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Rare variants in *WFS1* gene in patients with young-onset diabetes

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Motivation and Aim: Wolfram-like syndrome or WFLS (OMIM# 614296) is a rare endocrine disorder characterized by an autosomal dominant inheritance, and it is characterized by diabetes mellitus, optic atrophy, and progressive hearing impairment. Clinically, the disease is similar to autosomal recessive Wolfram syndrome, but with a milder phenotype. Early manifestation of WFLS begins with non-autoimmune diabetes, followed later by other complications [1, 2]. The *WFS1* gene (OMIM#606201) is located on chromosome 4p16 and includes eight exons encoding the 890 amino acid protein wolframin. This protein is primarily localized in the endoplasmic reticulum [3]. It has been shown that wolframin is involved in membrane transport, regulation of calcium homeostasis in the endoplasmic reticulum. Furthermore, it seems that the protein supports the normal function of pancreatic beta cells by promoting insulin synthesis and reducing endoplasmic reticulum stress. [4]. In this study, we performed a screening for rare variants of the *WFS1* gene in patients with young-onset diabetes.

Methods and Algorithms: An analysis of genes associated with monogenic forms of diabetes was conducted in 290 individuals from Western Siberia with non-autoimmune diabetes using next-generation sequencing.

Results: We identified 2 unrelated patients with young-onset diabetes who were heterozygous for a variants of uncertain significance in the *WFS1* gene. One of this, NM_006005.3(*WFS1*):c.1124G>A (p.Arg375His) variant has been previously reported [5] in a Russian child with non-type 1 diabetes mellitus and we identified it in woman with non-autoimmune diabetes, hearing impairment, and non progressive optic atrophy. The identified variant segregated with this pathological phenotype in the proband and her father.

A novel NM_006005.3(*WFS1*): c.1336A>C (p.Ser446Arg) variant was found in a young man with autoantibody-negative diabetes and hearing loss. This variant was predicted as deleterious by *in silico* analysis (REVEL, VARITY, AlphaMissense) and was absent in gnomAD (version 3.1.2) database. According to the proband, his ancestors had diabetes mellitus for two generations, but they were not available for analysis.

Conclusion: Molecular diagnostics is a necessary step in the clinical diagnosis of monogenic forms of diabetes, especially for family screening of individuals with borderline or moderate carbohydrate metabolism disorders.

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