

PATIENT

Legal Name: Patient, Sample
Accession #: 00-300896
DOB: 08/19/2015
Sex Assigned at Birth: Male
MRN: N/A
Indication: Diagnostic

TEST INFORMATION

Portal Order #: 0000000
Family #: 0000000
Specimen #: N/A
Specimen type: Blood EDTA
Collection date: 01/05/2026
Received date: 01/05/2026
Test Started: 01/05/2026
Final Report: 01/29/2026

MEDICAL PROFESSIONAL

Sample Doctor
Sample Facility

ADDITIONAL RECIPIENTS

Sample Genetic Counselor

UNCERTAIN: Candidate: Variant of potential clinical relevance detected

Reportable Findings

Single gene variants	Contiguous gene deletions/duplications	Mitochondrial genome
1(1)*	None	Not Ordered

* genes(variants)

Indication for Testing

Autism, developmental regression, seizures

Results

Gene (RefSeq ID)	Characterized/Uncharacterized Gene	Relevant Associated Syndrome	Mode of Inheritance	Genotype	Variant	Variant Classification
PABPC1 (NM_002568)	Uncharacterized	N/A	Autosomal dominant	Heterozygous, <i>de novo</i>	c.1900C>G (p.P634A)	Variant of Uncertain Significance

Interpretation

- Overall, the evidence suggests it is uncertain if the identified **PABPC1** variant is the cause of the patient's clinical symptoms. Clinical correlation is recommended.

Notes

- If secondary findings were requested, results were issued in a separate report.
- Please note this assay is not intended to confirm previously detected copy number variants.
- Genetic counseling is a recommended option for all patients undergoing genetic testing.

Electronically Signed By Sample Director, on 01/29/2026 at 0:00:00 PM

All content hereafter is supplemental information to the preceding report.

Samples Received, Metrics, and Coverage

Family Member (Accession #)	Affected	Depth of coverage	
		% Bases ≥ 10x	% Bases ≥ 20x
Proband* (00-300896)	Yes	98.5	98.2
Mother* (00-300898)	No	98.6	98.4
Father* (00-300907)	No	98.6	98.3

*Exome sequencing performed. Coverage is only available for individuals with exome sequencing.

All family members with samples received are represented in this table. Complete coverage data for the proband can be e-mailed or made available for download through AmbryPort by request.

Analyses Performed

i) Full exome sequencing, bioinformatics, filtering and manual review based on dominant and recessive inheritance models was performed. Medical review of characterized genetic etiologies did not reveal any variants with likely clinical relevance.

ii) Medical review of uncharacterized genes* and gene-disease relationships for potential candidate gene findings revealed variants with likely clinical relevance.

*Uncharacterized genes are not currently established to underlie Mendelian genetic conditions. An uncharacterized gene will be classified as a "candidate" when sufficient evidence, based on Ambry's comprehensive, rule-based scoring criteria, is available (Farwell Hagman, 2017).

Raw Data

A table with additional variant filtering details can be found with the raw data filtered variant list (if requested). This list includes clinically irrelevant characterized genes and uncharacterized genes which could not be ruled out (if analyzed); these variants are not systematically confirmed via Sanger sequencing. The filtered variant list can be requested via this form

(www.ambrygen.com/file/material/view/1262/Raw_Sequence_Data_Consent_0619_final.pdf).

PABPC1 Gene Details

Gene Symbol	RefSeq ID	Genomic Coordinates (GRCh37)	Genomic Size (bp)	Total Exons	Coding Exons	Number of Amino Acids
PABPC1	NM_002568	chr8:101715144-101734315	19172	15	14	636 aa

Lines of evidence to evaluate the involvement of PABPC1 in the patient's clinical phenotype:

PABPC1 is an uncharacterized gene:

The PABPC1 gene currently has limited evidence for involvement in human Mendelian disease based on the ClinGen clinical validity assessment criteria (aka "uncharacterized") (Rehm, 2015). The functional consequences of presumably deleterious variants within uncharacterized genes are typically unknown, including whether mutation mechanism is gain-of-function or dominant negative versus loss-of-function or whether a phenotype is produced in a dominant or recessive manner. While evidence may support the involvement with a patient's phenotype, not all variants in uncharacterized genes can be definitively stated as disease-causing until further functional studies and multiple case reports have proven their clinical significance.

As part of an ongoing process to better understand the clinical significance of the reported candidate gene finding in your patient and to characterize novel candidate disease genes, Ambry participates in data sharing and follow-up research collaborations with physicians, clinics, and researchers. Please let us know if you would like us to enroll your patient in a research collaboration if one is/becomes available by e-mailing ClinicalAssistants@ambrygen.com.

Supportive evidence:

Gene function:

The PABPC1 gene is located on chromosome 8q22.3 and encodes the polyadenylate-binding protein 1. PABPC1 is expressed ubiquitously in the adult human body. PABPC1 maintains a quality control surveillance mechanism that detects and degrades mRNAs with premature truncation mutations via nonsense-mediated decay. By binding the poly-A tail of mRNAs, polyadenylate-binding protein 1 promotes ribosome recruitment and regulates nonsense-mediated decay (Behm-Ansmant, 2007, Peixeiro, 2012).

Previously-reported patients:

Six individuals with de novo variants in PABPC1 have been reported in the literature, two missense variants from a large cohort without specific phenotypic information (Turner, 2019), and three missense variants and a single amino acid deletion in a well-phenotyped cohort (Wegler, 2022). Consistent features of affected individuals include developmental delay with both expressive speech and motor delay, intellectual disability, and behavioral abnormalities. Variable features included seizures, dysmorphic features, brain MRI abnormalities, hearing impairment, and feeding difficulties. In Ambry's internal cohort, patients with de novo alterations are reported with developmental delay, autistic features, and behavioral problems.

In vivo animal models:

PABPC1 is highly expressed in the developing mouse brain and shows decreased expression after birth. Knockdown of Pabpc1 in mouse brains impaired neural progenitor cell proliferation, suggesting an essential role for PABPC1 in neuronal development (Wegler, 2022).

PABPC1 c.1900C>G (p.P634A)

Variant description:

The c.1900C>G (p.P634A) alteration is located in exon 14 (coding exon 14) of the PABPC1 gene. This alteration results from a C to G substitution at nucleotide position 1900, causing the proline (P) at amino acid position 634 to be replaced by an alanine (A).

Population frequency:

This variant was not reported in population-based cohorts in the Genome Aggregation Database (gnomAD).

Conservation:

This amino acid position is highly conserved in available vertebrate species.

In silico:

The *in silico* prediction for this alteration is inconclusive.

Missense constraint:

This missense alteration is located in a region that has a low rate of benign missense variation (Lek, 2016; Firth, 2009).

Family inheritance:

Gene (RefSeq ID)	Variant	Exon	Proband (00-300896)	Mother (00-300898)	Father (00-300907)	Inheritance
PABPC1 [^] (NM_002568)	c.1900C>G (p.P634A)	CDS 14	Heterozygous	Negative	Negative	De novo [‡]

[^]Variant(s) confirmed by automated fluorescence dideoxy sequencing (aka "Sanger") sequencing.

[‡]Note that the possibility of germline mosaicism cannot be ruled out.

Based on the available evidence, the clinical significance of the PABPC1 c.1900C>G (p.P634A) variant is uncertain.

Report References

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- Wegler M, *et al.* (2022) *Genet Med* **24**(8):1761-1773. PMID:35511136

Resources Used for Bioinformatics, Medical Review Filtering, and Reporting

- Ambry Genetics Variant Classification Scheme: <http://www.ambrygen.com/variant-classification>
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ExomeNext® Assay Information

General Information: Ambry's ExomeNext® is a cost-effective, comprehensive, integrated whole exome sequencing assay designed to increase the diagnostic yield for genetic disorders that have eluded diagnosis using traditional diagnostic approaches. The exome represents all the protein-coding exons. It is estimated that exons contain about 85% of disease-causing variants. Whole-exome sequencing has been successfully applied to identify both inherited and *de novo* variants in a diverse variety of autosomal dominant, recessive, and X-linked disorders. In addition to the primary analysis, which is performed with the purpose of uncovering the underlying genetic cause for a given clinical presentation, the exome testing may also be utilized to detect secondary findings, which are pathogenic or likely pathogenic variants in select genes that lead to diseases unrelated to the patient's present clinical presentation.

Result Reports: A primary clinical report will only be generated for the proband regardless of number of family members submitted. However, it may be possible to infer information about family members' results based on the proband's report. Pathogenic variant(s) likely to factor into the patient's current clinical presentation are always reported as a relevant finding. Variants previously detected in the proband (not family members) that are provided at the time of testing will receive a report comment if the variant is detected by the assay (limit four variants in three genes). Copy number changes, somatic variants, and variants classified as benign or pseudodeficiency alleles are not eligible for comment. Common reasons a variant may not meet exome reporting criteria include inconsistent zygosity or inheritance, poor molecular support, and/or insufficient clinical overlap with the proband's reported features. Up to 5 genes of interest provided on the TRF were closely reviewed and all clinically significant variants are included on the report. As new scientific information becomes available on a regular basis, this could alter the interpretation of previously reported results. In the event of a change in interpretation, an unsolicited reclassification/amended report may be issued to the ordering clinician. Secondary findings within the ACMG recommended gene list are reported separately unless opted out (Kalia, 2017; Lee, 2025). Expanded childhood onset secondary findings are also available for prenatal exome orders. Gender identity (if provided) is not used in the interpretation of results, and sex assigned at birth is used in the interpretation of results only when necessary.

Test Limitations: This test was developed and its performance characteristics determined by Ambry Genetics. It has not been cleared or approved by the US Food and Drug Administration (FDA), which does not require this test to go through premarket review. It should not be regarded as investigational or for research. This test should be interpreted in context with other clinical findings and does not represent medical advice. Any questions or concerns regarding interpretation of results should be referred to a genetic counselor, medical geneticist, or other skilled medical provider. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. The following types of variants are detectable: nucleotide substitutions, small deletions/insertions, small indels, and gross deletions/duplications. The overall coverage of each gene varies and each individual may have slightly different coverage yield. Accurate exon-level gross deletion and duplication detection depends on several factors such as inherent sequence properties of the targeted regions, including shared homology, exon size, depth-of-coverage, capture efficiency, and degree of read depth variation in the reference samples. Therefore, the specificity and sensitivity of gross deletions and duplications may be reduced. Exome sequencing is not intended to analyze the following types of variants: gross rearrangements, deep intronic variations, long repeat sequences, portions of genes with highly homologous pseudogenes, trinucleotide repeat sequences, variants involved in tri-allelic inheritance, certain mitochondrial genome variants, epigenetic effects, oligogenic inheritance, and X-linked recessive variants in females who manifest disease due to skewed X-inactivation. A negative result from the analysis cannot rule out the possibility that the tested individual carries a rare undetected variant. Although molecular tests are highly accurate, rare diagnostic errors may occur such as sample mix-up, erroneous paternity identification, technical errors, clerical errors, and genotyping errors. Genotyping errors can result from trace contamination of PCR reactions, rare genetic variants that may interfere with analysis, or other sources.

Methodology: Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's provided specimen. Samples are prepared using the IDT xGen Exome Research Panel V1.0 (IDT). Each DNA sample is sheared, adaptor ligated, PCR-amplified and incubated with exome baits. Captured DNA is eluted and PCR amplified. Final quantified libraries are seeded onto an Illumina flow cell and sequenced using paired-end, 150 cycle chemistry on the Illumina NovaSeq, NextSeq or HiSeq. Initial data processing, base calling, alignments and variant calls are generated by various bioinformatics tools using genome assembly GRCh37/hg19. Data is annotated with the Ambry Variant Analyzer tool (AVA), including: nucleotide and amino acid conservation, population frequency, and predicted functional impact. Data analysis is focused on small insertions and deletions, canonical splice site variants, and non-synonymous variants. Gross deletion/duplication analysis is assessed for proband only for genes within the targeted exome using a custom pipeline based on coverage and/or breakpoint analysis from NGS data and is followed by a confirmatory orthogonal method as needed. The following sites are used to search for previously described variants: the Human Gene Mutation Database (HGMD), gnomAD, and online search engines (e.g., PubMed). Variants are then filtered further based on applicable inheritance models. Co-segregation studies are performed if family members are available. All relevant findings undergo confirmation either by automated fluorescence dideoxy (aka "Sanger") sequencing or via coverage and alternate read ratios above established confidence thresholds with manual review by molecular geneticists using integrated genomics software (IGV). Gross deletions/duplications are confirmed by SNP Microarray (Affymetrix® CytoScan™ HD Array), in-house targeted array, MLPA, or Sanger sequencing. Co-segregation results may be confounded by many factors which cannot be completely ruled out including reduced penetrance, age-of-onset, and/or variable expressivity. Relevant findings are evaluated from among the genes in Ambry's internal, dynamic gene database which classifies genes as characterized or uncharacterized Mendelian disease genes based on clinical validity (Smith, 2017). Characterized genes are those currently known to underlie at least one Mendelian genetic condition. Uncharacterized genes are those with no or insufficient evidence to be associated with a Mendelian genetic condition. Characterized genes are analyzed first, followed by reflex analysis of uncharacterized genes for potential identification of a candidate gene finding. The analysis of candidate gene findings is only performed when an informative trio is received for testing and focuses on *de novo*, autosomal recessive, or X-linked inherited variants. Each variant remaining after inheritance model filtering is manually analyzed to identify the most likely causative variant(s). Interpretation is based on the clinical and family information provided by the referring provider and the current genetic knowledge at the time of reporting. Screening and analysis of known mtDNA pathogenic variants related to the proband's clinical phenotype is included if ordered. Amplification of the entire mitochondrial genome is carried out by long distance PCR and sequencing of mtDNA is performed separately on Illumina MiSeq. If ordered, ribonucleic acid (RNA) is isolated from the patient's whole blood. RNA is converted to complementary DNA (cDNA) by reverse transcriptase polymerase chain reaction (RT-PCR). RNA analysis is performed for reportable germline DNA variants expected to affect splicing, provided such studies are likely to meaningfully inform variant classification. Variants in genes with limited expression in whole blood, limited gene-disease validity, or an inconsistent mechanism of disease do not qualify for RNA analysis. Additionally, secondary findings variants do not qualify for RNA analysis. For eligible variants, primers are designed to amplify the relevant region of the pertinent gene from cDNA. The splicing patterns in variant carriers are then compared to control individuals to identify aberrant splicing. The presence of aberrantly spliced RNA transcripts meeting quality thresholds is incorporated as evidence for the assessment and classification of the DNA variants.

Analysis of Variants: The following lines of evidence are used to assess the pathogenicity of a variant: presence in affected and healthy populations, co-segregation, functional studies, variant type, conservation, in silico predictions, and presence in a functional protein domain.

Analytical range: Approximately 75% of bases are expected to have quality scores of Q30 or higher, which translates to a base-calling error rate of 1:1000 and accuracy of 99.9%. Additionally, 90% and 95% of the exome will be covered at $\geq 20\times$ and $\geq 10\times$ respectively under current run conditions, generally sufficient for high quality heterozygous and homozygous variant calling for germline variants. For any given individual $\sim 10\%$ of the targeted exome is not sequenced well enough to make a confident call. Each individual may have slightly different coverage yield distributions within the exome. Exons plus at least 2 bases into the 5' and 3' ends of all the introns are analyzed and reported. The pipeline detects deletions and duplications >5 exons in size in sequences with sufficient resolution. The minimum depth of coverage for targeted mitochondrial bases is 1,000X.

Understanding Your Uncertain Exome Sequencing Test Result

INFORMATION FOR PATIENTS WITH ONE OR MORE UNCERTAIN RESULTS

Genes	Genes are instructions for how our bodies work and develop. Everyone has two copies of each gene, one from each parent. Variants (changes) in certain genes can cause genetic conditions. These gene changes may be passed down in families or not. Even if there is no history of the specific condition in your family, it can still be caused by a change in a gene.
Exome Sequencing	Exome sequencing is a test designed to look for genetic changes in genes that may be the cause of an existing medical condition. Some genetic tests just look for common mutations, while others may just look for changes in common genes. Exome sequencing analyzes all genes known to cause medical conditions.
Result	Exome sequencing found one or more variants (or changes) in one or more genes, but it is not clear if this test result is the cause for your existing medical condition.
Diagnosis	This testing does not change your diagnosis. If you have been diagnosed with a specific condition, that remains the same.
Reclassification	Collecting information about an uncertain result is an ongoing process. It is possible that your result may be better understood in the future. The healthcare provider that ordered your test will be notified if new information becomes available about your uncertain result.
Patient for Life	As part of Ambry's Patient for Life program, we keep your results on file. While we did not find a genetic cause of your medical condition today, future genetic discoveries may provide enough information to update your result. We will notify your healthcare provider if any clinically significant results are identified in the future.
Family Members	Your report will indicate if testing family members may help us learn more about your specific result.
Management Options	Management options vary by condition and other factors. Talk to your healthcare provider about which may be right for you.

Please discuss this information with your healthcare provider. The field of genetics is continuously changing, so updates related to your genetic testing result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.