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Identification of the Peroxisomal Biogenesis Factor 1 Gene Point Mutation in an Iranian Family with Zellweger Syndrome (ZS)

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ABSTRACT

Background & Objective: Peroxisome biogenesis disorders (PBDs) are a group of diseases with peroxisomal dysfunction. Wide range of symptoms are associated with the disease which are due to mutations in the *PEX* genes. The *PEX1* mutation occurs in Zellweger syndrome (ZS), a severe autosomal recessive condition with hypotonia, intellectual disability, and hepatic enlargement. The present study determined the molecular aspects of ZS in a family in South Khorasan Province, Iran.

Materials & Methods: Whole-exome sequencing (WES) was performed, clinical history was taken, and the family pedigree was drawn. Subsequently, Sanger sequencing was performed for unique primers. Afterwards, in terms of ZS phenotype, in silico studies were done to examine the changes that occurred in the protein structure.

Results: The *PEX1* (NC_000007.14) mutation was detected at location Chr7q21.2. This chromosomal location was anticipated as the disorder-causing variant. GGT (Glycine) changes to GAT (Aspartate) in codon 843 were confirmed by Sanger sequencing. Examination results of the mentioned family revealed a missense mutation in the *PEX1*.

Conclusion: In conclusion, our study indicated a mutation in the *PEX1* in the affected family. This mutation is a missense variant at codon 843 in ZS patients. It has an autosomal recessive inheritance pattern. This mutation may be widespread among Iranian population with ZS and can be used for a more desirable personalized medicine.

Keywords: Peroxisomal biogenesis factor, Point mutation, Whole exome sequencing, Zellweger syndrome

Introduction

Peroxisome is a ubiquitous cell organelle in human, which is essential for oxidation of branched-chain and very-long-chain fatty acids (VLCFAs), as well as the metabolism of plasminogens, amino acids, and ether lipids (1, 2). Peroxisome biogenesis disorders (PBDs) are a spectrum of diseases with peroxisomal defect and diverse peroxisomal metabolic dysfunctions due to mutations in the *PEX* genes (2,3). Reports demonstrated that the majority of Zellweger syndrome (ZS) cases have different mutations in the *PEX1*, *PEX6*, *PEX10*, *PEX12* and *PEX26* genes (4). ZS, also recognized as cerebrohepatorenal disorder, is a rare genetic condition which is defined by the absence or reduction of functional peroxisomes in the cells which are responsible for VLCFA beta-oxidation (5). Zellweger spectrum disorder (ZSD) and rhizomelic chondrodysplasia punctata type I (RCP) are classified into two categories. In addition, ZSD is categorized into three classes: neonatal adreno leukodystrophy (NALD) (the most common phenotype), infantile Refsum disease (IRD) and ZS (6). Epidemiological evidence shows that the ZS prevalence in the United States is estimated to be 1:50,000 births. Patients with serious disorders die in their first year of existence (7). However, a number of patients with milder phenotypes may survive until the second decade (8). A wide range

of symptoms such as enlarged liver, renal cysts, seizures, retinal dystrophy, and hearing loss may be manifested (9).

Essential proteins for peroxisome biogenesis and conservation are called peroxins (PEX proteins). The most recognized peroxins promote protein entry from cytosol synthesis location to the peroxisome matrix. PEX1 ATPase promotes regeneration of protein receptor PEX5 peroxisome complex, which is the most frequently involved peroxin in biogenesis diseases of mammalian peroxisome. Mutations in the *PEX1* are the frequent cause of PBDs in mammalian. In the lethal cases, the peroxisomes are not developed or the matrix proteins ingest ineffectively.

Therefore, a precise understanding of the molecular aspects of rare inherited disorders, such as ZS, requires genomic sequencing as a novel and effective strategy (10, 11). Presently, the whole-exome sequencing (WES) technology and the survey of protein-coding regions of genes in a genome, provide feasibilities for ZS investigation (12, 13). Herein, we aimed to present the molecular diagnosis of ZS in an Iranian family in the South Khorasan Province, using WES to detect the accurate etiology of idiopathic ZS.

Materials and Methods

Informed Consent and Ethics Guide

All participants from each family signed the informed consent, and the entire procedure was performed according to the tenets of the Helsinki Declaration. The ethics code was approved by the Institutional Research Ethic Committee of Birjand University of Medical Sciences (Ir.bums.REC. 1396.350).

Clinical Evaluations

The participated family included father, mother and one female proband who were supported by the Social Welfare Organization of South Khorasan Province, Iran. Total siblings consisted of one affected brother (twin) and four unaffected ones. Peripheral blood samples were obtained from all family members.

Whole-exome Sequencing Analysis

Proband Genomic DNA (gDNA) was extracted via standard salting out method (14-16). The quantity and quality of extracted DNA were determined by Nanodrop (Epoch, Biotek, USA), and 1.5% agarose gel. In this setting, WES was performed on the DNA sample of the affected twin and the parents by a HiSeq2000 instrument (Illumina, San Diego, CA) following the manufacturer's instructions. The mapped reads were aligned to the human genome sequence (UCSC GRCh37/hg19), and homozygous genotypes were filtered based on dbSNP as shown in the UCSC Genome Browser, HapMap project, and 1000 Genomes Project variant database.

The effects of protein sequence substituted on the molecular effects of variants were studied. To determine the accuracy of deleterious variant prediction, some in silico software tools, including SIFT, PANTHER, PolyPhen and PROVEAN were employed. According to the outcomes of the cited procedure, the variant effect on protein function was predicted based on the protein sequence and structure. Wild-type and mutant *PEX1* predictions of the three dimensional structure were performed by Iterative Threading Assembly Refinement (I-TASSER) server.

Also, in order to determine the conclusive connection between *PEX1* (wild and mutant) and *PEX6*, as a component of the PIG family, molecular docking was achieved. HEX server calculated the interaction energy of docking (http:/www.loria.fr/~ritchied/hex/).

DNA Sanger sequencing analysis was performed to confirm the variant effect on the disease. A pair of primers were designed for polymerase chain reaction (PCR) amplification and sequence analysis (Table 1).

Table 1. The primers sequence which were used to confirm PEX1 mutation

	Sequence	Len	Tm	GC%	Self Any	Self-End	Product Size
Forward Primer	GCGGGTTTGTGGCTAGAGATTTTACAGT	28	65.41	46.43	4.00	3.00	367
Reverse Primer	CTACTCTCTCGTGCAATTACCCCAGCTA	28	65.54	50.00	6.00	4.00	

Results

Clinical Outcomes

Two eight-year-old (twin) affected individuals were enrolled in the study. They belonged to the Persian race, from the South Khorasan Province, southeast of Iran. The probands with ZS were born to a fifth gestation (Figure 1). Nervous abnormalities, such as intellectual disability, speech difficulty, and seizure appeared. The patients had normal weight, height and head circumference at the time of birth (Figure 1). According to the pedigree analysis, family history, and transmission pattern, the autosomal recessive inheritance was suggested for the current family.

Whole-exome Sequencing Findings

The proband, an eight-year-old female, had a *PEX1* (NC 000007.14) missense mutation C.G2528A. It happens at the chromosome location of 7q21.2 which consists of 24 exons. This genomic mutation was

confirmed by Sanger sequencing analysis of the affected proband female and her twin brother (Figure 1). No additional variations that could be a pathogenic candidate have been detected. Other population databases such as ClinVar dataset, Exome Sequencing Project (GO-ESP), Human Gene Mutation Database (HGMD), and 1000 Genomes project have reported this variant. In the primary level of variant filtering, we studied the missense, nonsense and frameshift indels. Further impacts of deleterious variants were kept on the stable secondary structure and protein folding. Based on the pedigree analysis, the homozygous variants were indicative of the autosomal recessive pattern of inheritance. Variants with a minor allele frequency (MAF)>1% were removed based on dbSNP links and more variant databases. The *PEX1* gene, which is known to cause PBDs, was selected. A missense mutation was identified in exon 15 (22 out of 60 alleles) of the *PEX1* gene. The c.2528GRA is in the second functional AAA (D2) domain in patients with PBD. Exon 15 sequencing of the *PEX1* gene revealed homozygosity in the affected twin, and heterozygosity in the parents. DbSNP, 1000 Genomes Project, ExAC and Clinvar databases have identified the missense version. However, this mutation was absent in Iranian reports. The pathogenic related variants of *PEX1* gene are presented in Table 2.

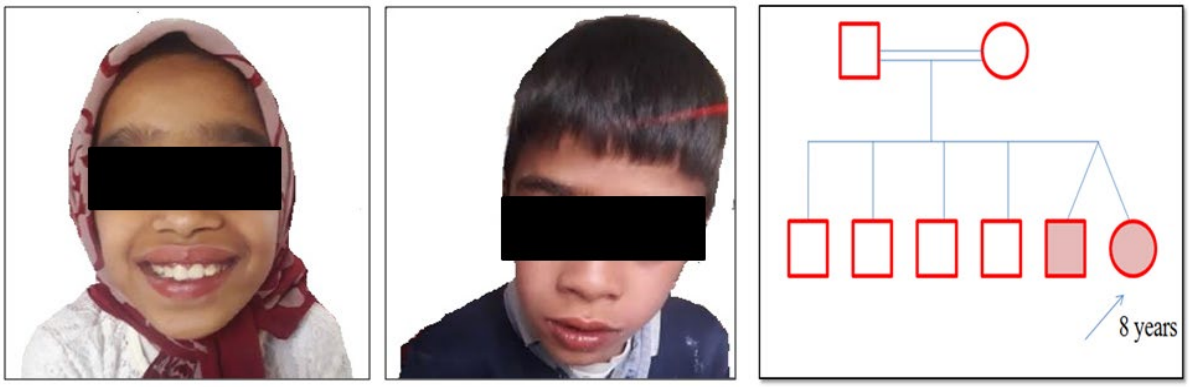

Figure 1. Identification of a missense PEX1 mutation. a) The proband indicated that specific characterize of Zellweger Syndrome in 8 years old including facial dysmorphology, speech difficulties and mental retardation; b) Consanguineous pedigree displayed affected members are II-4 and II-5 (twin). They are homozygous for the C.G2528A variant.

Table 2. The related Pathogenic variants of PEX*1* gene

Number	Variant ID	Variation (location)	Variation type	Condition(s)	Clinical significance (last reviewed)	Reference
1	22557	c.1906_2064del159 (p.Arg636_Leu688del)	Deletion	Zellweger syndrome	Pathogenic (Apr 14,1998)	(28)
2	217431	c.3750G>A (p.Trp1250Ter)	Single nucleotide	Deafness enamel hypoplasia nail defects	Pathogenic (Oct 1,2016)	(29)
3	488572	c.3579delA (p.Asp1194Ilefs)	Deletion	Zellweger syndrome	Pathogenic (Nov 16,2017)	(30)
4	371698	c.3574C>T (p.Gln1192Ter)	Single nucleotide	Zellweger syndrome, Deafness enamel hypoplasia nail defects, Peroxisome biogenesis disorder 1B	Pathogenic (Feb 2,2017)	(31)

Number	Variant ID	Variation (location)	Variation type	Condition(s)	Clinical significance (last reviewed)	Reference
5	167443	c.3505_3517delC AGTTGTTTTCAC (p.Gln1169Serfs)	Deletion	not provided	Pathogenic (Feb 11, 2014)	(32)
6	561079	c.3205C>T (p.Gln1069Ter)	single nucleotide variant	Zellweger syndrome	Pathogenic (Sep 1,2017)	(33)
7	224325	c.2966T>C (p.Ile989Thr)	single nucleotide variant	Zellweger syndrome, Deafness enamel hypoplasia nail defects	Pathogenic (Oct 1,2015)	(34)
8	188729	c.2926+1G>A	single nucleotide variant	Zellweger syndrome	Pathogenic (May 25, 2016)	(35)
9	371696	c.2922delA (p.Leu974Phefs)	Deletion	Zellweger syndrome, Peroxisome biogenesis disorder 1B	Pathogenic (Jun 16, 2016)	(36)
10	7516	c.2528G>A (p.Gly843Asp)	single nucleotide variant	Zellweger syndrome, Deafness enamel hypoplasia nail defects, Peroxisome biogenesis disorders, Leber congenital amaurosis	Pathogenic (Feb 6, 2015), Pathogenic (May31,2018)	(37, 38)

Discussion

We have detected a missense variation in *PEX1,* in an Iranian ZS patient. The proband had the common characteristics of ZS including facial dysmorphology, difficulty in speech and intellectual disability. Since the clinical appearance was not trustworthy, the affected individual was first distinguished based on the symptoms. The pedigree analysis demonstrated an autosomal recessive pattern (Figure 1). Subsequently, based on the WES findings of the proband, a missense variant (C.G2528A) was detected, with an autosomal recessive pattern in the second functional AAA domain (D2) (Figure 1).

PEX1 (MIM#602136) is a protein-coding gene located on chr7q21.2 location, which contains 24 exons. It produces a transcript of 4.4 kb. *PEX1* mutations are detected in almost 70% of ZS patients. Evidence suggests that *PEX1* can play a critical role as a matrix protein transporter in the peroxisomal membrane. The protein structure generally consists of four segments: N-terminal and C-terminal regions, and D1 and D2 domains. To date, 14 human *PEX* genes have been identified which encode peroxin proteins. They have function in different phases of peroxisome biogenesis, such as peroxisomal matrix protein importation, membrane formation, and peroxisome proliferation **(17, 18)**. Peroxisomal membrane proteins are active as signaling sites for the autophagy, which are caused by antiviral immunity and reactive oxygen species **(19)**. Glycine (Gly), a non-charged amino acid, is substituted with Aspartate (Asp) which is negatively-charged, and this could induce crucial functional and structural alterations. Phylogenetic protein sequence conservation analyses of *PEX1* reveals that Glycine 843 is a protected amino acid in the protein sequence of human *PEX1* (Figure 2). However, the exact protein function is not clearly known.

In a patient with Leber congenital amaurosis (LCA), the mutant *PEX1* (p.Gly843Asp) which has a transformation (Gly to Asp) in cDNA bp 2528 has been documented once before **(20)**. Reuber *et al.* reported that mutations in *PEX1* could be the most common cause of PBDs occurrenceThey indicated that *PEX1* deficient cells have different deficiencies in the peroxisomal targeting signal and protein matrix transfer. Figure 3 displays the projected functional partners of *PEX1*. Moreover, their results showed that the G843D allele is a common mutation in the PBDs **(21)**. The new mutation attenuates the protein function and is associated with mild peroxisomal condition of group 1 complementation (Figures 4 and 5).

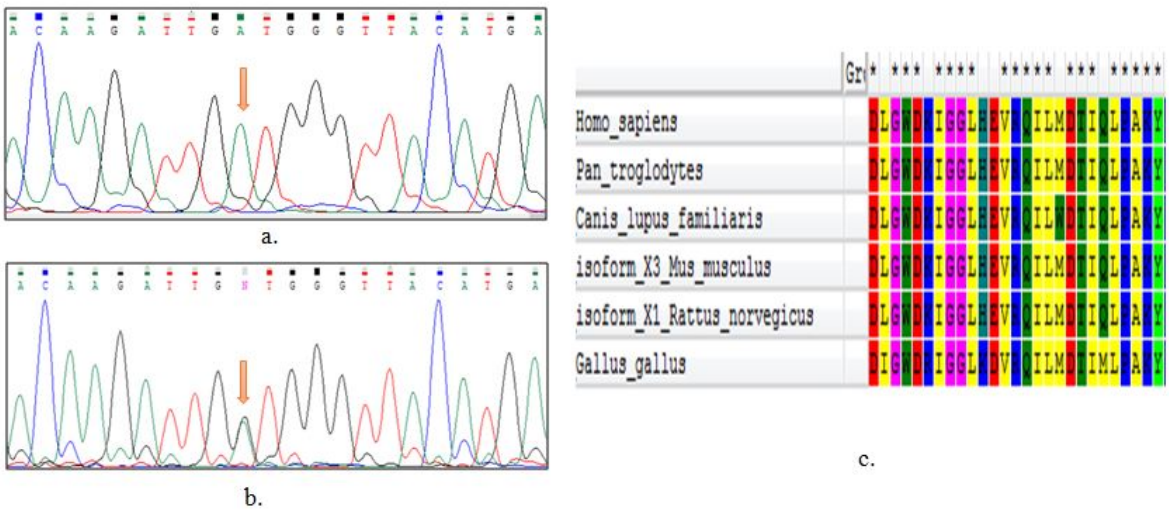

Figure 2. a) The Sanger sequencing analysis of homozygote affected. b) The Sanger sequencing analysis of heterozygote parent, an arrow shows the mutation; c) phylogenetic conservation studies of the *PEX1* protein sequence and Glycine is conserved amino acids in the human *PEX1* protein sequence

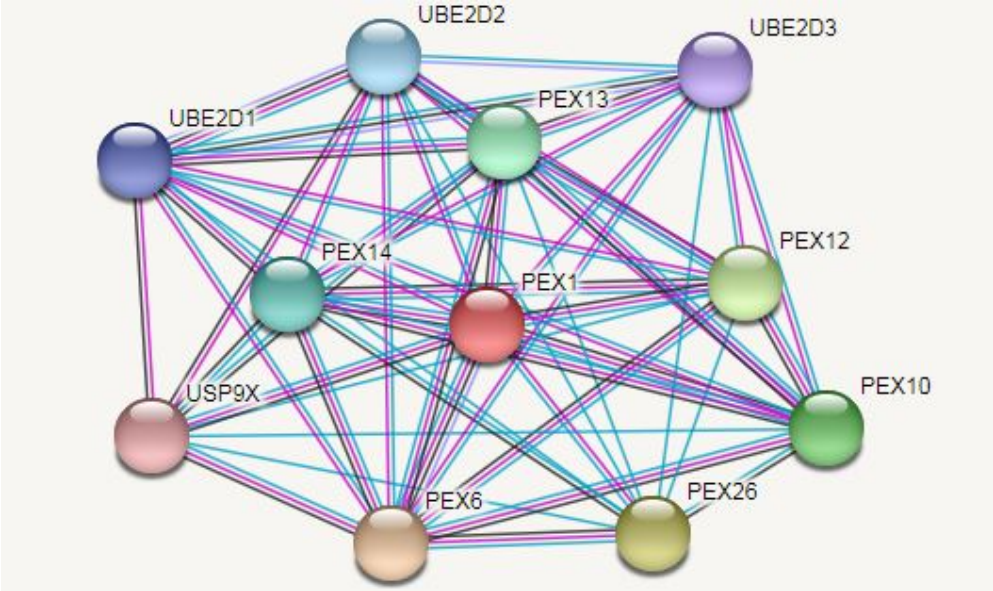

Figure 3. Predicted functional partners of PEX1

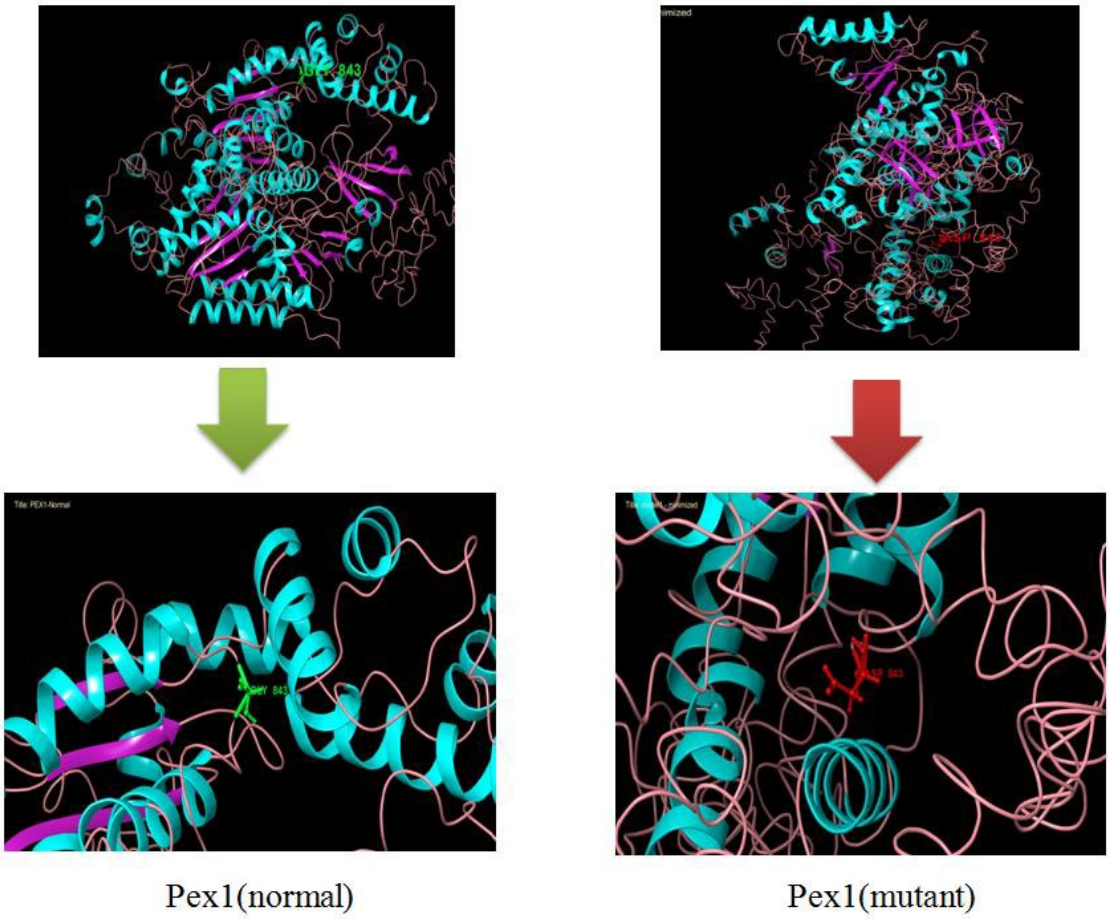

Figure 4. Prediction of PEX1 protein structure .To comprehend, the structural implications of mutations in PEX1, wild-type and mutant proteins were modeled using the online I-TASSER server.

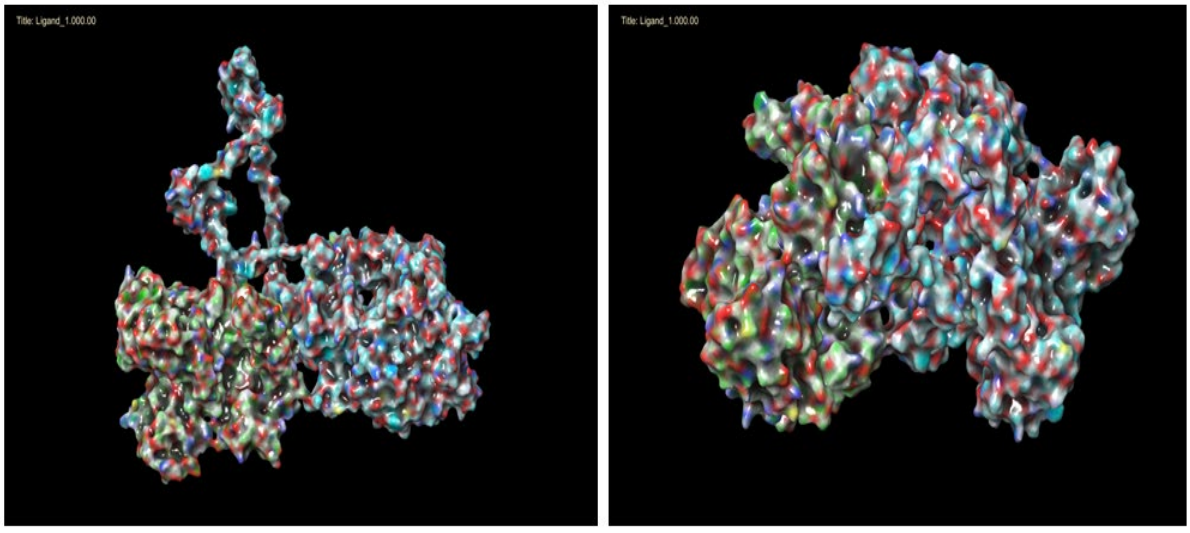

Figure 5. Docking proteins to find the effect of mutation on PEX1

Meng-Meng Ge *et al.* reported four novel mutations (c.2416+1 G>T and c.2489delT) (c.1483+1 G>A and c.1727dupG) in the *PEX1* gene using the WES technique (22). Ling Yu verified the homozygous mutations (c.818insCTTG) (p.Pro274Leufs*8) in the PEX6 gene by WES, which target gene panels of 'multiple congenital anomalies' and 'skeletal dysplasia' in ZS patients. Evidence showed that the two novel

mutations (p.Cys358* and p.Leu83Pro), have been known as pathogenic according to Genomics guideline. Phenotype-genotype associations were reported in the PBD-ZSD continuum patients **(23)**. Barillari and coworkers recognized two specific variants in PEX1 by sequencing. One of them was the missense variant p.(Val92Leu);c.274 G>C which has been mentioned in the PBD cases before. The second one was p.(Ser714 Gln715dup);c.2140 2145dupa, which is a non-frameshift variant. It is not found in normal samples **(24)**.

The researchers found that, in two Chinese newborns, all four mutations have critical control over the protein function. In addition, evidence indicates that the main causes of multiple organ dysfunction and neural disorder are β-oxidation deficiency, VLCFA accumulation, and docosahexaenoic acid (DHA) reduction **(22)**. Bousfiha *et al.* detected a new homozygous *PEX1* mutation (p. Leu1026Pro) in two deaf Moroccan siblings. Their reported symptoms included vision impairment, deep deafness and delay in development. They showed that this mutation can be because of ATP hydrolysis in the P-loop **(25)**.

Recent developments in high-throughput WES approaches and the next-generation sequencing method have now revealed the genetic basis of disorders with unknown etiology. Furthermore, exome sequencing is progressively being used as an investigative device for precise genetic diseases diagnosis, especially in the context of substantial phenotypic and genetic heterogeneity disorders **(26, 27)**. This result can be replicated as a result of consanguineous marriage in the future, which can be used for a more suitable customized treatment for ZS patients.

Conclusion

The results of the present study indicated a pathogenic heterozygous missense mutation in *PEX1* at the codon 843 in ZS patients. This finding can be repeated in the future in the cited family. It may happen as a result of consanguineous marriage. This mutation may be used for ZS patients for a more desirable personalized medicine. Additionally, it is a missense variant (p. Gly843Asp) with an autosomal recessive pattern. It may be widespread among Iranian populations with intellectual disability. Taken together, the results of this study provided novel perceptions into the diagnostic power of WES, and revealed that it is possible to consider and treat the recognized mutations, individually.

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This research resulted from an independent research without receiving any financial support.

Conflict of Interest

Authors declared no conflict of interest.

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