients exhibiting deficiencies in phosphoribosyltransferase enzymes overlap with those found in patients with *PRPS1*-related disorders. For instance, recurrent infections and early death resulting from the upper respiratory tract occurring in patients with Arts syndrome were first reported for uridine monophosphate synthetase (UMPS) deficiency (MIM 258900) (Ross et al, 1997). Patients with hypoxanthine–guanine phosphoribosyl transferase (HGPRT) deficiency or Lesch-Nyhan disease (MIM 300322) have uric acid overproduction similar to *PRS-I* superactivity and can also have mental retardation and hypotonia, as described in patients with Arts syndrome (Nyhan, 2005).

***PRPS1* mutations and their consequences**

Audiological features of *PRPS1* deafness

Hearing loss in male patients with *PRPS1* mutations is bilateral, moderate to profound (Table 2). Hearing loss can be prelingual or postlingual and progressive or non-progressive. Audiogram shapes associated with *PRPS1* deafness are usually residual or flat. Hearing in female carriers can be normal or abnormal. Vestibular function is normal in tested patients.

Non-syndromic sensorineural deafness (DFN2)

DFN2 is phenotypically complex. Petersen et al (2008) proposed the designation DFNX1 for this locus. So far, four families with DFNX1 (DFN2) have been described. Deafness in DFN2 is characterized by postlingual progressive nonsyndromic hearing loss (NSHL), although in the first DFN2 family to be identified, congenital profound NSHL was reported (Tyson et al, 1996). Hemizygous male patients in this British-American family had hearing loss at all frequencies, and obligate carrier females showed mild to moderate hearing loss affecting the high frequencies. In the second DFN2 family described by Manolis & colleagues (1999), the affected males in this American family exhibited an upward-sloping audio profile, with severe hearing impairment at both low and middle frequencies and better hearing in the high frequencies. The loss was postlingual and progressive, with an age at onset between 7 and 20 years. The obligate female carriers in this family had mild hearing impairment. Their audiogram showed a hearing loss affecting the low frequencies. Cui et al (2004) reported a large Chinese family with affected males who had profound congenital sensorineural hearing loss of all tones. Obligate carriers had mild to moderate low-tone hearing loss, very similar to the carriers in the family described by Manolis & colleagues (1999). The fourth DFN2 family has recently been reported consisting of a large, five-generation, Chinese pedigree (Liu et al, 2010). Affected male patients had symmetric, progressive, severe to profound hearing loss with flat-shaped audio profiles at 24–50 years of age. Obligate female carriers had either symmetric or asymmetric hearing loss ranging from mild to moderate in severity (Table 2). One carrier had completely normal hearing at age 52. Absence of detectable DPOAEs in affected males and female carriers tested is indicative of hair cell pathology (Liu et al, 2010). However, the exact mechanism of hearing loss in DFN2 remains to be determined.

Charcot-Marie-Tooth, X-linked recessive 5 (CMTX5), or Rosenberg-Chutorian syndrome

CMTX5 is an extremely rare genetic disorder; however, it may be under-diagnosed as a result of under-recognition by physicians. Prevalence has not been estimated. Two families with CMTX5 have been identified worldwide (Rosenberg & Chutorian, 1967, Kim et al, 2007). The disorder is characterized by the triad of peripheral neuropathy, early-onset (prelingual) bilateral profound sensorineural hearing loss with normal temporal bone and optic neuropathy. The age at onset of symptoms of peripheral neuropathy is between 10 and 12 years. Initial manifestations often include foot drop or gait disturbance. Onset of bilateral progressive visual impairment is between ages 7 and 20 years. Patients have bilateral optic disc pallor and decreased visual evoked potentials, indicative of optic nerve dysfunction. Pathologic examination of the sural nerve biopsy sample from the eldest living patient from a Korean family showed myelinated nerve fiber loss (Kim et al, 2007). Mental retardation and recurrent infections are not features found in patients with CMTX5 and there is no evidence that the life expectancy of affected individuals is shortened. Carrier females usually do not display findings of CMTX5.

Arts syndrome

Arts syndrome, is characterized by profound congenital sensorineural hearing impairment, early-onset hypotonia, delayed motor development, mild to moderate mental retardation, ataxia. Susceptibility to infections, especially of the upper respiratory tract, can result in early death (Arts et al, 1993; de Brouwer et al, 2007). Onset of all findings, except optic atrophy, is before age two years. Signs of peripheral neuropathy develop during early childhood. Up to today, two kindreds with Arts syndrome have been identified (de Brouwer et al, 2007). Up to 80% of reported patients with Arts syndrome died before age six, primarily from infectious complications. The oldest patient, then 16 years of age, was nearly blind due to optic atrophy, and lived in an institution for the visually and mentally handicapped (Kremer et al, 1996). Two loss-of-function mutations of the *PRPS1* gene have been identified, c.455T> C (p.L152P) in the original Dutch kindred, and c.398A > C (p.Q133P) in the Australian family. The PRS-I enzyme activity was shown to be decreased in cells from affected males. Obligate carrier females in the Dutch family often had isolated and milder symptoms of Arts syndrome, including hearing impairment, ataxic diplesia, hypotonia, and hyperreflexia (Arts et al, 1993). Normal hearing in the obligate carrier in the Australian family was noted (Table 2). In the only patient from the original Dutch Arts syndrome kindred in whom the central nervous system (CNS) could be examined at autopsy, almost complete absence of myelin in the posterior columns of the spinal cord was noted (Arts et al, 1993). In addition, a sural nerve biopsy of an affected boy from the Australian family, who had nerve conduction studies, showed mild paranodal demyelination, indicative of peripheral neuropathy.

PRS-I superactivity

PRS-I superactivity has been demonstrated to be clinically heterogeneous and an apparently rare disorder with approximately 30 families with the condition reported (Becker et al, 1988; Becker, 2008). There are two forms of PRS-I superactivity. A mild form reported in more than two thirds of these families, in which clinical manifestations are limited to the

appearance of gout in early adulthood. In families with the more severe form, affected hemizygous males exhibit infantile or early childhood onset of gout in association with neuro-developmental abnormalities, including sensorineural hearing loss, hypotonia, ataxia, and developmental delay (Becker et al, 1988). In patients with the more severe form of PRS-I superactivity, seven missense mutations (p.D52H, p.L129I, p.N114S, p.D183H, p.A190V, p.H193L, and p.H193Q) have been described in *PRPS1* as causing PRS-I superactivity. Interestingly, hemizygous males and affected females with the p.N114S and p.D183H mutations have been found to exhibit neurologic deficit, most commonly sensorineural deafness (Becker et al, 1988). Affected males with altered allosteric control of PRS-I activity generally have higher rates of PRPP production and, ultimately, greater acceleration of purine nucleotide and uric acid synthesis than individuals with isolated over-expression of normal PRS-I (Becker et al, 1987). However, repression of the *PRPS1* gene, a target of the edited miR-376 RNA, appears to be one of the mechanisms that ensure tight regulation of uric-acid levels in select tissues such as the cerebral cortex (Kawahara et al, 2007). The proposed mechanisms underlying inherited PRS-I superactivity include defective allosteric regulation of PRS-I activity (regulatory defects) and increased activity of the normal PRS-I isoform (catalytic superactivity) (Becker et al, 1995, 1996).

Management and treatment of patients with *PRPS1* defects

Hyperuricemia and hyperuricosuria are the consequences of excessive synthesis of purine nucleotide and, ultimately, uric acid overproduction in PRS-I superactivity. The metabolic manifestations include gouty arthritis, uric acid urolithiasis, tophus formation, and, potentially, renal failure. Prevention of recurrence of manifestations of these adverse events can usually be attained by measures aimed at lowering purine nucleotide and uric acid production, combined with efforts to prevent or reverse urate crystal deposition. Treatment of hyperuricemia involves the combination of allopurinol to decrease uric acid production, probenecid to increase uric acid clearance in patients with normal renal function, and urinary alkalization with potassium citrate to increase the solubility of uric acid, particularly when there has been uric acid stone gravel formation. Allopurinol inhibits the enzyme xanthine oxidase, thereby blocking the conversion of the oxypurines hypoxanthine and xanthine to uric acid. Allopurinol administration also leads to deceleration of the rate of *de novo* synthesis of purine nucleotides. This process potentiates the beneficial effects of xanthine oxidase inhibition to reduce uric acid, probably due to the enzyme hypoxanthine phosphoribosyltransferase (HPRT) mediated conversion of allopurinol to allopurinol nucleotide metabolites.

Despite the importance of PRS-I enzyme in *de novo* purine synthesis, purine nucleotides, specifically ATP can be produced by an alternative pathway utilizing *S*-adenosylmethionine (SAM) as a substrate (Montero et al, 1990; Simmonds et al, 1989; Smolenski et al, 1991, 1992). Methyltransferases are responsible for conversion of SAM into *S*-adenosylhomocysteine, which is catabolized by hydrolysis to adenosine and L-homocysteine in a reaction catalysed by *S*-adenosylhomocysteine hydrolase (AHCY) (EC 3.3.1.1) (Kanehisa & Goto, 2000; de Brouwer et al, 2010), or SAM can be converted directly to adenine, through the polyamine pathway (Palella et al, 1980; Smolenski et al, 1992). Adenine can subsequently be converted to AMP by adenine phosphoribosyltransferase

(APRT), utilizing PRPP as a substrate. An alternative purine source is salvage of adenosine via adenosine kinase to form purine nucleotides, which does not require PRPP as cofactor (Schuster & Kenanov 2005). AMP can then be converted to ATP, or may be de-aminated by the enzyme adenylate (AMP) deaminase to IMP, which can then be used to generate GTP. SAM can thus theoretically be used to replenish both ATP and GTP levels independently of PRPP. In addition, because SAM serves an important biological function as the sole methyl donor in a multitude of cellular methylation reactions (Chiang et al, 1996), it is a source of methionine, which could overcome a possible deficiency of methylation processes, including myelin synthesis. Importantly, SAM appears to be unique among purines in that it is able to cross the intestinal wall and has been shown to pass the blood-brain barrier. Supplementary SAM has been used as a treatment for many different and seemingly unrelated medical problems, including depression, neurologic disorders, liver disease, and osteoarthritis (Bottiglieri, 2002). Furthermore, administration of SAM to a patient with Lesch-Nyhan syndrome was shown to provide improvement in neurobehavioural and other neurological abnormalities (Glick, 2006), indicating that brain purine nucleotide levels can be elevated by SAM. A recent open-label clinical trial of oral supplementation of SAM set at 30 mg/kg/day in the two Australian brothers with Arts syndrome appears to have had significant benefit; the therapy has decreased the number of hospitalizations and eliminated the need for nocturnal bilevel positive airway pressure (BIPAP) support. The oldest boy was hospitalized for a total of 180 days in an 84 month period, including two pediatric intensive care unit admissions that required mechanical ventilation. In the 33 months since the beginning of the therapy, he has only been admitted to a general ward once, for five days. In an 84-month period prior to SAM therapy, his younger brother was admitted to the hospital for 82 days but has not required hospitalization over 33 months since starting SAM treatment. The progression of other symptoms including the ataxia and hearing impairment also seem to have been stabilized (de Brouwer et al, 2010). The coenzyme SAM that crosses both the gut and the blood-brain barrier may also be able to cross the blood labyrinth barrier and enter hair cells, which may explain the stabilization of hearing loss in the Art syndrome patients. The theoretical justification for treating purine disorders such as PRS-I and *HPRT* deficiencies with SAM is based on PRPP-independent path for conversion via adenosine into ATP and then GTP (Kanehisa & Goto, 2000; de Brouwer et al, 2010). However, there is the theoretical risk of SAM supplementation due to generation of homocysteine and resulting vascular toxicity.

Conclusions

PRPS1 is another rare example of a human disease gene in which activating and inactivating mutations cause distinct hereditary disorders and can lead to either syndromic or non-syndromic form of deafness. Genetic and phenotypic heterogeneity underlies the *PRPS1*-related disorders. The audiogram profile and clinical presentation of individuals with *PRPS1* mutations are easily distinguished from those of persons with other X-linked syndromic and non-syndromic deafness, which facilitates genetic testing of these X-linked hearing impairment. Expression of Prs-I in both vestibular and cochlea hair cells in early developing and postnatal mice, suggests a possible role in inner ear development and maintenance. Although PRPP synthetases are essential for *de novo* purine synthesis, ATP can be

specifically produced by an alternative pathway utilizing SAM as a substrate. Dietary supplementation with SAM in patients with Arts syndrome has been reported to alleviate the symptoms of patients based on reduced number of hospitalizations and stabilization of nocturnal bilevel positive airway pressure (BIPAP) requirements. In addition, the progression of hearing impairment appears to have been stabilized (de Brouwer et al, 2010). This suggests that patients with DFN2 and CMTX5, and mildly affected carrier females, may also benefit from SAM supplementation in their diet by replenishing purine nucleotides independent of PRPP production.

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Abbreviation

PRPS1 Phosphoribosylpyrophosphate synthetase 1

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Table 1Phenotypic spectrum of disorders caused by loss of function mutation in *PRPS1*.

Disorders	Clinical findings	Residual PRS-I activity in cells from affected males (%)
DFN2	Congenital/postlingual onset HL	45 in erythrocytes
		56 in fibroblasts
CMTX5	Early onset HL	38 in fibroblasts
	Optic neuropathy	
	Peripheral neuropathy	
Arts syndrome	Congenital HL	Absent in erythrocytes
	Mental retardation	8 in fibroblasts
	Early onset hypotonia	
	Delayed motor development	
	Ataxia	
	Optic atrophy	
	Risk for infection	

HL: Hearing loss.

Table 2

Deafness-associated *PRPS1* mutations.

Disorder	Hemizygous male patients							Hearing status in female carriers
	Nucleotide change	Amino acid change	Functional change	Hearing status	Severity	Progression	Audiogram shape	
PRS-I	c.341A> G	p.N114S ¹	Gain of function	Congenital HL	Profound	No	–	HL, no detail available
Superactivity	c.547G> C	p.D183H ¹	Gain of function	Congenital HL	Profound	No	–	HL, no detail available
Arts syndrome	c.398A> C	p.Q133p ²	Loss of function	Congenital HL	Profound	No	–	Normal
	c.455T> C	p.L152p ²	Loss of function	Congenital HL	Profound	No	–	Low and high tone loss, slope
Intermediate phenotype	c.424G> C	p.V142L ⁸	Gain of function	Congenital HL	Profound	No	–	HL, no detail available
PRS-I superactivity + Arts syndrome	–	–	Loss of function	Prelingual onset HL	–	–	–	–
CMTX5	c.129A> C	p.E43D ³	Loss of function	Prelingual onset HL	Profound	No	–	Normal
	c.344T> C	p.M115T ³	Loss of function	HL onset 5 to 15 years old, affecting all tones	Profound	No	–	Normal
DFN2	c.193G> A	p.D65N ⁴	Loss of function	Congenital HL, affecting all tones	Severe to profound	Yes	Flat	Symmetric or asymmetric loss
	c.259G> A	p.A87T ^{4,5}	Loss of function	Congenital HL, affecting all tones	Profound	No	Flat	High tone loss, slope
	c.869T> C	p.I290T ^{4,6}	Loss of function	HL onset 7 to 20 years old, low and mid-frequencies are more affected	Profound	No	Flat	Low tone loss, ascending
	c.916G> A	p.G306R ^{4,7}	Loss of function	–	–	–	–	Low tone loss, ascending

HL: Hearing loss.

¹Roessler et al, 1991;

²de Brouwer et al, 2007;

³Kim et al, 2007;

⁴Liu et al, 2010;

⁵Tyson et al, 1996;

⁶Cui et al, 2004;

⁷Manolis et al, 1999;
⁸Moran et al, 2012.

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