Chia-Ling Wu
Sex Assigned at Birth: Female
Date of Birth: 06/15/2019
Sample ID: SM09123
Sample Type: BLOOD
Collection Date: 02/01/2024
Received Date: 02/03/2024

Clinic: Medical Genetics Center
Physician: David Valle, M.D.
Phone: 510-555-0000
NPI: 1234567890

Requisition ID:
RQ-0000059
Report Number:
RP235
Report Date:
03/19/2025

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TEST INFORMATION

MyOme Rare Disease, Whole Genome Analysis, Trio

Indication for testing: ataxia, developmental delay, feeding difficulties, hearing loss, hypotonia, osteopenia

Positive — Clinically relevant variant(s) detected

LOCATION	CONDITION (MODE OF INHERITANCE)	VARIANT	ZYGOSITY	INHERITED FROM	CLASSIFICATION
PEX1	Peroxisome biogenesis disorder (Autosomal Recessive)	c.2916del, p.Gly973AlafsTer16	Heterozygous	Paternal	Pathogenic
PEX1	Peroxisome biogenesis disorder (Autosomal Recessive)	c.1359+601A>G	Heterozygous	Maternal	Uncertain Significance

INTERPRETATION

A pathogenic variant was detected in the PEX1 gene. A variant of uncertain significance was detected in the PEX1 gene.

Two heterozygous variants, one pathogenic and one of unknown significance, were identified in PEX1 which may be consistent with the clinical signs and symptoms noted for this individual. The data are consistent with these variants being in trans: one inherited from the mother and one from the father.

NEXT STEPS

- These results should be interpreted in the context of this individual's clinical findings, family history, and other laboratory data.
- Genetic counseling is recommended to discuss the significance of these results.

MyOme, Inc.
1455 Adams Drive, #1150
Menlo Park CA 94025
Email: clinical@myome.com
Phone: +1-628-265-3818

Lab Director:
Brynn Levy M.Sc.(Med)., Ph.D., FACMG
CLIA #05D2203070 CAP #8939502

VARIANT SUMMARY

PEX1 gene, NM_000466.3:c.2916del, p.Gly973AlafsTer16, Pathogenic

EVIDENCE

Frameshift variant p.Gly973AlafsTer16 in PEX1 leads to a premature stop codon and is predicted to undergo nonsense-mediated decay resulting in a truncated or absent protein. Loss of function is an established disease mechanism for this gene. This variant is present in population databases (gnomAD: 0.011%). ClinVar has an entry for this variant and clinical labs have classified this variant as pathogenic/likely pathogenic (Variation ID: 189043). This variant has been reported in the literature in individuals with PEX1-related disease, including patients seen homozygous and phase unknown with other pathogenic variants in the PEX1 gene (PMID: 12032265, 19105186, 21031596, 33708531, 34534157). Based on the evidence above and according to the ACMG/AMP variant interpretation guidelines, this variant has been classified as pathogenic for PEX1-related disease.

GENE INFORMATION

This gene encodes a member of the AAA ATPase family, a large group of ATPases associated with diverse cellular activities. This protein is cytoplasmic but is often anchored to a peroxisomal membrane where it forms a heteromeric complex and plays a role in the import of proteins into peroxisomes and peroxisome biogenesis. Alternatively spliced transcript variants have been found for this gene [provided by RefSeq, Sep 2013]. Pathogenic variants in the PEX1 gene are known to cause peroxisome biogenesis disorder. (PMID: 22871920, 9398847) This condition is characterized by neurodevelopmental disorders, hypotonia, vision and hearing loss, liver dysfunction, and skeletal abnormalities. (PMID: 17055079, 26750748) There is variable presentation and severity ranging from severe neonatal presentation to milder adult-onset forms. PEX1 related peroxisome biogenesis disorder is inherited in an autosomal recessive manner.

PEX1 gene, NM_000466.3:c.1359+601A>G, Uncertain Significance

EVIDENCE

Non-canonical splice variant c.1359+601A>G located in intron 6 of the PEX1 gene is predicted by computational tools to create a cryptic splice site. This could lead to disrupted production of the PEX1 gene product. This variant is absent from large population databases, including gnomAD. This variant was not found in ClinVar. This variant has not been reported in the literature. Based on the evidence above and according to the ACMG/AMP variant interpretation guidelines, this variant has been classified as a variant of uncertain significance. Additional information is needed to resolve the significance of this variant.

GENE INFORMATION

This gene encodes a member of the AAA ATPase family, a large group of ATPases associated with diverse cellular activities. This protein is cytoplasmic but is often anchored to a peroxisomal membrane where it forms a heteromeric complex and plays a role in the import of proteins into peroxisomes and peroxisome biogenesis. Alternatively spliced transcript variants have been found for this gene [provided by RefSeq, Sep 2013]. Pathogenic variants in the PEX1 gene are known to cause peroxisome biogenesis disorder. (PMID: 22871920, 9398847) This condition is characterized by neurodevelopmental disorders, hypotonia, vision and hearing loss, liver dysfunction, and skeletal abnormalities. (PMID: 17055079, 26750748) There is variable presentation and severity ranging from severe neonatal presentation to milder adult-onset forms. PEX1 related peroxisome biogenesis disorder is inherited in an autosomal recessive manner.

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TEST METHODS

- Specimen receipt, accessioning, data analysis, and interpretation is performed by MyOme Inc., 1455 Adams Drive, Suite 1150, Menlo Park, CA 94025, CLIA# 05D2203070. Whole Genome Sequencing, excluding data analysis and interpretation, is performed by Broad Clinical Labs LLC, 27 Blue Sky Dr, Burlington, MA 01803, CLIA#22D2055652.
- Genomic DNA obtained from submitted samples is sequenced using Illumina technology. Reads are aligned to the NCBI GRCh38 reference assembly
- Information about the patient's phenotype is used to prioritize variants across a large number of genes. Variants are interpreted and reported based on the standards and guidelines set forth by the American College of Medical Genetics and Genomics (ACMG). Classification categories include pathogenic (P), likely pathogenic (LP), variants of unknown significance (VUS), likely benign (LB) and benign (B). Reported variants only include those which are classified as P, LP, or VUS, overlap with the tested individual's indication for testing and are consistent with the expected pattern of inheritance (when parental samples are submitted).
- All reported variants are confirmed by a secondary technology: SNVs are confirmed using Sanger sequencing; CNVs are confirmed using arrays, MLPA or PCR depending on the nature of the copy number variant.
- Mean depth of coverage: 35.8X; 95.3% of bases with coverage of at least 10X.

TEST LIMITATIONS

- This test is designed to detect clinically relevant single-nucleotide variants, small insertions and deletions, and copy number variants (CNVs) across the genome. There are certain regions that are not well covered and will not be analyzed such as segmentally duplicated regions. Regions of homozygosity (ROH) are reported when greater than 5 Mb and determined to be clinically significant.
- The sensitivity of this test to detect deletions and duplications may vary depending on the depth of coverage, the size of the variant or other inherent sequence properties. For example, sensitivity to detect all CNVs 50-100 bp in size and duplications < 1kb is reduced.
- This test does not interrogate mitochondrial DNA.
- This analysis does not detect tandem repeats, balanced alterations (reciprocal translocations, Robertsonian translocations, inversions, and balanced insertions) or other complex structural variants, methylation abnormalities, genomic imbalances in segmentally duplicated regions and mosaicism; possible cases of mosaicism may be investigated at the discretion of the laboratory director. Sensitivity to detect variants may be reduced in low complexity regions such as homopolymer regions.
- A history of stem cell or bone marrow transplantation, or recent blood transfusion may impact the accuracy of the results.
- Like most tests, this test carries a risk of false negative or false positive results, which may be caused by, without limitation, sample contamination from biological or non-biological sources, specimen marking issues, rare genetic variants interfering with analysis, and other technical issues and limitations.

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DISCLAIMERS

- This test was developed, and its performance characteristics were determined, by MyOme, Inc., a clinical laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and College of American Pathologist (CAP) accredited to perform high complexity clinical laboratory testing. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA).
- Like most tests, this test carries a risk of false negative or false positive results. Testing is unavailable for samples damaged by human error, lost/destroyed due to weather, transit issues or other problems beyond the control of MyOme. Test results should always be interpreted by a clinician in the context of clinical and familial data with the availability of genetic counseling when appropriate. MyOme is not responsible for the content of third-party websites referenced in this report.
- The interpretation of variants is based on our current understanding of the genome. These interpretations may change over time as more information about these alterations becomes available. Possible diagnostic errors include variant call errors, sample misidentification, and other sources.

REVIEWED BY

MyOme

MyOme Example Lab Director

03/19/2025

Date

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