CASE REPORT

A NOVEL DE NOVO LIKELY PATHOGENIC VARIANT OF *WFS-1* GENE IN A PAKISTANI CHILD WITH NON-CLASSIC WFS-1 SPECTRUM DISORDER

Misbah Iqbal Hanif[1], Hamza Ahmed[2], Mohsina Noor Ibrahim[3], Syed Jamal Raza[1], Syed Ajaz Ahmed[4]

[1]Sindh Institute of Child Health and Neonatology, Karachi-Pakistan
[2]Dow International Medical College, Karachi-Pakistan
[3]National Institute of Child Health, Karachi-Pakistan
[4]Kaiser Permanente, Riverside, CA-USA

Wolfram syndrome is a progressive neurodegenerative disorder caused by an alteration in the *WFS-1* gene, located on chromosome 4p16.1 and is characterized by the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness). *WFS-1* gene encodes for a transmembrane protein termed Wolframin found in the membrane of the endoplasmic reticulum. Although Wolfram Syndrome is generally considered an autosomal recessive disorder, a milder non-classic autosomal dominant form has been reported in association with a single pathogenic or likely pathogenic variant in *WFS-1* gene. Objective was to date more than 200 variants have been identified in the *WFS-1* gene. This case report aims to highlight and explain a novel de-novo likely pathogenic variant of the *WFS-1* gene in a Pakistani child, which is highly plausible to induce non-classic WFS-1 spectrum disorder (MedGen UID: 481988). **Case Discussion:** Our patient, a seven-year-old boy, initially sought medical attention at our endocrine clinic for diabetic control. Besides diabetes, other notable features included short stature, sensorineural deafness and a history of bilateral cataracts. Family history was significant for parental consanguinity. A clinical diagnosis of Wolfram Syndrome was suspected and a multi gene panel test which included the *WFS-1* gene was ordered. Initial report noted a variant of uncertain significance in the *WFS-1* gene at c.2586G>T (p.Lys862Asn), which was later reclassified as a likely pathogenic variant by the laboratory based on the patient's clinical presentation. **Conclusion:** Access to genetic testing is not readily available in Pakistan and our population is under studied and these complex diagnoses are often missed. In this study, we present a novel de novo likely pathogenic variant in the *WFS-1* gene that causes non-classic *WFS-1* spectrum disorder in a child from our population.

Keywords: *WFS-1*; Non-classic WFS-1 spectrum disorder; Pakistan

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INTRODUCTION

WFS-1 spectrum disorder (WFS-1 SD: OMIM 222300) is a rare neurodegenerative genetic disorder with a global prevalence of 1 in 500,000. It is characterized by the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) and is associated with juvenile-onset diabetes mellitus, optic atrophy, and sensorineural deafness.[1] Additional clinical features may include renal abnormalities, ataxia, dementia, mental retardation, and various psychiatric illnesses. The disorder is caused by variations in the *WFS-1* gene located on chromosome 4p16.1, which encodes the ER membrane-embedded protein wolframin.[2] Wolframin plays a crucial role in ER stress reduction, maintaining Ca2+ homeostasis, biosynthesis of secretory proteins (such as insulin), oxidation-reduction reactions, and cell fate decisions.[3–5] While classic WFS-1 SD follows a recessive mode of inheritance, autosomal dominant non-classic WFS-1 S has been increasingly reported. This type is characterized by progressive low- and middle-frequency sensorineural hearing impairment, type 1 diabetes mellitus, and optic atrophy.[2]

In a country like Pakistan where the rate of consanguineous marriages are very high, autosomal recessive disorders are more likely to be prevalent. However, access to genetic testing is very limited because of the high cost associated with sending testing abroad and therefore our population is under studied and often these complex diagnoses are missed.[6,7] In this study, we present a novel de novo likely pathogenic variant in the *WFS-1* gene that causes non-classic WFS-1 spectrum disorder in a child from our population.

CASE REPORT

We present the case of a 7-year-old boy who was referred to our endocrine outpatient department for the

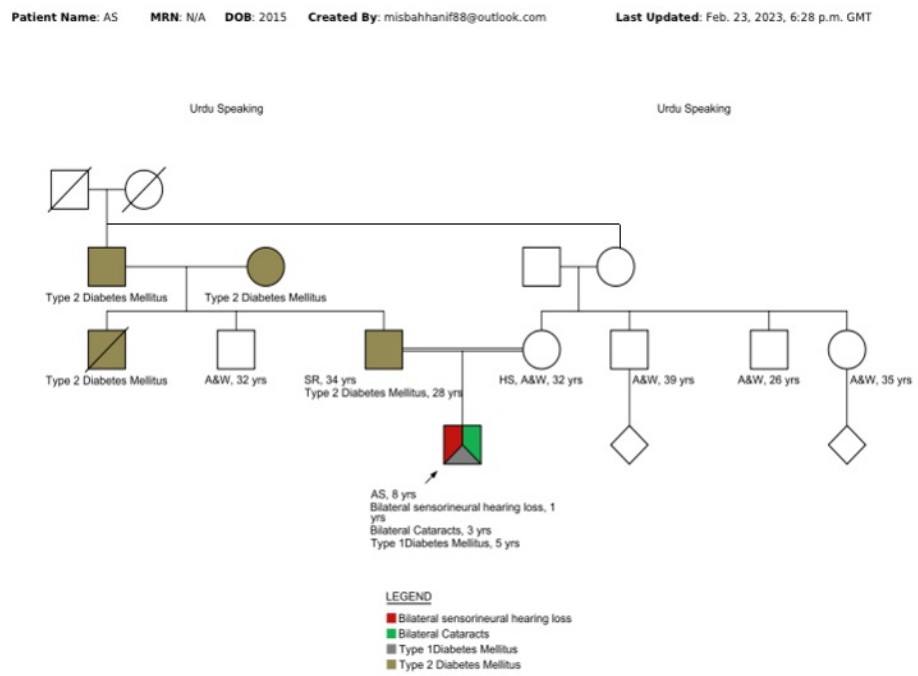
management of uncontrolled type 1 diabetes mellitus. The proband is the first child of consanguineous parents, with a family history of type 2 diabetes mellitus in his father and grandfather. The child was born through a C-section without significant prenatal or birth complications. Early milestones were age appropriate. At one year of age, a Brain Evoked Response Auditory (BERA) test revealed sensorineural hearing loss, leading to the implantation of a hearing aid device. By the age of three, bilateral cataracts were noted and he underwent bilateral cataract-removal surgery. At the age of five, he had poor growth, weight loss, polyuria, and polydipsia and was diagnosed with diabetes. He presented to our clinic at 7 years of age with uncontrolled diabetes (HbA1C level of 14%). He also had experienced recurrent episodes of diarrhoea and vomiting, which were attributed to lactose intolerance. C-peptide, anti-insulin antibodies, creatinine, electrolytes, and thyroid function tests, yielded normal results. In addition to his medical issues, the child's parents were worried about his height, as he exhibited short stature with a -4.55 SDS score. Based on parental consanguinity and his clinical features Wolfram syndrome was suspected. To confirm the diagnosis, monogenic diabetes multi gene panel (28 genes that included the *WFS-1* gene) was sent to Invitae laboratory. Initial report noted a heterozygous variant of uncertain significance c.2586G>T (p.Lys862Asn) in the *WFS-1* gene. In order to reclassify this variant, parental studies were performed which yielded normal results. Based on his clinical presentation of sensorineural deafness, bilateral cataracts and diabetes mellitus and de novo occurrence of this variant the c.2586G>T (p.Lys862Asn) variant was reclassified as a likely pathogenic.(8) Subsequent fundus examination revealed progressive optic atrophy which is also a feature of WFS-1 SD.

DISCUSSION

WFS-1 spectrum disorder (WFS-1 SD) is a rare familial disorder characterized by a variable and complex genotype. It is a progressive disease that typically begins in childhood. Early diagnosis and effective management are of utmost importance, as no treatment currently exists to halt or reverse the progression of the disease. Unfortunately, WFS-1 SD is often misdiagnosed as insulin-dependent non-autoimmune diabetes mellitus, further emphasizing the need for accurate recognition.[9] Symptoms and severity can vary even among family members with the same genetic variation.[10] This finding is supported by preliminary evidence of autosomal dominant congenital cataracts resulting from variation in the *WFS-1* gene (MedGen UID: 811742). Abu-El-Haija *et al*. in 2021 also observed the cataract in their 9-year-old patient. It was later discovered that she had novel likely pathogenic variant in the *WFS-1* gene.[11] In our case report, the boy was found to have a likely pathogenic variant in Exon 8 of the *WFS-1* gene, specifically at c.2586G>T. This sequence alteration leads to the substitution of lysine with asparagine at codon 862 of the wolframin protein (p.Lys862Asn). Notably, this variant is absent from population databases such as ExAC. Advanced modelling of the protein sequence and biophysical properties performed at the Invitae laboratory confirmed that this variant is consistent with a predisposition to, or diagnosis of, autosomal dominant WFS-1-related conditions. ClinVar also includes an entry for this variant (https://www.ncbi.nlm.nih.gov/clinvar/variation/1523010) submitted by Invitae Laboratory. In a study by Prochazkova *et al*. in 2016, a similar case of non-classic WFS-1 SD was reported in a boy presenting with type 1 diabetes mellitus, deafness, and cataracts. This individual was found to have an autosomal mono-allelic pathogenic variation in the *WFS-1* gene at c.2425G>A, p.(Glu809Lys).[12] Non-classic WFS-1 SD was initially described in 2006, presenting with similar phenotypes and a missense mutation at exon 8 (c.2590G>A, p.(Glu864Lys)).[13] Another study by De Franco *et al.* in 2017 reported a child presenting with congenital cataracts, insulin-dependent diabetes mellitus, and sensorineural deafness. Genetic analysis revealed a novel mutation in the *WFS-1* gene at c.2425G>A, p.Glu809Lys in exon 8.[14] The *WFS-1* gene consists of eight exons and encodes the 890-amino-acid-long wolframin protein, which functions as an endoplasmic reticulum calcium channel. It is highly expressed in pancreatic beta cells and plays a vital role in the processing and release of cyclic AMP, which aids in reducing cell apoptosis. To date, more than 200 variations have been reported in the *WFS-1* gene, with many of them occurring in exon 8.[15] This exon encompasses the transmembrane and C-terminal domains of the wolframin protein, making its integrity crucial for protein functionality. Various researchers have reported patients with similar phenotypes resulting from alterations in the wolframin protein caused by mutations in the *WFS-1* gene.

CONCLUSION

In summary, the clinical evaluation of both classic and non-classic WFS-1 SD is challenging due to diverse phenotypes. Genetic testing should be considered in patients meeting early-onset diabetes mellitus and optic atrophy criteria. Management necessitates early diagnosis and a multidisciplinary healthcare team. Genetic assessment, alongside clinical examination, is vital for prompt and accurate diagnosis. Exploring the genetic landscape of the Pakistani population is crucial for understanding disease causation.



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Address for Correspondence:

Misbah Iqbal Hanif, Sindh Institute of Child Health and Neonatology, Karachi-Pakistan
Cell: +92 332 308 3167
Email: misbahhanif88@outlook.com