The Application of Clinical Genetics

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Detection of a Novel Homozygous PEX5 Stop-Loss Variant Associated with Zellweger Syndrome in a Highly Endogamic Family

Ingrid Tatyana Bernal-Bonilla[1], Juan Sebastian Arias-Florez[1], Sandra Ximena Ramirez[2], Bibiana Alejandra Bayona-Gomez[3], Lina Castro-Castillo[3], Valeria Correa-Martinez[4], Yasmín Sanchez-Gomez[5], Natalia Santiago-Tovar[6], Cristian Camilo Gaviria-Sabogal[6], Nora Constanza Contreras Bravo[6], Rodrigo Cabrera[6], Adrien Morel[6], Dora Janeth Fonseca-Mendoza[6], Carlos M Restrepo[6]

[1]Department of Morphology, Institute of Human Genetics, Universidad Nacional de Colombia. Grupo Investigación Genética Clínica UNAL, Bogotá D.C, Colombia; [2]Department of Internal Medicine, Hospital Universitario Mayor-Mederi, Universidad Del Rosario, Bogotá D.C, Colombia; [3]Department of Pediatrics, La Cardio, and Universidad Del Rosario, Bogotá D.C, Colombia; [4]School of Medicine, Universidad Nacional de Colombia, Bogotá D.C, Colombia; [5]Universidad de Boyacá. Medisens IPS, Tunja, Colombia; [6]School of Medicine and Health Sciences, Center for Research in Genetics and Genomics (CIGGUR), Institute of Translational Medicine (IMT). Universidad del Rosario, Bogotá D.C, Colombia

Correspondence: Carlos M Restrepo, Email carlos.restrepo@urosario.edu.co

Abstract: Zellweger syndrome (ZS) is a heterogeneous group of clinical conditions that commonly manifest with neurodevelopmental delay, multiple neurological abnormalities, visual and auditory impairments, and adrenocortical dysfunction. ZS is an autosomal recessive peroxisomal disorder resulting from mutations in one of over 13 identified genes. We report the case of a male child with episodic seizures starting at 18 days of life, followed by neurodevelopmental delay and neuroimaging findings of asymmetric polymicrogyria and cortical abnormalities. His healthy parents were consanguineous, and notably, a brother, who passed away at the age of 5 years-old, had epilepsy and adrenoleukodystrophy. Exome sequencing allowed the identification of a novel stop-loss homozygous variant in the *PEX5* gene in the index case. The phenotype associated to this gene, Zellweger syndrome, as well as the inheritance mechanism, is consistent with that observed in both the patient and his brother.

Keywords: peroxisome biogenesis disorder, zellweger syndrome, neonatal adrenoleukodystrophy, heimler syndrome, very long chain fatty acids, molecular variant

Introduction

Zellweger syndrome (ZS) is a rare autosomal recessive condition of neonatal onset characterized by severe dysfunction of the central nervous system, liver, and kidneys. ZS was first described in 1964 in children with failure to thrive, congenital glaucoma, craniofacial dysmorphism, and early death.[1] Then, in 1965, polycystic kidneys and intrahepatic biliary dysgenesis were added as additional features,[2] leading to the designation cerebro-hepato-renal dysgenesis, which was later renamed as ZS.[3] The causal association between ZS and the absence of peroxisomes in hepatocytes and renal proximal tubules was established in 1973.[4]

ZS is clinically characterized by neuronal migration disorders, early-onset seizures, dysmorphic facial features, skeletal abnormalities resembling chondrodysplasia punctata, muscle weakness, developmental delay, renal cysts, and severe liver disease. Death usually occurs within the first year of life.[1,5–8] The metabolic dysfunction is expressed by the accumulation of very long-chain fatty acids, pristanic acid, phytanic acid, and total bile acids; along with reduced plasmalogens in erythrocytes.[9,10] ZS is caused by mutations in at least one of several *PEX* genes, which encode peroxisome assembly proteins involved in complex catabolic and anabolic pathways. ZS represents the predominant type of peroxisome biogenesis disorders (PBDs); it is mainly caused by mutations in the *PEX1* gene, which accounts for

Received: 20 February 2025
Accepted: 28 May 2025
Published: 4 September 2025

approximately 60% of all PBDs cases, but it can be caused by any of the ZS-*PEX* genes, regardless of their specific phenotype.[5,6,8,11–13] This spectrum entails a clinical continuum of various phenotypes, ranging from the most severe manifestation known as Zellweger syndrome; to milder forms such as neonatal adrenoleukodystrophy, infantile Refsum disease, and Heimler syndrome.[5,6,11–13]

PTS1R (Peroxisomal Target Signal 1 Receptor, also known as *PEX5*), is a peroxin, a group of proteins that are essential for the formation of functional peroxisomes, cellular organelles derived from the endoplasmic reticulum that are involved in multiple metabolic pathways. *PTS1R* is located in the cytosol and peroxisomes and is part of both the formation and degradation of these organelles. First, it recognizes and binds matrix proteins containing the C-terminal tripeptide peroxisome target sequence (PTS) to import them into the peroxisome through an ATP-requiring action, acting as a receptor.[14] On the other hand, during peroxisome degradation known as pexophagy, PTS1R is phosphorylated by ATM protein and then ubiquitinated at L209 by the peroxisomal E3-ligase, PEX2/10/12, to be recognized by the autophagic adaptor SQSTM1/p62.[15,16]

PTS1R also participates in autophagy regulation outside the peroxisome through inhibition of the mTORC1 pathway, and it has been shown that its absence impairs the cell's ability to start this process under stress situations.[16] It is encoded by the *PEX5* gene located at 12p13.31, containing 16 exons. It has multiple isoforms, with two main coding for functional proteins derived from alternative splicing of exon 7: PEX5S (short) and PEX5L (long). The short isoform only imports PTS-1 sequences while the long one also recognizes PTS-2.[1] Even though the testis and brain are the tissues with the highest expression, *PEX5* is ubiquitous in human samples, explaining the multiorgan dysfunction seen in patients with peroxisomal biogenesis disorders caused by *PEX5* deleterious variants: Peroxisome Biogenesis Disorder 2A (PBD2A), Peroxisome Biogenesis Disorder 2B (PBD2B) and Rhizomelic Chondrodysplasia Punctata type 5 (RCDP5).[14–17] Variants are found in the entire gene, however, exons 12 and 14 have a particularly high number of them, with the most common variant being c.1578T>G p.(Asn526Lys).[18]

There is no data regarding the incidence of ZS in Colombia, however worldwide data indicates that the highest incidence was estimated to be 1 in 12.000 in the French-Canadian region of Quebec.[19] The incidence in the United States is around 1 in 50.000 newborns[7] and in Japan, is estimated to be 1 in 500.000 births.[20]

We describe a highly consanguineous family with two affected siblings, one of whom was found to carry a novel variant in the *PEX5* gene. Our clinical findings, together with the molecular analysis of the variant, enable us to propose it as the causative mutation of the disease.

Case Report

Index case (VI-4) is a male, born from the second pregnancy of healthy consanguineous parents. He was delivered via cesarean section following premature rupture of membranes. Birth weight was 2.590 g (5th percentile) and height was 49 cm (32nd percentile). At 18 days of life, he debuted with gaze deviation and tonic seizure; at two months, the seizures had progressed to generalized tonic-clonic seizures with cyanosis. Treatment with oxcarbazepine and levetiracetam was initiated, leading to seizure remission. At 4 months, the patient developed social smiling, could bring his hands to his mouth, and later grasp objects with one hand and produce monosyllables, but he was unable to support his head and maintain sitting position. The patient presented global hypotonia and distinctive facial features, as described in Figure 1. A magnetic resonance imaging (MRI) scan revealed asymmetric polymicrogyria with more extensive involvement of the left hemisphere, along with additional cortical alterations indicative of cortical encephalopathy. Shortly after the first consultation, the patient was hospitalized due to his severe neurological phenotype. Given that his neuroimaging was indicative of a neuronal migration disorder, all studies performed were aimed primarily towards the diagnosis of a neurological pathology, without suspecting a disease that would involve other systems.

The patient's older brother (VI-3) showed severe global developmental delay, focal epilepsy and leukodystrophy. He died at the age of five, remaining undiagnosed with a suspected rare genetic disorder.

Their parents, aged 37 (mother) and 29 years (father), were healthy and consanguineous with two endogamous matings in their family history (Figure 1B). The couple had three pregnancies: the patient, his older brother who died at the age of five due to respiratory complications during ICU hospitalization, and a spontaneous abortion at eight weeks. The mother has another healthy daughter from a previous non-consanguineous union. Additionally, there is a history of epilepsy in a maternal second-degree relative.

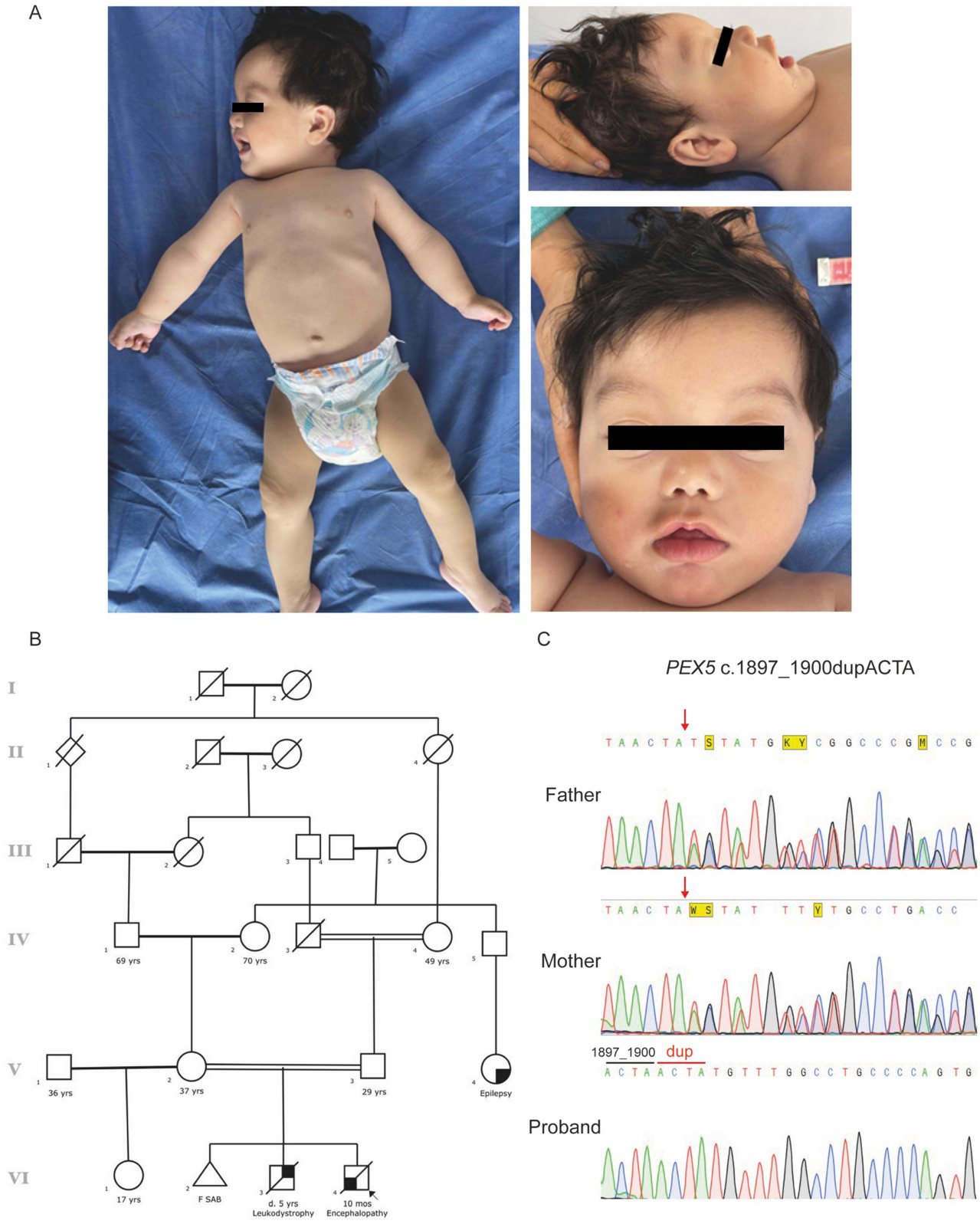

Figure 1 Clinical and Molecular Findings; (**A**) Phenotype: brachycephaly, broad forehead with frontal bossing, medially sparse eyebrows, telecanthus, ocular proptosis, midfacial hypoplasia, depressed nasal bridge, small nose, short and deep philtrum, cupid's bow upper lip and tent-shaped mouth, open book posture due to severe hypotonia. (**B**) Pedigree. The proband (VI-4) is described with cortical abnormality and epilepsy, his brother (VI-3) with epilepsy and leukodystrophy and a paternal cousin (V-4) with epilepsy. Two consanguinity unions have been identified. (**C**) Sanger sequencing. The mother and father show a heterozygous duplication of 4 nucleotides. The proband displays a homozygous duplication pattern in the electrophoretogram, red arrow indicates the position of the duplication in *PEX5*:c.1897_1900ACTA.

https://doi.org/10.2147/TACG.S518636

Molecular Analyses

The DNA of the patient and both parents was extracted from a whole-blood sample using the Quick-DNA 96 plus kit (Zymo Research). After assessing the quality and quantity of the DNA, a genomic library was prepared using MGIEasy FS DNA Library Prep Kit and fragments ranging from 200 to 400pb were obtained. The regions of interest were captured through the Exome Capture V5 probe and streptavidin beads. The final PCR reaction was enriched and employed specific primers. Sequencing and library preparation were performed using MGI DNBSEQ-G50 platform for Gencell Pharma (Bogotá, Colombia). The reads obtained were mapped and aligned to the reference genome (hg19) and variant calling was performed using the GATK v4.0.5.1 tool.[11] Analyses of coverage and depth were conducted using the BAMBA tool, and 50X was the acceptable threshold. The variants obtained in VCF format (variant call format) were imported into VarSeq software (Golden Hélix v2.2.3) for annotation and filtering according to different criteria. Filtered candidate variants were assessed using the American College of Medical Genetics and Genomics guidelines (ACMG). Bioinformatics procedures were performed in the laboratory of the Genetics and Genomics Research Center of the Universidad del Rosario (CIGGUR), Bogotá (Colombia).

Through trio exome sequencing the homozygous variant (NM_001131025.2):c.1897_1900dupACTA p.(Met634Asnfs*16) in the *PEX5* gene was identified. Despite its classification as a variant of uncertain significance (VUS), given the history of parental consanguinity and the diagnosis of leukodystrophy in a sibling, the diagnosis of Zellweger syndrome, an autosomal recessive peroxisome biogenesis disorder, was made. The identified molecular variant was confirmed by Sanger sequencing (SS) in the patient and both parents (Figure 1C), demonstrating parental segregation.

Discussion

We identified two siblings with epilepsy, congenital hypotonia, developmental delay, dysmorphic facies, and different neuroimaging abnormalities. In the oldest sibling adrenoleukodystrophy vs metabolic disease was suspected and in the youngest one, our index case, cortical encephalopathy diagnosis was proposed. Despite both children showing similar symptoms and neuroimaging findings suggesting a shared clinical landscape, a clear consensus on the diagnosis could not be reached.

We performed an exome trio analysis identifying the homozygous variant (NM_001131025.2):c.1897_1900dupACTA p.(Met634Asnfs*16) in the *PEX5* gene. This variant is a four-nucleotide duplication at position 1897 of the cDNA, located within exon 16 of the gene, classified as a VUS by the ACMG criteria PM4, PM2 and PP1. It induces a stop-loss mutation which results in the downstream extension of 9 amino acids in the protein. The allelic frequency of this variant remains unknown in the GnomAD population database, and it has not been reported in clinical databases or in scientific literature reviewed.

A series of frameshift variants located in the last exon of different *PEX* genes, which result in the extension of the protein by a stop codon loss mechanism, have been identified in the literature in association with ZS. Ebberink et al (2010) provided a comprehensive overview of all variants identified in their genetic complementation studies of more than 600 skin fibroblast cell lines from patients with Zellweger syndrome spectrum disorders, diagnosed based on metabolite analysis in plasma and/or detailed studies in fibroblasts. To identify which *PEX* gene was defective in each cell line, the researchers employed functional analyses, including a polyethylene glycol (PEG)-mediated cell fusion assay and a *PEX* cDNA transfection assay. Once the defective *PEX* gene was identified, researchers performed Sanger sequencing of the coding region and flanking intronic sequences, or alternatively, sequenced *PEX* genes cDNAs prepared from RNA extraction and RT-PCR to characterize their molecular variants. They identified stop-loss variants across *PEX1, PEX2, PEX10* and *PEX16* genes, highlighting the contribution of this type of molecular variants in the etiology of ZS.[21] Similarly, Régal et al (2010) reported a 8.5 year-old child with cerebellar atrophy, slowly progressive ataxia, axonal motor neuropathy and posterior column dysfunction. Two mutations in *PEX10* were found in the child, one of them was the pathogenic variant (NM_153818.1):c.764_765insA p.(Leu256Alafs*103), previously reported in patients with Zellweger syndrome, which is predicted to extend the protein product.[22–25] In addition, Ebberink et al (2010) described two siblings with progressive spastic paraparesis and ataxia, who developed cataracts and peripheral neuropathy. They showed a characteristic pattern of progressive leukodystrophy and brain atrophy on MRI scan. The subsequent sequencing of all known *PEX* genes revealed the homozygous frameshift variant (NM_004813):c.984delG p.(Ile330Serfs*27) in *PEX16* gene, which results in a stop-codon loss, introducing a termination codon at amino acid position 357 in a protein with 337 amino acids.[26] These findings

suggest that stop-loss is a common mechanism within the *PEX* gene family by which frameshift variants elongate, rather than truncate, functional protein products. This phenomenon plays a significant role in the molecular pathogenesis of Zellweger spectrum disorders.

In addition to existing evidence regarding the impact of terminal frameshift mutations in PEX genes, it is important to highlight that the mutation identified in our patient is located at the C-terminal end of the PEX5 protein, potentially affecting the last 7th tetratricopeptide repeat (TPR) motif within the TPR domain, which spans residues 321 to 639. The TPR domain is essential for binding to the peroxisomal targeting signal type 1 (PTS1) present on peroxisomal matrix proteins. This interaction is critical for the recognition and import of these proteins into peroxisomes.[27,28]

Additionally, the C-terminal region of PEX5 is involved in forming complexes with other peroxisomal proteins, such as PEX14, a key component of docking and translocation machinery at the peroxisomal membrane. This interaction is essential for the translocation of the PEX5–cargo complex into the peroxisomal matrix.[29] The dual role of the C-terminal domain in both PTS1 recognition and interaction with peroxisomal membrane components underscores its functional relevance in the peroxisomal protein import cycle and its potential link to Zellweger spectrum disorders.[30]

Molecular variants affecting this critical functional domain, are expected to impair peroxisomal function, leading to the accumulation of very long chain fatty acids (VLCFA) and other metabolic abnormalities.[31] In our patient, biochemical profiling that could confirm the dysregulation of these metabolites could not be performed due to the unavailability of specialized testing in the rural area from which the patient originated. Nevertheless, as in previously reported cases, the combination of clinical features and the molecular finding was sufficient to support the diagnosis of the syndrome.

There have been many case reports on pathogenic variants in *PEX5*. First, Baroy et al, described the first cases of rhizomelic chondrodysplasia punctata 5 (RCDP5); they found two families in Pakistan, both consanguineous, with children affected by severe global developmental delay, multiple skeletal anomalies, epilepsy and congenital cataracts.[32] Later, Ali et al also described a Pakistani family with two consanguineous marriages; 12 individuals were studied, with 5 affected by severe global developmental delay, epilepsy, hypotonia and congenital cataracts.[33] On the other hand, Pronicka et al sequenced 113 patients with possible mitochondrial diseases due to clinical manifestations and found one with a pathogenic mutation in *PEX5* that led to developmental regression, deafness and leukoencephalopathy, classifying it as ZS,[34] showing the wide range of differential diagnosis of this disease (Table 1).

Table 1 Comparison of Index Case (VI-4) with Reported Patients with PEX5 Pathogenic Variants

Author	Present Study Case 1 (VI-4)	Case 2 (VI-3)	Baroy et al (2015)	Ali et al (2021)	Pronicka et al (2016)
Variant(s)	*PEX5* (NM_001131025.2): c.1897_1900dupACTA p.(Met634Asnfs*16)	N/A	*PEX5* (NM_001131023.1): c.722dupA p.(Val242Glyfs*33)	*PEX5* (NM_001131026): c.653 T > C; p.(Phe218Ser)	*PEX5* (NM_001131025.1): c.1669C>T p.(Arg557Trp); c.1799C>T p.(Ser600Leu)
#Patients Per variant	1	N/A	4	12	1
Ethnicity	Colombian	Colombian	Pakistani	Pakistani	Unknown
Method of identification	WES, SS	N/A	WES, SS	WES, SS	WES, SS

(*Continued*)

Table 1 (Continued).

Author	Present Study Case 1 (VI-4)	Case 2 (VI-3)	Baroy et al (2015)	Ali et al (2021)	Pronicka et al (2016)
Pathogenicity according to ACMG guidelines	Uncertain Significance	N/A	Pathogenic	Not stated	Pathogenic
History of consanguinity	+	+	+	+	Unknown
Neuroimage findings	Asymmetric polymicrogyria with more extensive involvement on the left side along with other cortical alterations.	Leukodystrophy	Not provided	Not provided	Leukoencephalopathy
Distinctive craniofacial features	+		+		
Poor feeding				+	
Hypotonia	+				
Growth retardation			+		
Global developmental delay	+	+	+		+
Seizures	+	+	+	+	
Intellectual disability			+		
Hearing loss					+
Vision impairment			+	+	
Congenital cataracts			+	+	
Chondrodysplasia punctata			+		
Peripheral neuropathy			+		

Abbreviations: AR, autosomal recessive; N/A, Non-applicable, WES, Whole Exome Sequencing; SS, Sanger Sequencing.

Based on the patient's genetic findings, the family history of consanguinity, the spectrum of neurological disorders between the siblings and the literature review about stop-loss variants associated with different peroxisomal disorders in *PEX5* and other ZS genes (*PEX6, PEX10, PEX12, PEX16, PEX19*), wee can assert that the novel homozygous stop-loss variant *PEX5* (NM_001131025.2):c.1897_1900dupACTA p.(Met634Asnfs*16), is causing an autosomal recessive peroxisome biogenesis disorder that explains the phenotype observed in both siblings. In this context, it is important to consider that in certain cases, genetic variants classified as VUS according to ACMG may be considered causative of the observed phenotype based on clinical findings. Although these variants do not fulfill all the established criteria for pathogenicity, their correlation with the patient's clinical presentation, family history, and, when available, functional studies, supports their role in the disease etiology. Such cases highlight the importance of integrating clinical judgment with genetic findings to provide a more comprehensive interpretation of rare disorders.

Limitations

After the first clinical consultation, the patient suffered significant neurological deterioration leading to hospitalization in a local hospital, where advanced biochemical studies were not available. Although the results of the genetic test were obtained during the hospitalization, the patient died shortly after, before further studies could be carried out in search of abnormalities in other systems, such as X-rays and ultrasound scans, or new samples could be taken to carry out functional studies.

Conclusion

We report a novel molecular variant in *PEX5* associated with Zellweger Spectrum Disorder (ZSD). Although the variant meets ACMG criteria for being classified as a VUS, it is unequivocally responsible for the disease. This conclusion is supported by the clinical phenotype of the patient and his sibling, parental segregation, and the established role of *PEX5* in peroxisomal disorders. In addition, the *PEX5* variant identified may impair the TPR domain, which is essential for mediating PTS1 cargo recognition. A mutation at position 634 could therefore result in defective import of matrix proteins into peroxisomes.

Also, the same type of variants (stop loss) have been associated with the disease in other ZSD-related genes. This case highlights the importance of considering genetic diseases as potential diagnoses in the context of severe neurological pathology with parental consanguinity history. Early genetic tests can allow the diagnosis of specific genetic pathologies, improve the medical approach by identifying other systems that may be compromised, and provide timely genetic counseling that can prevent the occurrence of new cases of the disease.

Abbreviations

ZS, Zellweger syndrome; MRI, A magnetic resonance imaging; ACMG, American College of Medical Genetics and Genomics guidelines; VUS, variant of uncertain significance; SS, Sanger sequencing; PBDs, peroxisome biogenesis disorders; PTS1R, Peroxisomal Target Signal 1 Receptor; PBD2A, Peroxisome Biogenesis Disorder 2A; PBD2B, Peroxisome Biogenesis Disorder 2B; RCDP5. Rhizomelic Chondrodysplasia Punctata type 5.

Data Sharing Statement

All the used data are included in this article.

Consent for Publication and Ethics Approval

Written informed consent and medical photographs parental approval for publication was obtained from the patient's parent. The study was approved by the Ethics Committee of Universidad del Rosario (Approval DVO005-1614-CV1441, June 2021).

Acknowledgments

We thank our colleagues from the Universidad Nacional de Colombia's population genetics team for opening a space with the community and supporting us with data collection. We also thank the laboratory team, especially Maria Alejandra Coronel from the Universidad Nacional de Colombia, who helped us with sample collection and processing, and Sophya Villamil from the Universidad del Rosario clinical team, who provided feedback on the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This project was supported by the Ministry of Science, Technology, Innovation, Minciencias. Project in health promoting personalized medicine and translational research, Grant 632-2021 (November 2021), Universidad Nacional de Colombia, Medisens IPS and Universidad del Rosario (Grant QAN BG273).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bose M, Yergeau C, D'souza Y, et al. Characterization of severity in zellweger spectrum disorder by clinical findings: a scoping review, meta-analysis and medical chart review. *Cells*. 2022;11(12):1891. doi:10.3390/cells11121891
2. Smith DW, Opitz JM, Inhorn SL, Madison W. *A Syndrome of Multiple Developmental Defects Including Polycystic Kidneys and Intrabepatic Tn'liary Dysgenesis in 2 Siblings*. Vol. 617.
3. Gilchrist KW, Gilbert EF, Goldfarb S, Goll U, Spranger JW. *Studies of Malformation Syndromes of Man XIB: The Cerebro-Hepato-Renal Syndrome of Zellweger: Comparative Pathology**. Vol. 121. Springer-Verlag; 1976.
4. Goldfischer S, Moore CL, Johnson AB, et al. Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. *Science*. 1973;182 (4107):62–4. doi:10.1126/science.182.4107.62
5. Lu P, Ma L, Sun J, Gong X, Cai C. A Chinese newborn with Zellweger syndrome and compound heterozygous mutations novel in the PEX1 gene: a case report and literature review. *Transl Pediatr*. 2021;10(2):446–453. doi:10.21037/TP-20-167
6. Steinberg SJ, Raymond GV, Braverman NE. *Zellweger Spectrum Disorder*. 2003.
7. Argyriou C, D'Agostino MD, Braverman N. Peroxisome biogenesis disorders. *Trans Sci Rare Dis*. 2016;1(2):111–144. doi:10.3233/trd-160003
8. Braverman NE, Raymond GV, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: an overview of current diagnosis, clinical manifestations, and treatment guidelines. *Mol Genet Metab*. 2016;117(3):313–321. doi:10.1016/j.ymgme.2015.12.009
9. Yogi P, Bahik C, Yadav R, Bhattarai P, Pandey R, Manandar SR. Zellweger syndrome: a case report. *J Nepal Med Assoc*. 2024;62(270):155–157. doi:10.31729/jnma.8467
10. Wanders RJA, Waterham HR. Biochemistry of mammalian peroxisomes revisited. *Annu Rev Biochem*. 2006;75:295–332. doi:10.1146/annurev.biochem.74.082803.133329
11. Klouwer FCC, Berendse K, Ferdinandusse S, Wanders RJA, Engelen M, Poll-The BT. Zellweger spectrum disorders: clinical overview and management approach Inherited metabolic diseases. *Orphanet J Rare Dis*. 2015;10(1). doi:10.1186/s13023-015-0368-9
12. Poll-The BT, Saudubray JM, Ogier HAM, et al. *Pediatrics Infantile Refsum Disease: An Inherited Peroxisomai Disorder Comparison with Zellweger Syndrome and Neonatal Adrenoleukodystrophy*. Vol. 46. 1987.
13. Ratbi I, Falkenberg KD, Sommen M, et al. Heimler syndrome is caused by hypomorphic mutations in the peroxisome-biogenesis genes PEX1 and PEX6. *Am J Hum Genet*. 2015;97(4):535–545. doi:10.1016/j.ajhg.2015.08.011
14. McKusick V. Peroxisome biogenesis factor 5; PEX5. Omim. 2019. Available from: https://omim.org/entry/600414. Accessed December 19, 2024.
15. Eun SY, Lee JN, Nam IK, et al. PEX5 regulates autophagy via the mTORC1-TFEB axis during starvation. *Exp Mol Med*. 2018;50(4). doi:10.1038/s12276-017-0007-8
16. Tripathi DN, Walker CL. The peroxisome as a cell signaling organelle. *Curr Opin Cell Biol*. 2016;39:109–112. doi:10.1016/j.ceb.2016.02.017
17. PEX5 peroxisomal biogenesis factor 5 [Homo sapiens (human)]. National Center for Biotechnology Information. 2024. Available from: https://www.ncbi.nlm.nih.gov/gene/5830. Accessed December 19, 2024.
18. Waterham HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. *Biochim Biophys Acta Mol Basis Dis*. 2012;1822(9):1430–1441. doi:10.1016/j.bbadis.2012.04.006
19. Levesque S, Morin C, Guay SP, et al. A Founder Mutation in the PEX6 Gene Is Responsible for Increased Incidence of Zellweger Syndrome in a French Canadian Population; 2012. Available from: http://www.biomedcentral.com/1471-2350/13/72. Accessed August 12, 2025.
20. Shimozawa N, Nagase T, Takemoto Y, Ohura T, Suzuki Y, Kondo N. Genetic heterogeneity of peroxisome biogenesis disorders among Japanese patients: evidence for a founder haplotype for the most common PEX10 gene mutation. *Am J Med Genet*. 2003;120 A(1):40–43. doi:10.1002/ajmg.a.20030
21. Ebberink MS, Mooijer PAW, Gootjes J, Koster J, Wanders RJA, Waterham HR. Genetic classification and mutational spectrum of more than 600 patients with a Zellweger syndrome spectrum disorder. *Hum Mutat*. 2011;32(1):59–69. doi:10.1002/humu.21388
22. *Phenotype-Genotype Relationships in PEX10-Deficient Peroxisome Biogenesis Disorder Patients D S Warren 1*, Wolfe BD, Gould SJ.
23. Steinberg S, Chen L, Wei L, et al. The PEX gene screen: molecular diagnosis of peroxisome biogenesis disorders in the Zellweger syndrome spectrum. *Mol Genet Metab*. 2004;83(3):252–263. doi:10.1016/j.ymgme.2004.08.008
24. Turner CLS, Bunyan DJ, Simon Thomas N, et al. Zellweger syndrome resulting from maternal isodisomy of chromosome 1. *Am J Med Genet A*. 2007;143(18):2172–2177. doi:10.1002/ajmg.a.31912
25. Régal L, Ebberink MS, Goemans N, et al. Mutations in PEX10 are a cause of autosomal recessive ataxia. *Ann Neurol*. 2010;68(2):259–263. doi:10.1002/ana.22035
26. Ebberink MS, Csanyi B, Chong WK, et al. Identification of an unusual variant peroxisome biogenesis disorder caused by mutations in the PEX16 gene. *J Med Genet*. 2010;47(9):608–615. doi:10.1136/jmg.2009.074302
27. Harper CC, Berg JM, Gould SJ. PEX5 binds the PTS1 independently of Hsp70 and the Peroxin PEX12*. *J Biol Chem*. 2003;278(10):7897–7901. doi:10.1074/jbc.M206651200
28. Gaussmann S, Gopalswamy M, Eberhardt M, et al. Membrane interactions of the peroxisomal proteins PEX5 and PEX14. *Front Cell Dev Biol*. 2021:9–2021. doi:10.3389/fcell.2021.651449.

29. Schliebs W, Saidowsky J, Agianian B, Dodt G, Herberg FW, Kunau WH. Recombinant human peroxisomal targeting signal receptor PEX5: Structural basis for interaction of PEX5 with PEX14*. *J Biol Chem*. 1999;274(9):5666–5673. doi:10.1074/jbc.274.9.5666
30. Waterham HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. *Biochimica et Biophysica Acta*. 2012;1822 (9):1430–1441. doi:10.1016/j.bbadis.2012.04.006
31. Lee PR, Raymond GV. Child neurology: zellweger syndrome. *Neurology*. 2013;80(20):e207–e210. doi:10.1212/WNL.0b013e3182929f8e
32. Barøy T, Koster J, Strømme P, et al. A Novel Type of Rhizomelic Chondrodysplasia Punctata, RCDP5, Is Caused by Loss of the PEX5 *Long Isoform Downloaded From*; 2015. Available from: http://hmg.oxfordjournals.org/. Accessed August 12, 2025.
33. Ali M, Khan SY, Rodrigues TA, et al. A missense allele of PEX5 is responsible for the defective import of PTS2 cargo proteins into peroxisomes. *Hum Genet*. 2021;140(4):649–666. doi:10.1007/s00439-020-02238-z
34. Pronicka E, Piekutowska-Abramczuk D, Ciara E, et al. New perspective in diagnostics of mitochondrial disorders: two years' experience with whole-exome sequencing at a national paediatric centre. *J Transl Med*. 2016;14(1). doi:10.1186/s12967-016-0930-9