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Spectrum of genetic alterations in patients with peroxisome biogenesis defects in the Iranian population: a case series study

Sheyda Khalilian[1,2†], Mohadeseh Fathi[1,2†], Sanaz Jamshidi[3], Rasoul Madannejad[3], Arezou Sayad[2,3], Soudeh Ghafouri-Fard[2*] and Mohammad Miryounesi[2,3*]

Abstract

Peroxisomal disorders are a group of hereditary metabolic disorders that happen when peroxisomes are defective. Around 80% of individuals affected by peroxisomal disorders are classified within the spectrum of Zellweger syndromes with autosomal recessive inheritance pattern that results from mutations in one of the 13 *PEX* genes. Clinical exome sequencing plays a vital role in the diagnosis where the symptoms are atypical. In the current study, we used this technique to find the underlying genetic cause in 14 Iranian patients with peroxisomal disorders. *PEX1* variants were detected in five patients. *PEX2*, *PEX5*, *PEX6* and *PEX7* variants were detected in three, one, one, and two cases, respectively. Finally, *ACOX1* variants were identified in two cases. All cases except two cases were homozygote for the suspected variants in Zellweger syndrome-related genes. Two cases were compound heterozygote for variants in the *PEX1* gene. In total, two novel variants were identified, including c.313 C>T (p.Gln105*) and c.961 A>T (p.Ile321Phe) in the *PEX1* and *ACOX1* genes, respectively. The present research expands the range of genetic variations observed in Iranian individuals diagnosed with various forms of Zellweger spectrum disorders.

Keywords Peroxisomal disorders, Zellweger syndrome, PEX1, PEX2, PEX5, PEX6, PEX7, ACOX1

Introduction

Peroxisomes are organelles in the eukaryotic cells that perform β-oxidation of fatty acids. Their cellular presence and performance level are influenced by metabolism and physiological conditions, with the highest concentrations in liver and kidney tubular cells [1]. Fatty acid oxidation is carried out by mitochondria and peroxisomes. Short-, medium-, and long-chain fatty acids oxidation occurs in the mitochondria organelle, whereas peroxisomes are responsible for the oxidation of very long-chain fatty acids [2, 3]. These two organelles play a crucial role in detoxifying reactive oxygen species (ROS) as well as xenobiotics [4, 5].

The disruption of peroxisome biogenesis or its maintenance leads to peroxisome biogenesis disorders (PBDs).

†Sheyda Khalilian and Mohadeseh Fathi have contributed equally to the work.

*Correspondence:
Soudeh Ghafouri-Fard
s.ghafourifard@sbmu.ac.ir
Mohammad Miryounesi
miryounesi@gmail.com
[1]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Table 1 Summary of clinical and molecular findings in patients with peroxisomal disorders

Case number	Gene	Transcript	Variant	Associated disease	OMIM	Inheritance	Zygosity	dbSNP rsID	Clinvar*	ACMG classification*	Frequency in gnome AD	Frequency in Iranome	Age	Sex	Consanguinity	Indication	Ref
1	*PEX1*	NM_000466.3	c.2528G>A p.Gly843Asp	Peroxisome biogenesis disorder 1 A (Zellweger) & 1B	214,100 601,539	AR	Hom	rs61750420	Pathogenic	Pathogenic	0.062%	No observation	1 year	M	N	history of asphyxia, seizure from age of 5 months, hepatomegaly, developmental delay and pallor of optic disk	[15, 16]
2	*PEX1*	NM_000466.2	c.2876G>C p.Arg959Pro	Heimler syndrome 1 Peroxisome biogenesis disorder 1 A /1B (Zellweger)	234,580 214,100 601,539	AR	Hom	rs773206107	Likely Pathogenic	VUS	0.0%	No observation	8 years	M	N	abnormal gait, progressive spasticity, incontinence and normal metabolic test	
3	*PEX1*	NM_000466.3	c.2528G>A p.Gly843Asp	Heimler syndrome 1 Peroxisome biogenesis disorder 1 A (Zellweger) Peroxisome biogenesis disorder 1B (NALD/IRD)	234,580 214,100 601,539	AR AR AR	Het	rs61750420	Pathogenic	Pathogenic	0.062%	No observation	6 months	F	N	microcephaly, hypotonia, respiratory distress, and hearing loss	[15, 16]
			c.1136_1140del p.Glu379Glyfs*12				Het	-	Pathogenic	Likely Pathogenic	0.0%	No observation					
4	*PEX1*	NM_000466.3	c.2528G>A p.Gly843Asp	Heimler syndrome 1 Peroxisome biogenesis disorder 1 A (Zellweger) Peroxisome biogenesis disorder 1B (NALD/IRD)	234,580 214,100 601,539	AR	Het	rs61750420	Pathogenic	Pathogenic	0.062%	No observation	16 months	F	N	hypotonia, elevated liver enzyme, strabismus and retinal disorder	[15, 16]
			c.313 C>T p.Gln105*				Het	-	Likely Pathogenic	NR	0.0%	No observation					NR
5	*PEX1*	NM_000466.2	c.2783+6T>C	Heimler syndrome 1 Peroxisome biogenesis disorder 1 A (Zellweger)/ 1B(NALD/ IRD)	234,580 214,100 601,539	AR	Hom	rs1585224298	VUS	VUS	0.0%	No observation	9 years	M	Y	seizure at 8 months, motor delay, hearing loss, developmental delay	

Table 1 (continued)

Case number	Gene	Transcript	Variant	Associated disease	OMIM	Inheritance	Zygosity	dbSNP rsID	Clinvar*	ACMG classification*	Frequency in gnome AD	Frequency in Iranome	Age	Sex	Consanguinity	Indication	Ref
6	*PEX5*	NM_000319.5	c.1775 C>T p.Pro592Leu	Peroxisome biogenesis disorder 2 A (Zellweger) Peroxisome biogenesis disorder 2B Rhizomelic chondrodysplasia punctata, type 5	214,110 202,370 616,716	AR AR AR	Hom	rs748956654	Likely Pathogenic	Conflict	0.0%	No observation	5 years	M	Y	motor delay	[17]
	ATL3	NM_015459.5	c.16 C>T p.Arg6*	Neuropathy, hereditary sensory, type IF	615,632	AD	Het	rs1455374554	Likely Pathogenic	VUS	0.0%	No observation					[18]
7	*PEX6*	NM_000287	c.2626 C>T p.Arg876Trp	Heimler syndrome 2 Peroxisome biogenesis disorder 4 A Peroxisome biogenesis disorder 4B	616,617 614,862 614,863	AR	Hom	rs267608246	Likely Pathogenic	VUS	<0.0001%	No observation	31 years	F	Y	hearing loss, visual impairment, and MR	[19, 20]
8	*PEX7*	NM_000288	c.946 C>T p.Pro316Ser	Rhizomelic chondrodysplasia punctata, type 1 Peroxisome biogenesis disorder 9B	215,100 614,879	AR AR	Hom	rs746310299	VUS	VUS	0.003%	No observation	1.5 years	M	N	developmental delay, hypotonia and hearing loss	
9	*PEX7*	NM_000288	c.257G>A p.Cys86Tyr	Peroxisome biogenesis disorder 9B Rhizomelic chondrodysplasia punctata, type 1	614,879 215,100	AR	Hom	-	Likely Pathogenic	Likely Pathogenic	0.0%	0.06%	1 year	F	Y	developmental delay, cataract, rhizomelic extremities and clinical diagnosis of Rhizomelic chondrodysplasia punctata	[21–23]

Table 1 (continued)

Case number	Gene	Transcript	Variant	Associated disease	OMIM	Inheritance	Zygosity	dbSNP rsID	Clinvar*	ACMG classification*	Frequency in gnome AD	Frequency in Iranome	Age	Sex	Consanguinity	Indication	Ref
10	*PEX12*	NM_000286	c.959 C>T p.Ser320Phe	Peroxisomal Biogenesis Disorder 3	601,758 614,859	AR	Hom	rs28936697	Pathogenic	Pathogenic	< 0.001%	No observation	5 years	M	N	developmental delay, seizure, motor retardation, nystagmus and hearing loss	[24]
11	*PEX12*	NM_000286.3	c.625 C>T p.Gln209Ter	Peroxisome biogenesis disorder 3 A (Zellweger) Peroxisome biogenesis disorder 3B	614,859 266,510	AR	Hom	rs61752106	Pathogenic	Pathogenic	0.02%	No observation	5 months	F	Y	seizure, hypotonia, ASD, hearing loss, and agenesis of cerebellar vermis and corpus callosum in brain MRI	[25]
12	*PEX12*	NM_000286	c.204_206delTCT p.Leu68del	Peroxisome biogenesis disorder 3 A (Zellweger) and 3B	614,859 266,510	AR	Hom	rs61752098	VUS	VUS	0.0%	No observation	6 months	F	Y	severe hypotonia, hearing loss, intractable seizures, developmental delay and Sleep Apnea	[26]
13	*ACOX1*	NM_004035.7	c.961 A>T p.Ile321Phe	Peroxisomal acyl-CoA oxidase deficiency	264,470	AR	Hom	-	VUS	NR	0.0%	No observation	4 years	F	Y	hypotonia, developmental delay, aphasia and right partial polygyria in brain MRI	NR
	KIF5C	NM_004522	c.1666 A>T p.Lys556*	Cortical dysplasia, complex, with other brain malformations	615,282	AD	Het	-	VUS	NR	0.0%	No observation					
14	*ACOX1*	NM_004035	c.1478+1G>A	Peroxisomal acyl-CoA oxidase deficiency	264,470	AR	Hom	-	Likely Pathogenic	Likely Pathogenic	0.0%	No observation	7 years	F	Y	history of developmental regression	

AR: autosomal recessive, Hom: homozygote, Het: heterozygote, VUS: Variant of uncertain significance, NR: not reported; M: male, F: female, Y: yes, N: No

*ACMG/Clinvar classification criteria: pathogenic, likely pathogenic, Variant of uncertain significance, likely benign, and benign

Around 80% of individuals affected by PBD are classified within the spectrum of Zellweger syndromes (ZS) with autosomal recessive inheritance pattern that results from mutations in one of the 13 PEX genes [6–8]. ZS encompasses three distinct phenotypes: severe ZS, neonatal adrenoleukodystrophy (NALD), and the least severe infantile Refsum disease (IRD). These phenotypes were identified before their biochemical and molecular mechanisms were understood [9]. The clinical manifestations of ZS encompass hepatic dysfunction, developmental delays, various neurological disorders, adrenal cortical insufficiency, and impairments in both hearing and vision [10].

Due to overlapping symptoms in Zellweger disorders, numerous studies indicate that accurate diagnosis requires thorough clinical examination, laboratory testing, and multi-disciplinary collaboration [11–13]. Clinical exome sequencing plays a vital role in the diagnosis where the symptoms are atypical [11]. The present research expands the range of genetic variations observed in Iranian individuals diagnosed with various forms of Zellweger spectrum disorders.

Case presentation

This study was performed on 14 Iranian cases of Zellweger spectrum disorders. Cases were assessed in the Comprehensive Genomic Center, Tehran, Iran during 2018–2024. Genetic counseling and molecular diagnosis were performed in this center. Informed consent forms were signed by legal representatives of patients. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by ethical committee of Shahid Beheshti University of Medical Sciences.

Molecular diagnosis

Genomic DNA was obtained from the peripheral blood of patients using the standard salting-out procedure. The concentration and quality of DNA were evaluated using a NanoDrop 1000 (Thermo Fisher Scientific, USA). Genomic DNA of probands was subjected to whole exome sequencing (WES) using an Illumina HiSeq4000 system with paired-end reads of 101 bp and 100X coverage. Exonic and adjoining exon-intron border regions were enriched using SureSelectXT2 V6 kits. After exclusion of low-quality reads, the reads were mapped to the human genome reference (hg37 build) using the Burrows-Wheeler Aligner. Next, Sequence Alignment/Map (SAM) tools were used for detection and removal of duplicates. Then, recalibration and single nucleotide polymorphism/indel calling were conducted. Variant calling and filtering were done using the Genome Analysis Toolkit.

Variant prioritization strategy involved a multi-step filtering process. Initially, we filtered variants based on quality metrics, including read depth, genotype quality, and allele frequency in public databases (e.g., gnomAD, dbSNP). We then prioritized rare variants (MAF < 1%) and focused on those predicted to be deleterious by in silico tools (e.g., SIFT, PolyPhen-2, and CADD). We applied a recessive inheritance model to identify potential disease-causing pairs. Parental consanguinity was also evaluated. In fact, all variants were assessed according to the accessible data from these sources: databases (including HGMD, ClinVar, LSDBs, NHLBI Exome Sequencing Project, 1000 Genomes, and dbSNP), published articles, clinical correlation, segregation analyses, functional assessments, and the predicted functional or splicing influence based on evolutionary conservation analyses and in silico tools (AlignGVGD, MAPP, MutationTaster, PolyPhen-2, SIFT, and SNAP).

Variants were classified according to the criteria in the ACMG guidelines into five tiers: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign and benign [14].

The identified variants were verified by Sanger sequencing in the probands. Segregation analysis was performed in the families of cases 1, 2, 3, 4, 6, 8, 9 and 12. In other cases, family members were not available for segregation studies.

Results

Table 1 shows the summary of clinical and molecular data of enrolled subjects, including eight females and six males. The clinical symptoms and signs were viable among patients with most of cases presenting hypotonia and developmental delay. Seven patients had hearing loss. Eight patients were born to consanguine parents. *PEX1* variants were detected in five patients. *PEX2*, *PEX5*, *PEX6* and *PEX7* variants were detected in three, one, one, and two cases, respectively. Finally, *ACOX1* variants were identified in two cases (Fig. 1).

All cases except two cases (cases 3 and 4) were homozygote for the suspected variants in ZS-related genes. Case 3 was compound heterozygote for two pathogenic variants in the *PEX1* gene, namely c.2528G > A (p.Gly843Asp) and c.1136_1140del (p.Glu379Glyfs*12). Similarly, case 4 was compound heterozygote for two *PEX1* variants (c.2528G > A [p.Gly843Asp] and c.313 C > T [p.Gln105*]), which were classified as pathogenic and likely pathogenic variants, respectively. Figure 2 shows Sanger chromatogram of this case.

In total, two novel variants were identified, including c.313 C > T (p.Gln105*) and c.961 A > T (p.Ile321Phe) in the *PEX1* and *ACOX1* genes, respectively. We explored several databases such as DANN, and BayesDel to assess the functional consequences of novel variants. DANN is a functional prediction score based on a deep neural network. The score can range from 0 to 1, when higher

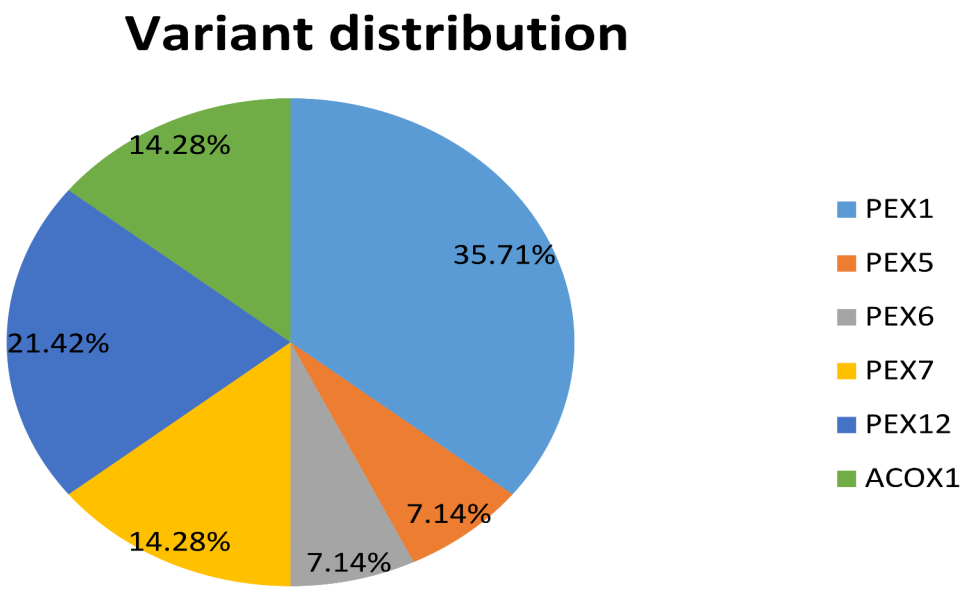

Fig. 1 Distribution of identified variants within genes

values are more likely of being deleterious. According to this database both c.313 C > T (p.Gln105*) and c.961 A > T (p.Ile321Phe) variants are deleterious with scores of 1 and 0.99, respectively.

BayesDel is a functional prediction deleteriousness meta-score. The range of the score is from − 1.29334 to 0.75731. The higher the score, the more likely the variant is pathogenic. According to this database the c.313 C > T (p.Gln105*) variant is deleterious (strong) (score: 0.66). Moreover, the c.961 A > T (p.Ile321Phe) variant is also deleterious (supporting) (score: 0.24).

Discussion

Identification of spectrum of genetic mutations in ZS in each population has significance in the genetic counseling and prenatal diagnosis. The current study aimed to show the spectrum of *PEX* mutations among Iranian patients with this type of metabolic disorders. *PEX1* gene included the highest rate of mutations in this study, being mutated in five out of 14 patients. Notably, the c.2528G > A (p.Gly843Asp) within this gene was detected in three unrelated patients in the heterozygous state. This variant was also reported in the homozygous state in two sibling (non-identical twins) born to a consanguineous Iranian parent [27]. The patients had the common features of ZS including dysmorphic face and intellectual disability, but no hearing loss was reported in these patients [27]. The c.2528G > A variant was reported to be the most common mutation in *PEX1*, by far. It changes the glycine located in the second ATP-binding domain into an aspartic acid, thus reducing the binding between PEX1 and PEX6 [28]. The biological impact of this mutation was found relatively mild and cells of patients with this mutation often exhibit peroxisomal mosaicism when cultured at 37 °C [29]. Notably, case 3 in this study had c.2528G > A variant together with a frameshift variant (p.Glu379Glyfs*12); and presented with hearing loss. Taken together, this mutation seems to be widespread among Iranian patients with ZS. However, the related phenotypes with this mutation should be assessed in future studies. Since p.Gly843Asp is a misfolded protein responsive to chaperone therapy [28], identification of the relative frequency of this mutation among Iranian patients would facilitate establishment of personalized treatment modalities among these patients.

Other studies among Iranian patients reported a homozygous VUS in the *PEX6* (c.1992G > C [p. Glu664Asp]) [30], c.743_744delTCinsA mutation in the *PEX11β* [31], and a homozygous missense mutation in the *PEX12* gene (c.541T > G [p.Tyr181Asp]) [32]. Moreover, the compound heterozygous mutations, p.Arg949Trp and p.Gly970Ala, were identified in another Iranian patient with ZS [33]. The p.Arg949Trp occurred in a conserved arginine residue, thus the mutation hampers the substrate processing of the PEX1/PEX6 complex. The p.Gly970Ala may also preclude appropriate interaction of PEX1 and PEX6 proteins [33].

Different PEX mutations have been reported in other countries. For instance, a study in the USA reported a homozygous variant in the *PEX6* (c.1409G > C [p.Gly470Ala]) [34]. Also, two novel *PEX6* intronic variants, c.315G > A and c.2095–3 T > G, were found in a Chinese neonate. The c.2095–3 T > G variant has led to abnormal mRNA splicing [35]. Moreover, another study has reported a recurrent p.Arg294Trp variant in the *PEX13* gene in three out of five families with ZS. These

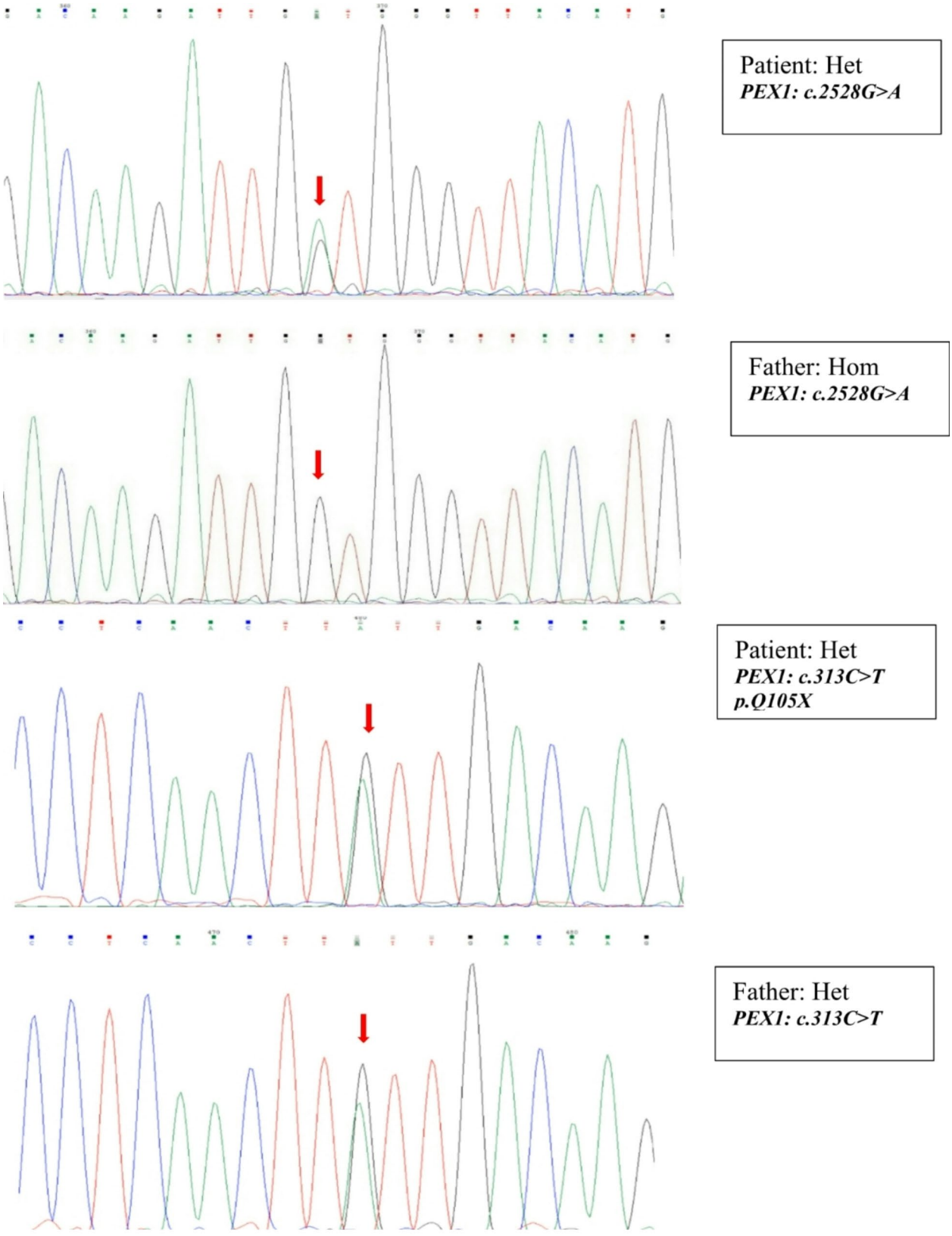

Fig. 2 Sanger chromatogram of case 4. According to the result, this compound heterozygous mutation is confirmed in this patient

patients had different clinical manifestations, such as hypotonia, developmental regression, hearing/vision defects, progressive spasticity and brain leukodystrophy [36]. In brief, the spectrum of genetic variants leading to Zellweger spectrum disorders in different ethnic groups is quite wide.

In brief, we provided an overview of *PEX* mutations among Iranian patients. We also identified two novel variants, namely c.313 C > T (p.Gln105*) and c.961 A > T (p.Ile321Phe) in the *PEX1* and *ACOX1* genes, respectively. While the segregation of the former variant was confirmed in the family, family members were not available for segregation studies of the latter variant. This information would pave the way for proper genetic counseling of the affected families. Moreover, the occurrence of more than 42% of affected patients in non-consanguineous families implies high prevalence of *PEX* mutations among Iranian population. This should be considered in pre-marital genetic counseling.

In total, the spectrum of *PEX* mutations among Iranian patients is not fully understood, necessitating further studies in this field. Moreover, assessment of the functional consequences of novel variants and recognition of their responsiveness to chaperon therapy facilitate establishment of personalized treatment modalities for ZS.

Abbreviations

ZS	Zellweger syndromes
NALD	Neonatal adrenoleukodystrophy
IRD	Infantile refsum disease
WES	Whole exome sequencing

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Author contributions
M.F. and S.K. evaluated patients' genetic reports. S.GF wrote the manuscript. M.M and A.S assessed the patients. S.J and R.M participated in laboratory experiments. S.GF, and MM supervised the study. All the authors read and approved the submitted version.

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Data availability
The datasets generated and/or analysed during the current study are available in the Clinvar repository (https://www.ncbi.nlm.nih.gov/clinvar/?term=%22pex1%22%5BGENE%5D).

Declarations

Ethics approval and consent to participate
Informed consent forms were signed by legal representatives of patients. All methods were carried out in accordance with relevant guidelines and regulations. The study adhered to the Declaration of Helsinki. All experimental protocols were approved by ethical committee of Shahid Beheshti University of Medical Sciences.

Consent for publication
Written informed consent for publication of clinical details and/or clinical images was obtained from the parents of the patient.

Competing interests
The authors declare no competing interests.

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