Published in final edited form as:

J Gene Med. 2016 November ; 18(11-12): 353–358. doi:10.1002/jgm.2935.

Functional Characterization of a Novel Loss-of-Function Mutation of *PRPS1* related to Early-Onset Progressive Nonsyndromic Hearing Loss in Koreans (DFNX1): Potential Implications on Future Therapeutic Intervention

So Young Kim, MD^{1,*}, Ah Reum Kim, PhD^{2,*}, Nayoung K. D. Kim, PhD³, Chung Lee, PhD^{3,4}, Jin Hee Han, MS⁵, Min Young Kim, MS⁵, Eun-Hee Jeon, BS⁵, Woong-Yang Park, PhD^{6,7}, Rahul Mittal, PhD⁸, Denise Yan, PhD⁸, Xue Zhong Liu, MD, PhD⁸, and Byung Yoon Choi, MD, PhD^{5,9}

¹Department of Otorhinolaryngology-Head and Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

²Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

³Samsung Genome Institute, Samsung Medical Center, Seoul, Korea

⁴Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Suwon, Korea

⁵Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

⁶Samsung Genome Institute, Samsung Medical Center, Seoul, Korea

⁷Department of Molecular Cell Biology, School of Medicine, Sungkyunkwan University, Seoul, Korea

⁸Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, FL 33136, USA

⁹Wide River Institute of Immunology, Seoul National University College of Medicine, Hongcheon, Korea

Abstract

Background—The symptoms of phosphoribosyl pyrophosphate synthetase 1 (*PRPS1*) deficiency diseases have been reported to be alleviated by medication. Herein, we report

Corresponding author: Byung Yoon Choi, MD, Associate Professor, Department of Otorhinolaryngology -Head & Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 300 Gumi-dong, Bundang-gu, Seongnam 463-707, Republic of Korea, Tel: +82-031-787-7406, Fax: +82-031-787-4057, choiby@snubh.org.

*These authors contributed equally to this work.

Conflict of interest

The authors declare that they have no competing interests.

And no potential conflict of interest relevant to this article was reported.

biochemical data to favor *PRPS1* deficiency-related hearing loss as a potential target for pharmaceutical treatment.

Methods—We recruited 42 probands from subjects under the age of 15 years with a moderate degree of nonsyndromic autosomal-recessive or sporadic sensorineural hearing loss (SNHL) in at least one side. Molecular genetic testing, including targeted exome sequencing (TES) of 129 deafness genes, and *in silico* prediction were performed.

Results—A strong candidate variant—p.A82P—of *PRPS1* is co-segregated with SNHL in X-linked recessive inheritance from one Korean multiplex SNHL family. Subsequent measurement of *in vitro* enzymatic activities of *PRPS1* from erythrocytes of affected and unaffected family members as well as unrelated normal controls has confirmed a pathogenic role of this variant. In detail, compared with normal hearing controls (0.23 – 0.26 nmol/ml/h), the proband, affected sibling, and their normal hearing mother demonstrated a significantly decreased *PRPS1* enzymatic activity (0.07, 0.03, and 0.11 nmol/ml/h, respectively). This novel loss-of-function mutation of *PRPS1*—p.A82P—is the 9th and 6th most reported mutation in the world and in Asia, respectively.

Conclusions—DFNX1 turned out to account for about 2.4% (1/42) of moderate SNHL in a Korean pediatric population. Confirmation of *PRPS1* activity deficiency and an audiologic phenotype that initially begins in a milder form of SNHL, as in our family, should indicate the necessity for rigorous genetic screening as early as possible.

Keywords

PRPS1; p.A82P; DFNX1 (X-linked nonsyndromic sensorineural deafness type 1); Korean; S-adenosylmethionine (SAM)

Introduction

Mild-to-moderate sensorineural hearing loss (SNHL) is considerably attributed to genetic causes. In our previous study, genetic causes accounted for approximately 45.4% of all SNHL simplex cases [1]. Several genes, including *OTOG*, *OTOGL*, *STRC*, *SERPINB6*, *GPR98*, and *PDZ7*, are related to moderate SNHL [1,2,3,4]. In addition, some genes of severe to profound SNHL are also associated with moderate SNHL [5,6]. Several molecular genetic approaches, including phenotypic-driven genetic testing strategy [7], targeted exome sequencing (TES)[8], and whole exome sequencing (WES)[1], have been used to efficiently investigate rare but important causative mutations.

Because many moderate SNHL mutations show a delayed onset during childhood, it is highly probable to miss the early intervention period without suspicion. Identifying the molecular etiology of moderate SNHL is crucial for early intervention, allowing to minimize related complications and to alleviate its progression. Delayed intervention, on the other hand, can result in the neurological and intellectual developmental delays and can compromise cognitive functions [9].

The treatment of phosphoribosylpyrophosphate synthetase 1 (*PRPS1*) (MIM 311850)-related diseases using a metabolic compensation with S-adenosylmethionine (SAM) has been suggested recently [10]. The X-linked mutations of *PRPS1* are associated with both

syndromic and nonsyndromic (DFNX1) SNHL [11]. The audiologic phenotypes of *PRPS1* mutations show a wide spectrum of moderate to profound, prelingual or postlingual, and progressive or non-progressive forms [12]. The SNHL can be manifested in all of the *PRPS1*-related disorders, including Arts syndrome, X-linked Charcot-Marie-Tooth disease-5 (CMTX5), DFNX1, and PRS1 superactivity with various degrees [13,14,15,16,17,18]. However, the association between audiologic phenotypes and PRS1 activities has not been well established thus far.

Recently, we identified X-linked missense mutation of *PRPS1*, using TES in a multiplex family. The frequency of DFNX1 in moderate nonsyndromic SNHL pediatric subjects with recessive or sporadic inheritances was estimated. Additionally, their audiologic phenotypes and PRS1 activities were analyzed and the association between the two has been discussed. Importantly, our data favors *PRPS1* deficiency-related SNHL as the potential target of pharmaceutical treatment by showing a narrow margin between the enzymatic activity of the affected male siblings and the normal carrier mother. To the best of our knowledge, this is the first report that presents *PRPS1*-related nonsyndromic SNHL in a Korean family.

Material & method

Ethical considerations

This study was approved by the institutional review boards (IRBs) at Seoul National University Hospital (IRBY-H-0905-041-281) and Seoul National University Bundang Hospital (IRB-B-1007-105-402). Written informed consent was obtained from all participating subjects. For children, written informed consent was obtained from their parents or guardians.

Clinical evaluation

The 42 probands under the age of 15 years, with a moderate degree of nonsyndromic autosomal-recessive or sporadic SNHL in at least one side, and their families were examined for any history of hearing loss and other syndromic features at the otolaryngology clinics in the two institutions aforementioned between September 2010 and February 2016. Clinical characteristics included gender, date of birth, medical history, physical examination, pure-tone audiometry, auditory brainstem response (ABR), and speech evaluation. The presence of any phenotypic markers, indicating syndromic SNHL, was thoroughly investigated in the proband and related family members. Imaging evaluations were conducted using temporal bone computed tomography (TBCT) and internal auditory canal magnetic resonance imaging (IAC MRI) to identify inner ear anomalies, such as an enlarged vestibular aqueduct in subjects. All family members were investigated for the presence of any type of hearing loss. The pure-tone thresholds were recorded at 0.25, 0.5, 1, 2, 4, and 8 kHz. The hearing threshold was calculated by averaging the thresholds of 0.5, 1, 2, and 4 kHz, and was classified as subtle (16–25 dB), mild (26–40 dB), moderate (41–70 dB), severe (71–95 dB), or profound (> 95 dB). Based on the results of the retrieved clinical and audiologic evaluations, probands and their families without any phenotypic markers were screened for the presence of deafness mutation with phenotypic-driven genetic testing approaches [7].

DNA samples and phenotypic-driven genetic testing focused on the candidate genes

Genomic DNA was extracted from the peripheral blood using standard protocols (Gentra Puregene Blood Kit, Qiagen, Venlo, Limburg, Netherlands). Sanger sequencing of *GJB2* was performed, as previously described [5,19]. Further genetic tests were conducted for Sanger sequencing of p.P240L of *CDH23*, which is the founder mutation of *CDH23* in Koreans [20]. Next, the presence of causative mutations in other deafness genes was investigated by a targeted capture technique of exons and flanking sequences of 129 deafness genes, followed by massively parallel sequencing of DNA libraries, as previously described [21]. Variant detection was accomplished as previously described [21].

Investigation of pathogenicity of the PRPS1 variant

In silico predictions of the pathogenicity of *PRPS1* variant were performed using PolyPhen-2 [22]. The segregation analysis was performed for the detected variations of *PRPS1*. The prevalence of *PRPS1* variants among the 120 Korean normal-hearing control X chromosomes and 1244 Korean control alleles derived from the Korean Reference Genome Database (KRGDB) (<http://152.99.75.168/KRGDB/menuPages/firstinfo.jsp>) was estimated. The conservation of residues of the *PRPS1* variants among different species was evaluated. The *in vitro* assay of phospho-ribosylpyrophosphate synthetase 1 (PRS1) enzymatic activity was performed in the proband (SH 178–396), sibling (SH 178–411), and their heterozygote carrier mother (SH 178–397) using patient-derived erythrocytes with the ELISA kit from the NOVOCIB Company (Lyon, France). Normal hearing unrelated controls of one male and a female were compared to the PRS1 enzyme activity. Each PRS1 activity assay was conducted three times to ensure reliability of the results.

Statistical Analysis

The difference of PRS1 activity between the groups of affected, unaffected, and carrier subjects were compared by using Mann-Whitney U test. *P*-values of less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS ver. 21.0 (IBM, Armonk, NY, USA).

Results

Clinical characteristics

Proband from a boy (SH178–396) showed moderate-to-severe bilateral SNHL, which was first detected at age 3 years. At that time, his pure-tone threshold in the right and left ears was 80 and 65 dB HL, respectively (Fig. 1a). However, this was aggravated to 90 dB HL bilaterally over a 7-year period (Fig. 1a). Finally, he underwent right-sided cochlear implantation at age 12 years. He did not show any syndromic features, including peripheral or central neuropathy, mental retardation, and ataxia. He did not show uric acid abnormality or susceptibility to infections. The inner ear structure was intact in TBCT and IAC MRI.

His older brother (SH178–411) also suffered from moderate bilateral SNHL, which was first detected at age 7 years and gradually progressed (Fig. 1a). Syndromic features or inner ear anomaly was identified in this patient. All other family members did not have any history of hearing impairment or syndromic features.

Phenotypic –driven molecular genetic approaches

Because *GJB2* mutation is the most prevalent causative deafness mutation in Koreans, we initially conducted *GJB2* screening for autosomal recessive or sporadic cases, followed by *CDH23* p.240L sequencing. In the aforementioned boy, SH178–396, there were no mutations in either deafness genes. Through TES, we identified a candidate variant of p.A82P (c.244G>C) of *PRPS1*, co-segregating with SNHL in an X-linked recessive inheritance manner (Figure 1a).

Validation of pathogenic potential of *PRPS1* p.A82P variants

PolyPhen-2 analysis predicted that *PRPS1* p.A82P was probably damaging with a score of 0.977 (sensitivity: 0.76; specificity: 0.96). Moreover, the p.A82 residue was well conserved from *C.elegans* to humans. There was no p.A82P variant in 120 Korean normal-hearing control X chromosomes and 1244 Korean control alleles derived from the KRGDB. While normal hearing controls showed PRS1 activities of 0.23–0.26, both the affected siblings showed a significantly lower PRS1 activity—0.07 in the younger brother (SH178–396) and 0.03 in the older brother (SH178–411) (Figure 1b) ($P = 0.01$, Mann-Whitney U test), confirming the pathogenic role of this variant in SNHL. Their carrier mother (SH178–397) showed a PRS1 activity of 0.11, which was only slightly higher than the two siblings (0.03 and 0.07) ($P = 0.13$, Mann-Whitney U test), but still markedly lower than the normal controls (0.23–0.26); it is worth noting that there was no statistical significance, probably due to a small number of samples ($P = 0.07$, Mann-Whitney U test).

Discussion

We identified a novel *PRPS1* mutation through phenotypic-driven molecular genetic approaches. According to this study, DFNX1 turned out to account for about 2.4% (1/42) of moderate SNHL in a Korean pediatric population. Because the X-linked inheritance pattern could not be convinced from the beginning, prevalent autosomal recessive genes including *GJB2* and *CDH23* were initially investigated, followed by TES, identifying possible pathogenic variants of *PRPS1*. The pathogenicity of the selected variant of *PRPS1* was examined by an *in silico* analysis of PolyPhen2 and the presence of variant in the normal control group. Moreover, the PRS1 activity assay provided solid evidence for the pathogenicity.

To date, 24 *PRPS1* mutations have been identified [14]. It was presumed that the protein structural positions of *PRPS1* mutations—related to the PRS1 activity—determine the severities of *PRPS1*-related disorders [14]. The active hexamer configuration of *PRPS1* has a catalytic site that provides the binding sites for ATP and ribose 5-phosphate, and an allosteric site that regulates the enzyme activity [23,24]. *PRPS1* mutations in the allosteric site hinder the feedback regulation of PRS1 enzyme activity, thereby causing PRS1 superactivity [25,26]. On the other hands, the destabilization of ATP-binding site result in *PRPS1* deficiency-related disorders, encompassing the most severe forms of *PRPS1*-deficiency syndrome [15], Arts syndrome, intermediate form between CMTX5 and Arts syndrome [27,28], and CMTX5, in accordance with the residual PRS1 activities. DFNX1 mutations usually influence neither the allosteric site nor the ATP-binding site, but induce

the local protein structural changes or effect the interface of trimers [27]. However, the structural loci of *PRPS1* mutations is not always the determining factor of the types of *PRPS1*-deficiency disorders. Identical *PRPS1* mutations were reported to cause nonsyndromic and syndromic *PRPS1*-deficiency disorders in a family [28,29].

The severity of *PRPS1*-related disorders from DFNX1 to recently reported most severe *PRPS1*-deficiency syndrome with prenatal growth restriction, retinal dystrophy, diabetes insipidus and white matter diseases was suggested to be related with PRS1 activities [14,15]. A few studies on DFNX1 demonstrated the significantly decreased PRS1 activity in the affected subjects compared with the unaffected or carrier subjects [11,28,29]. However, it is still elusive that audiologic phenotypes of *PRPS1* mutations are also correlated with PRS1 activities. Our affected siblings—SH178–396 and SH178–411—showed severe and moderate SNHL, respectively. SH178–411 with moderate SNHL showed a lower PRS1 activity than SH178–396 with severe SNHL. Subtle discrepancy between the degree of SNHL and residual PRS1 activities in our affected siblings is not unprecedented [27]. A previous study also reported with similar results of intrafamilial phenotypic heterogeneities [29]. A previous study showed that even an identical *PRPS1* mutation of p.Gly306Glu caused both nonsyndromic and syndromic features [29]. In females, this can be originated from the skewed inactivation of mutant X-chromosome [27,28]. However, in our affected male subjects, this discrepancy between the degree of SNHL and residual PRS1 activities cannot be explained by the skewed X-chromosome inactivation. Instead, intrafamilial variable *PRPS1* expression can be mediated by tissue-specific modifier functions or by test errors [11]. For instance, microRNA-376 is known to regulate *PRPS1* levels only in specific organs, including cerebral cortex, heart, and kidney [30]. The differences in the expressions of tissue-specific microRNA can lead to the variation of *PRPS1* expression with an identical genetic configuration. In addition, compensatory metabolic pathways or paralogs of *PRS*, such as *PRPS2* (NM_001039091.2), *PRPS3* (NM_175886.2), *PRPSAP1* (NM_002766.2), and *PRPSAP2* (NM_002767.3), may compensate *PRPS1* functions [10,29].

Our female heterozygote carrier (SH178–397) showed a normal hearing level and did not show any phenotypic markers. Her PRS1 activity was significantly decreased compared with that of normal controls, but it was not as low as that of the affected male siblings aforementioned (SH178–396 and SH178–411). Although most female carriers in families with *PRPS1* mutations were noted to be asymptomatic [16], some studies reported that female carriers in families with Art syndrome were known to occasionally exhibit a delayed onset of hearing impairment combined with ataxia and neuropathy [13,27,28,31]. The tissue-specific PRS1 expressions due to the skewed X-chromosome inactivation and unrevealed modifiers could result in a relatively higher PRS1 activity of cochlear than that of erythrocytes in our carrier. It is likely that the residual PRS1 activity of our female carrier, albeit significantly reduced, is still enough to maintain normal hearing function. Because there have been only anecdotal reports on PRS1 activities of DFNX1 cases [11,28,29], the degree of deficiency of PRS1 activity leading to SNHL has not been documented to date. Previously, significant differences in PRS1 activities between syndromic patients and non-symptomatic carriers were reported [32,33]. However, the enzyme activity from non-syndromic SNHL, which is obligatorily related to a lesser degree of PRS1 deficiency, would provide a better clue to the minimal therapeutic level of PRS1. Indeed, our current study

showed a much smaller difference of PRS1 activities between the affected nonsyndromic SNHL subjects and no symptomatic *PRPS1* carriers and also provided an experimental value of PRS1 activity (0.11), at or above the normal level in which hearing is maintained. This level of PRS1 activity, which needs to prevent the symptoms of PRS1 deficiency including SNHL, can be useful in selecting the indication to compensate for PRS1 activity using SAM.

Our proband (SH178–396) demonstrated the progression of SNHL. Because his hearing impairments were associated with diminished PRS1 activity, which resulted in the depletion of nucleotides synthesis, we can presume that early SAM supplement prior to the progression of hearing impairments might attenuate SNHL. Therefore, early diagnosis of *PRPS1*-related hearing impairment is important to prevent and alleviate further progression of SNHL. Moreover, because DFNX1 is the mildest form of *PRPS1*-deficiency disorders and all of the *PRPS1*-deficiency disorders can accompany variable range of SNHL, hearing loss could function as an index symptom for *PRPS1*-deficiency syndromes, including Arts syndrome, CMTX5, and PRS1 superactivity. Identification of *PRPS1* mutations in these syndromic SNHL subjects might be helpful for the early diagnosis and management of accompanying syndromic features.

Our proband (SH 178–396) underwent cochlear implantation and showed good hearing outcomes. It has been established that hearing loss in DFNX1 subjects is originated from the impairments in auditory hair cells [11]. To date, there have not been any reported cases of auditory neuropathy. Therefore, hearing rehabilitation with cochlear implantation may be favorable for DFNX1 subjects with intact auditory neural pathway.. However, the possible effects of *PRPS1* on spiral ganglion or auditory neural systems should not be excluded because *PRPS1* is also expressed in spiral ganglion cells [11]. Therefore, the pathogenic roles of *PRPS1* in the inner ear needs further exploration in future studies with various types of *PRPS1* mutations.

Because *PRPS1* is a rare cause of genetic SNHL, studies pertaining to *PRPS1* could be expensive and time-consuming. However, phenotypic-driven molecular genetic approaches efficiently ruled out the common deafness genes, and subsequent TES could identify a DFNX1 family with novel missense mutation of *PRPS1* p.A82P. In this current study, the progression of SNHL was shown by a proband. This suggests the possibility for medical interventions in preventing and alleviating genetic SNHL. The differences of PRS1 activity among normal controls, normal hearing female carriers, and affected male subjects may suggest a correlation between PRS1 activity and audiologic phenotypes. Moreover, the small differences of PRS1 activity between the normal carrier mother and the affected siblings provide a good indication and target level for possible medical interventions to normalize PRS1 deficiency. Further studies on the expression and regulation of *PRPS1* will allow genetic counseling and customized medical or surgical treatments possible for affected subjects.

Acknowledgments

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C1867 to B.Y. Choi and HI12C0014) and National Institutes of Health grants (R01DC005575, R01DC012115 and R01DC012546 to XZL).

References

1. Kim NK, Kim AR, Park KT, Y S, et al. Whole-exome sequencing reveals diverse modes of inheritance in sporadic mild to moderate sensorineural hearing loss in a pediatric population. *Genet Med*. 2015; 17:901–911. [PubMed: 25719458]
2. Francey LJ, Conlin LK, Kadesch HE, et al. Genome-wide SNP genotyping identifies the Stereocilin (STRC) gene as a major contributor to pediatric bilateral sensorineural hearing impairment. *Am J Med Genet A*. 2012; 158A:298–308. [PubMed: 22147502]
3. Schraders M, Ruiz-Palmero L, Kalay E, et al. Mutations of the gene encoding otogelin are a cause of autosomal-recessive nonsyndromic moderate hearing impairment. *Am J Hum Genet*. 2012; 91:883–889. [PubMed: 23122587]
4. Yariz KO, Duman D, Seco CZ, et al. Mutations in OTOGL, encoding the inner ear protein otogelin-like, cause moderate sensorineural hearing loss. *Am J Hum Genet*. 2012; 91:872–882. [PubMed: 23122586]
5. Kim SY, Park G, Han KH, et al. Prevalence of p.V37I variant of GJB2 in mild or moderate hearing loss in a pediatric population and the interpretation of its pathogenicity. *PLoS One*. 2013; 8:e61592. [PubMed: 23637863]
6. Kim SY, Kim AR, Kim NK, et al. Unraveling of Enigmatic Hearing-Impaired GJB2 Single Heterozygotes by Massive Parallel Sequencing: DFNB1 or Not? *Medicine (Baltimore)*. 2016; 95:e3029. [PubMed: 27057829]
7. Park JH, Kim NK, Kim AR, et al. Exploration of molecular genetic etiology for Korean cochlear implantees with severe to profound hearing loss and its implication. *Orphanet J Rare Dis*. 2014; 9:167. [PubMed: 25373420]
8. Kim BJ, Kim AR, Park G, et al. Targeted Exome Sequencing of Deafness Genes After Failure of Auditory Phenotype-Driven Candidate Gene Screening. *Otol Neurotol*. 2015; 36:1096–1102. [PubMed: 25830873]
9. Francois M, Boukhris M, Noel-Petroff N. Schooling of hearing-impaired children and benefit of early diagnosis. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2015; 132:251–255. [PubMed: 26384781]
10. de Brouwer AP, van Bokhoven H, Nabuurs SB, et al. PRPS1 mutations: four distinct syndromes and potential treatment. *Am J Hum Genet*. 2010; 86:506–518. [PubMed: 20380929]
11. Liu X, Han D, Li J, et al. Loss-of-function mutations in the PRPS1 gene cause a type of nonsyndromic X-linked sensorineural deafness, DFN2. *Am J Hum Genet*. 2010; 86:65–71. [PubMed: 20021999]
12. Liu XZ, Xie D, Yuan HJ, et al. Hearing loss and PRPS1 mutations: Wide spectrum of phenotypes and potential therapy. *Int J Audiol*. 2013; 52:23–28. [PubMed: 23190330]
13. Arts WF, Loonen MC, Sengers RC, et al. X-linked ataxia, weakness, deafness, and loss of vision in early childhood with a fatal course. *Ann Neurol*. 1993; 33:535–539. [PubMed: 8498830]
14. Mittal R, Patel K, Mittal J, et al. Association of PRPS1 Mutations with Disease Phenotypes. *Dis Markers*. 2015; 2015:127013. [PubMed: 26089585]
15. Al-Maawali A, Dupuis L, Blaser S, et al. Prenatal growth restriction, retinal dystrophy, diabetes insipidus and white matter disease: expanding the spectrum of PRPS1-related disorders. *Eur J Hum Genet*. 2015; 23:310–316. [PubMed: 24961627]
16. Kim HJ, Sohn KM, Shy ME, et al. Mutations in PRPS1, which encodes the phosphoribosyl pyrophosphate synthetase enzyme critical for nucleotide biosynthesis, cause hereditary peripheral neuropathy with hearing loss and optic neuropathy (cmtx5). *Am J Hum Genet*. 2007; 81:552–558. [PubMed: 17701900]
17. de Brouwer, APM., Duley, JA., Christodoulou, J. Phosphoribosylpyrophosphate Synthetase Superactivity. In: Pagon, RA, Adam, MP, Ardinger, HH, Wallace, SE, Amemiya, A, Bean, LJH, Bird, TD, Fong, CT, Mefford, HC, Smith, RJH., Stephens, K., editors. *GeneReviews(R)*. Seattle (WA): 1993.
18. Sperling O, Eilam G, Sara Persky B, et al. Accelerated erythrocyte 5-phosphoribosyl-1-pyrophosphate synthesis. A familial abnormality associated with excessive uric acid production and gout. *Biochem Med*. 1972; 6:310–316. [PubMed: 4340256]

19. Han SH, Park HJ, Kang EJ, et al. Carrier frequency of GJB2 (connexin-26) mutations causing inherited deafness in the Korean population. *J Hum Genet.* 2008; 53:1022–1028. [PubMed: 19043807]
20. Kim SY, Kim AR, Kim NK, et al. Strong founder effect of p.P240L in CDH23 in Koreans and its significant contribution to severe-to-profound nonsyndromic hearing loss in a Korean pediatric population. *J Transl Med.* 2015; 13:263. [PubMed: 26264712]
21. Choi BY, Park G, Gim J, et al. Diagnostic application of targeted resequencing for familial nonsyndromic hearing loss. *PLoS One.* 2013; 8:e68692. [PubMed: 23990876]
22. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods.* 2010; 7:248–249. [PubMed: 20354512]
23. Chen P, Liu Z, Wang X, et al. Crystal and EM structures of human phosphoribosyl pyrophosphate synthase I (PRS1) provide novel insights into the disease-associated mutations. *PLoS One.* 2015; 10:e0120304. [PubMed: 25781187]
24. Li S, Lu Y, Peng B, et al. Crystal structure of human phosphoribosylpyrophosphate synthetase 1 reveals a novel allosteric site. *Biochem J.* 2007; 401:39–47. [PubMed: 16939420]
25. Chen P, Li J, Ma J, et al. A small disturbance, but a serious disease: the possible mechanism of D52H-mutant of human PRS1 that causes gout. *IUBMB Life.* 2013; 65:518–525. [PubMed: 23509005]
26. Becker MA, Smith PR, Taylor W, et al. The genetic and functional basis of purine nucleotide feedback-resistant phosphoribosylpyrophosphate synthetase superactivity. *J Clin Invest.* 1995; 96:2133–2141. [PubMed: 7593598]
27. Almoguera B, He S, Corton M, et al. Expanding the phenotype of PRPS1 syndromes in females: neuropathy, hearing loss and retinopathy. *Orphanet J Rare Dis.* 2014; 9:190. [PubMed: 25491489]
28. Synofzik M, Muller vom Hagen J, Haack TB, et al. X-linked Charcot-Marie-Tooth disease, Arts syndrome, and prelingual non-syndromic deafness form a disease continuum: evidence from a family with a novel PRPS1 mutation. *Orphanet J Rare Dis.* 2014; 9:24. [PubMed: 24528855]
29. Gandia M, Fernandez-Toral J, Solanellas J, et al. Mutations in PRPS1 causing syndromic or nonsyndromic hearing impairment: intrafamilial phenotypic variation complicates genetic counseling. *Pediatr Res.* 2015; 78:97–102. [PubMed: 25785835]
30. Kawahara Y, Zinshteyn B, Sethupathy P, et al. Redirection of silencing targets by adenosine-to-inosine editing of miRNAs. *Science.* 2007; 315:1137–1140. [PubMed: 17322061]
31. de Brouwer, APM., Duley, JA., Christodoulou, J. Arts Syndrome. In: Pagon, RA. Adam, MP. Ardinger, HH. Wallace, SE. Amemiya, A. Bean, LJH. Bird, TD. Fong, CT. Mefford, HC. Smith, RJH., Stephens, K., editors. *GeneReviews(R)*. Seattle (WA): 1993.
32. Robusto M, Fang M, Asselta R, et al. The expanding spectrum of PRPS1-associated phenotypes: three novel mutations segregating with X-linked hearing loss and mild peripheral neuropathy. *Eur J Hum Genet.* 2015; 23:766–773. [PubMed: 25182139]
33. Maruyama K, Ogaya S, Kurahashi N, et al. Arts syndrome with a novel missense mutation in the PRPS1 gene: A case report. *Brain Dev.* 2016 [Epub ahead of print].

Figure 1. (a) Segregation study and pure tone audiograms of SH178, (b) *PRPS1* activities in the erythrocytes of affected subjects, carrier, and normal controls