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PRPS1 Gene Mutation Causes Complex X-Linked Adult-Onset Cerebellar Ataxia in Women

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Inherited retinal dystrophies (IRD) comprise a heterogeneous group of disorders that affect visual function. IRD occur in isolated forms or in association with systemic abnormalities.[1] Over 300 disease-causing genes have been identified in IRD.

We report an unusual form of syndromic IRD with a complex neurologic phenotype caused by a mutation in *PRPS1* gene. Pathogenic variants in *PRPS1* lead to Arts syndrome, X-linked deafness 1, *PRPS*-related gout, or Charcot-Marie-Tooth 5 (CMTX5) in boys,[2] but it has been recently shown that women may also be symptomatic and display hearing loss, ophthalmologic abnormalities, and neurologic manifestations.[3]

Case Report

A 30-year-old woman, born from nonconsanguineous parents, presented with a 5-year history of progressive ataxia. She also had congenital strabismus, infantile-onset hearing loss, and a retinal dystrophy with progressive visual loss for the past 10 years. The visual acuity was 20/200 on the right eye and 20/40 on the left eye. Fundus examination revealed pale optic discs, attenuated vessels, and atrophic areas containing whitish fine dots, reticular pigmentation, and bone spicules bilaterally. Examination showed cerebellar ataxia, dysarthria, and gaze-evoked nystagmus. Audiometry confirmed bilateral sensorineural hearing loss. Brain MRI showed atrophy in the pons, middle cerebellar peduncles, vermis, and cerebellar hemispheres (figure). The genetic test for Friedreich ataxia was negative. Alpha-fetoprotein, albumin, vitamin E, creatine kinase, and lactate were normal. Whole-exome sequencing disclosed a heterozygous missense variant c.359G>T(p.Gly120Val) in one of her *PRPS1* alleles.

Discussion

PRPS1 is located in X chromosome and codes the enzyme phosphoribosyl pyrophosphate (PRPP) synthetase 1. This enzyme is involved in the synthesis of PRPP from ATP and ribose-5-phosphate, which is essential in the production of purines (adenine and guanine) and pyrimidines (cytosine, thymine, and uracil) nucleotides, the building blocks of life. Pathogenic variants in *PRPS1* cause 4 distinct conditions in males: CMTX5, X-linked deafness 1 (*DFNX1*), Arts syndrome, and an inherited form of gout (PRPS-related gout). Sensorineural hearing loss is the only common manifestation of these disorders and the isolated finding of *DFNX1*. Patients with CMTX5 and Arts syndrome additionally have peripheral neuropathy, ataxia, and optic atrophy.[2,4] Severe cognitive decline, recurrent infections, and early death complicate the clinical course in Arts syndrome, the most severe phenotype.[5] Individuals with PRPS-related

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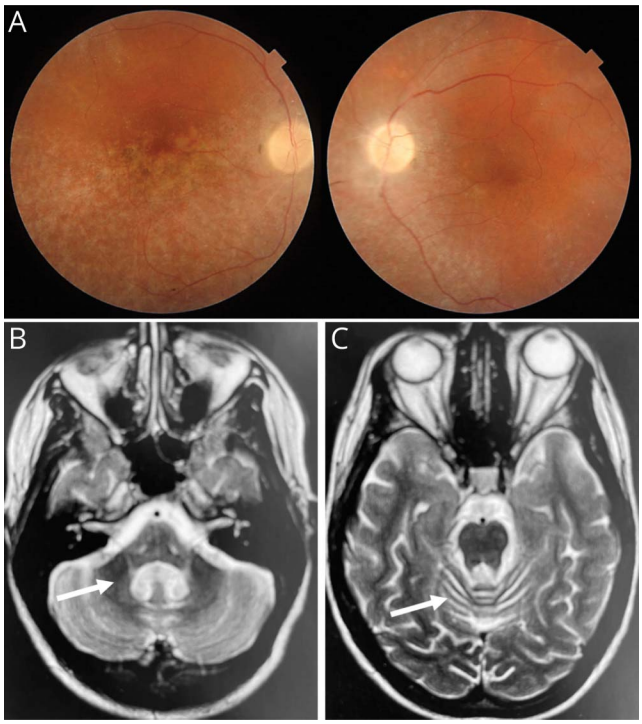
Figure Ophthalmologic and Radiologic Findings



Color fundus photographs of both eyes depicting pale optic discs, attenuated retinal vessels, and atrophic areas containing whitish fine dots with reticular pigmentation (A). The pattern of retinal dystrophy is remarkably asymmetric and more severe on the right eye, in which the macula is affected. Axial T2-weighted sequence of brain MRI shows atrophy in the cerebellar peduncles and pons (B) and in cerebellar hemispheres (C) (white arrows).

gout, the most common form, have hyperuricemia, but some exhibit mental retardation, ataxia, and hypotonia.[2]

The variant found in our patient, c.359G>T(p.Gly120Val), is novel and was confirmed by Sanger sequencing. Also, it was absent in the parents characterizing a de novo mutation. Moreover, this variant is absent in 178,000 X chromosomes. It affects a highly conserved residue, and in silico prediction indicates a deleterious effect. The combination of the molecular mechanism, location, and the correlation with clinical features suggests that this variant is most likely pathogenic.

Female patients with *PRPS1* mutations are usually asymptomatic and rarely present with neurologic symptoms.[6] The female disease spectrum ranges from isolated sensorineural hearing loss to the combination of retinal dystrophy, optic atrophy, peripheral neuropathy, ataxia with cerebellar atrophy in MRI, and developmental delay.[3,4,7] Our patient presented early-onset hearing loss, retinal dystrophy, and cerebellar ataxia. Her phenotype is consistent with the one described in 2 women from a Spanish family.[3] Fiorentino et al.[7] reported similar phenotypic features in a Japanese mother and her daughter, who had retinal dystrophy, optic atrophy, sensorineural hearing loss, and gait ataxia. A pathophysiologic explanation for a late-onset phenotype in a woman related to *PRPS1* is the X inactivation. De novo variants and skewed inactivation of X chromosome have been described.

The work by Fiorentino et al.[7] demonstrated 7 of 9 patients with *PRPS1*-related retinal dystrophy had asymmetric retinal abnormalities. A high proportion of women with X-linked IRD have fundus changes, which are frequently asymmetric. This may be a consequence of skewed inactivation of X chromosomes in females, causing a higher proportion of retinal cells to express the pathogenic variant of *PRPS1* gene, rather than the wild-type allele. The degree of skewed X-chromosome inactivation and PRPP synthetase residual activity are the likely determinants of phenotype severity in women with pathogenic variants of *PRPS1*.[4]

It is noteworthy that *PRPS1*-related disorders might be treatable. Dietary S-adenosylmethionine supplementation (SAM) exploits an alternative route of ATP biosynthesis, which may alleviate the shortage of adenosine-derived nucleotides. Of interest, in 2 individuals with Arts syndrome, SAM supplementation resulted in clinical improvement.[2]

In conclusion, this report illustrates the remarkable phenotypic variability of *PRPS1* mutations, which may cause a rare form of X-linked adult-onset cerebellar ataxia. Asymmetric retinal dystrophy might represent a clue for the diagnosis of *PRPS1* spectrum disease in women with hearing loss and cerebellar signs.

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Disclosure

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Appendix *(continued)*

Name	Location	Contribution
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References

1. Ellingford JM, Barton S, Bhaskar S, et al. Molecular findings from 537 individuals with inherited retinal disease. J Med Genet 2016;53:761–767.
2. de Brouwer APM, van Bokhoven H, Nabuurs SB, Arts WF, Christodoulou J, Duley J. PRPS1 mutations: four distinct syndromes and potential treatment. Am J Hum Genet 2010;86:506–518. doi: 10.1016/j.ajhg.2010.02.024.
3. 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.
4. Synofzik M, Müller 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;9:1–8.
5. De Brouwer APM, Williams KL, Duley JA, et al. Arts syndrome is caused by loss-of-function mutations in PRPS1. Am J Hum Genet 2007;81:507–518.
6. 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.
7. Fiorentino A, Fujinami K, Arno G, et al. Missense variants in the X-linked gene PRPS1 cause retinal degeneration in females. Hum Mutat 2018;39:80–91.

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