Helix

Helix Whole Exome+ Sequencing

EXPR1, EXDU1, EXTR1, EPAR1 I Diagnostic Test

Overview

Test Description

The Helix Whole Exome+ Sequencing test evaluates the coding regions of the human genome including the mitochondrial genome to identify genetic variants associated with the clinical features described at ordering. This test is available as Proband-only (EXPR1), Duo (EXDU1), or Trio (EXTR1). When parental samples are provided (using EPAR1 for ordering in EHR), segregation analysis is performed to aid in variant interpretation. Mitochondrial genome analysis is included by default, with heteroplasmy detection at ≥2% for blood and buccal specimens and ≥3% for saliva.

Genetics Information

This test utilizes next-generation sequencing to detect single nucleotide variants, insertions and deletions up to 20 bp, and copy number variants in genes associated with the symptoms described at ordering. The mitochondrial genome is also analyzed for reportable variants with heteroplasmy detection levels ≥2% for blood and buccal specimens, ≥3% for saliva specimens.

Indications For Testing

Individuals with clinical features suggestive of a genetic etiology where broad genetic evaluation is clinically indicated.

Clinical Descriptions

Whole exome sequencing evaluates the protein-coding regions of the genome, which comprise approximately 1-2% of the genome but harbor an estimated 85% of disease-causing variants. This test is designed for individuals with clinical features suggestive of a genetic condition, including but not limited to developmental delay, intellectual disability, congenital anomalies, neurological conditions, and other suspected Mendelian disorders.

The analysis is guided by the clinical features provided at the time of ordering, which are then translated into an HPO term guided gene list. Identification of a pathogenic variant may establish a molecular diagnosis, inform prognosis and management, and facilitate genetic counseling for the patient and their family members.

When parental samples are provided (Duo or Trio), segregation analysis enhances variant interpretation by identifying de novo variants (Trio), confirming phase, and clarifying inheritance patterns.

Clinical Descriptions

Mitochondrial genome analysis is performed by default, enabling detection of variants associated with mitochondrial disorders. If the mother's sample is available, it is included as a comparator during mitochondrial analysis.

Genome-wide copy number analysis is also included to evaluate for clinically relevant copy number variants across the genome, independent of HPO terms.

Test Details

Genes Tested

All protein-coding genes in the human nuclear genome are evaluated. Analysis and reporting are guided by the clinical features (HPO terms) described at ordering. The mitochondrial genome is also analyzed.

Methods & Limitations

Extracted DNA is enriched for targeted regions and then sequenced using the Helix Exome+ (R) assay on an Illumina DNA sequencing system. Data is then aligned to a modified version of GRCh38 and all genes are analyzed using the MANE transcript and MANE Plus Clinical transcript, when available. Small variant calling is completed using a customized version of Sentieon's DNAseq software, augmented by a proprietary small variant caller for difficult variants. Copy number variants (CNVs) are then called using a proprietary bioinformatics pipeline based on depth analysis with a comparison to similarly sequenced samples. Genome-wide copy number analysis is also performed to detect clinically significant large-scale copy number changes, independent of the clinical features provided at ordering. Reportable variants in PMS2 exons 11-15 are confirmed by PacBio long reads. Both the MSH2 Boland inversion (exons 1-7) and the BRCA2 Alu insertion are detected by identifying discordant read-pairs spanning the breakpoints. The mitochondrial genome is sequenced and analyzed for variants with heteroplasmy levels ≥2% for blood and buccal specimens and ≥3% for saliva specimens; when the mother's sample is available, it is utilized for mitochondrial analysis. For Duo and Trio orders, parental samples are sequenced and used for segregation analysis to aid in variant interpretation, including identification of de novo variants. Interpretation is performed by Revvity, Inc. (CLIA #39D0673919, Address 250 Industry Drive, Suite 400 Pittsburgh, PA 15275-1017). Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available. Interpretation is limited to the transcripts indicated on the report, +/- 10 bp into intronic regions, except as noted below. Helix variant classifications include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Variants classified as pathogenic, likely pathogenic, or VUS are included in the report. Variants in genes of uncertain significance are not reported unless highly suspicious. Unless a mitochondrial disorder is indicated, only pathogenic and likely pathogenic mitochondrial variants are included. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Benign and likely benign variants are not reported but are available upon request. Risk estimations and management guidelines included in this report are based on analysis of primary literature and recommendations of applicable professional societies, and should be regarded as approximations.

Based on validation studies, this assay delivers > 99% sensitivity and specificity for single nucleotide variants and insertions and deletions (indels) up to 20 bp. Larger indels and complex variants are also reported but sensitivity may be reduced. Most deletions and duplications that are at least three exons in length are reliably detected, depending on the context of the underlying sequence. This test may not detect variants in challenging regions (such as short tandem repeats, homopolymer runs, and segmental duplications), CNVs spanning fewer than 3 exons, chromosomal aneuploidy, or variants present at levels suggestive of mosaicism. Phasing will be attempted and reported, when possible. Structural rearrangements such as inversions, translocations, complex rearrangements, and gene conversions are not tested in this assay unless explicitly indicated. Additionally, deep intronic, promoter, and enhancer regions may not be covered. It is important to note that this assay cannot detect all variants known to increase disease risk, and that a negative result does not guarantee that the tested individual does not carry a rare, undetectable variant in the genes analyzed. In addition to this test, providers may order the Helix Hereditary Actionable Diseases Screen for any of the submitted samples, which reports secondary findings in accordance with ACMG recommendations. Any potential incidental findings outside of the genes and conditions evaluated will not be identified, nor reported. The results of a genetic test may be influenced by various factors, including bone marrow transplantation, blood transfusions, or in rare cases, hematolymphoid neoplasms.

Gene Specific Notes:

For specific questions regarding genes, reference transcripts, or specific regions covered, contact Helix Clinical Support at clinicalsupport@helix.com.

Disclaimer

This test was developed and validated by Helix, Inc. with interpretation services provided by Revvity, Inc. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The Helix laboratory is accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA #: 05D2117342) to perform high-complexity clinical tests. This test is used for clinical purposes. It should not be regarded as investigational use only or for research use only.

Interpretation

Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

- Phenotype-Driven Prioritization — Variants are prioritized for reporting based on their correlation with the patient's clinical phenotype, leveraging available clinical information to focus analysis on the most relevant findings.

- Standardized Classification Framework — All variant classification is performed in accordance with ACMG and ClinGen guidelines, ensuring consistency, evidence-based interpretation, and clinical validity.

- Structured Review & Documentation — Personnel follow established procedures for variant interpretation, with all supporting evidence documented in a structured, consistent format. Evidence for pathogenicity and final variant classifications are reviewed by ABMGG-trained and board-certified laboratory directors (or equivalent) to confirm classification accuracy and appropriateness for reporting.

Reclassification

Helix reviews variant classifications annually when they arise in routine processes and upon request from providers. The timing of re-review depends on clinical risk. Providers can request a variant re-review by contacting Helix Customer Support. If a classification by Helix is updated, Helix identifies affected past patients and issues revised reports. Updated results are communicated to providers prior to results being uploaded to the EHR, and patients are notified through the EHR patient portal.

Variant Evaluation

Variant classification is performed using the guidelines set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, with modifications as suggested by domain specific Expert Panels of the Clinical genome Resource (ClinGen) when available. Variant pathogenicity is categorized as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic.

Laboratory Details

Turnaround Time - Standard	Typically 3 to 5 weeks	**Turnaround Time - Requery (SOQO®)**	Typically 1 to 3 weeks if all samples in the order qualify as SOQO® orders
Available in NY State	Yes	**Procedure Code**	EXPR1: H00126-8 EXDU1: H00226-8 EXTR1: H00326-8 EPAR1: H00426-8
Test Classification	This test was developed, and its performance characteristics determined, by Helix, Inc. in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.		
Regulatory Information	• CLIA Complexity: High • Test Classification: Non-Waived/ Laboratory Developed Test		
CLIA Category	Chemistry / Routine Chemistry		
Performing Laboratory Information	• CLIA Laboratory Number: 05D2117342 • Laboratory Hours of Operation: Monday-Saturday (7AM-10:30PM PST) • Address: 10170 Sorrento Valley Road, Suite 100, San Diego, CA 92121 • Helix Customer Support: (844) 211-2070 • Email: support@helix.com • Interpretation Services Provided By: Revvity, Inc. (CLIA 39D0673919 Address 250 Industry Drive, Suite 400 Pittsburgh, PA 15275-1017		