Helix

THIS IS A DIAGNOSTIC TEST

Helix Whole Exome+ Sequencing, Trio

Patient Name: John Doe	**Patient ID:** XXXXXXXXX	**Provider Name:** HELIX GENOMICS	**Order Date:** 07-20-2026
Date of Birth: 01-01-1970	**Helix ID:** XXXXXXXXX	**Collection Date:** 07-20-2026	**Report Date:** 08-10-2026

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
LIKELY PATHOGENIC	FBN1	c.7025_7026del	p.Glu2342GlyfsTer24	Heterozygous (de novo)	AD

One de novo Likely Pathogenic variant was detected in the FBN1 gene.

Pathogenic sequence variant related to phenotype detected.No reportable copy number variants (CNVs) related to phenotype detected. Correlation with clinical profile and family history is required.

HPO terms used in this analysis
Joint laxity, Pectus excavatum, arachnodactyly, mitral valve prolapse

These results indicate a predisposition to, or diagnosis of, autosomal dominant FBN1-related conditions. This finding is consistent with the patient's clinical presentation.

The FBN1 gene is associated with the following condition(s):
- autosomal dominant Marfan syndrome (MedGen UID: 44287)
- autosomal dominant familial thoracic aortic aneurysm and aortic dissection (TAAD) (MedGen UID: 1644766)
- autosomal dominant Weill-Marchesani syndrome, type 2 (MedGen UID: 358388)
- autosomal dominant geleophysic dysplasia (MedGen UID: 481684)
- autosomal dominant stiff skin syndrome (MedGen UID: 348877)
- autosomal dominant acromicric dysplasia (MedGen UID: 78549)
- autosomal dominant progeroid and marfanoid aspect-lipodystrophy syndrome (MedGen UID: 934763)
- autosomal dominant MASS syndrome (MedGen UID: 346932)

Individuals with a pathogenic variant in FBN1 may develop Marfan syndrome, familial thoracic aortic aneurysm and aortic dissection (TAAD), Weill-Marchesani syndrome, geleophysic dysplasia, stiff skin syndrome, acromicric dysplasia, progeroid and marfanoid aspect-lipodystrophy syndrome or MASS syndrome. Clinical correlation is advised.

Marfan syndrome is a connective tissue disorder and individuals with Marfan syndrome often have very long arms, legs, fingers, and toes, and may be taller than average. The condition can also affect the heart, eyes, blood vessels, and bones, leading to problems such as aortic aneurysms (a bulging of the main blood vessel from the heart) and lens dislocation in the eyes. Individuals with Marfan syndrome may also have a curved spine, flexible joints, and a chest that sinks in or sticks out.

Familial thoracic aortic aneurysm and aortic dissection (TAAD) is a condition that affects the aorta, the large blood vessel that carries blood from the heart to the rest of the body. The walls of the aorta become weakened and can bulge, creating an aneurysm in affected indviduals, potentially leading to a rupture (aortic dissection). Symptoms can include chest pain, back pain, or shortness of breath, but some people may not notice any symptoms until a serious event occurs. Treatment often includes medications to control blood pressure and, in some cases, surgery to repair or replace the affected portion of the aorta, helping to prevent complications.

Weill-Marchesani syndrome (WMS) is a connective tissue disorder and individuals with WMS have short stature, short fingers and toes, and joint stiffness. Symptoms can also include ocular issues such as microspherophakia (small, spherical lenses), glaucoma, lens dislocation, and ultimately, severe loss of vision. WMS is typically diagnosed in childhood in individuals with short stature or ocular issues.

Geleophysic dysplasia is characterized by short stature, short limbs, and distinctive facial features such as a round face with full cheeks and a small upturned nose. Individuals with this condition often have thickened skin and joint stiffness, and can have cardiac involvement such as heart valve abnormalities. Geleophysic dysplasia is progressive and typically presents in the first year of life, with possible severe progression leading to death in early childhood.

Stiff skin syndrome is a connective tissue disorder in which affected individuals have abnormally thick and hard skin all over their bodies. This can result in joint stiffness and decreased mobility, and can sometimes also include muscle weakness.

Acromicric dysplasia is characterized by short stature, short limbs, and skin thickening. Individuals with acromicric dysplasia present with distinctive facial features and radiological findings such as delayed bone age and shortened long tubular bones.

Progeroid and marfanoid aspect-lipodystrophy syndrome is a condition that combines features of aging, connective tissue problems, and loss of

body fat. Individuals with this condition often experience premature aging, with signs such as wrinkled skin, hair loss, and joint stiffness appearing earlier than usual. They may also have physical features similar to Marfan syndrome, such as long limbs, a tall, thin build, and joint hypermobility. In addition, individuals with this syndrome often have lipodystrophy, which is the abnormal loss of fat from certain parts of the body, leading to an unusual body shape.

MASS syndrome is a connective tissue disorder that includes features such as mitral valve prolapse, myopia (nearsightedness), aortic enlargement, and skeletal similarities to Marfan syndrome but without severe cardiovascular complications. It is typically diagnosed in families with successive generations exhibiting the same features.

The age of onset, severity, and types of symptoms associated with FBN1-related conditions can vary widely, even among affected individuals from the same family.

MEDICAL MANAGEMENT recommendations and/or guidelines are available for FBN1-related conditions: PMID: 20301510, 39129620, 36322642

This variant was not identified in the maternal or paternal samples tested. Biological family members may still be at risk for carrying this variant and developing autosomal dominant FBN1-related condition(s).

The Variant Interpretation section below may provide additional details regarding the reported variant(s). Genetic test results should be interpreted in the context of an individual's personal medical and family history. It is important to note that this assay cannot detect all variants known to increase disease risk. Genomic regions not associated with the patient's clinical presentation are not analyzed or reported on this test. Genetic counseling is recommended. Clinical correlation is advised.

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.

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.

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
LIKELY PATHOGENIC	FBN1	c.7025_7026del	p.Glu2342GlyfsTer24	Heterozygous (de novo)	AD

Transcript:	Genomic Change:
NM_000138.5	NC_000015.10:g.48427747_48427748del

Variant Interpretation

This variant (NM_000138.5:c.7025_7026del p.Glu2342GlyfsTer24) results in the creation of a premature stop codon in the FBN1 gene. It is predicted to result in nonsense-mediated mRNA decay or in the production of a truncated protein, leading to loss-of-function (LOF). LOF variants in this gene are known to be deleterious (PMID: 2180284, 15254584). It is a rare variant that is absent from the large gnomAD population database (v4.1, https://gnomad.broadinstitute.org). To our knowledge, this variant has not been reported in individuals with FBN1-related conditions in the published literature. This variant is present in ClinVar (Variation ID: 3759766). In conclusion, this variant has been classified as Likely Pathogenic.

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.

Report Signed By

Matthew J Ferber, PhD, FACMGG

Helix's Sequence Once, Query Often® Model

When your provider orders a genetic test through Helix, we use our proprietary Sequence Once, Query Often® model to perform whole exome sequencing and analyze the specific genes related to the test. Helix securely stores your whole exome for future clinical use. With your permission, this allows your health care providers to order future medically necessary genetic tests from Helix without needing another sample. Instead, these tests are conducted through digital analysis of your stored genetic information.

To learn more about how Helix protects the privacy and security of your genetic information and learn more about your rights, please visit https://www.helix.com/privacy-and-policy-highlights .