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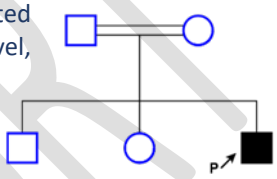
Name: John Doe
Medical Request No. 1234567

D.O.B:	dd/mm/yyyy	Referring physician:	Dr. Doctor name
Sex:	Male	Referring facility:	Medical Center, Country
Subject ID:	8xxxx	Email physician:	doctorname@email.com
Order ID:	2xxxxx	Report type:	myLifeExome
Device/ Material ID:	ARCxxxxxx	Date of report:	11/05/2024
Specimen type:	Buccal swab		
Specimen arrival date:	dd/mm/2024		

Requested Test: **myLifeExome -Solo**
Indication for test: Elevated circulating alkaline phosphatase concentration, Elevated gamma-glutamyltransferase level, Increased circulating IgE level, Pancytopenia, Severe generalized osteoporosis



Consanguineous parents: Yes
Consent for evaluation: Primary findings: Yes
Incidental findings: Yes
Carrier findings: Yes

SUMMARY OF GENETIC FINDINGS

PRIMARY	INCIDENTAL	CARRIER STATUS
Positive	Positive	Positive

Primary Findings

Primary findings describe genetic variants that are relevant to the indication for which sequencing was ordered.

Results: A homozygous pathogenic variant was identified in the SGSH gene. This result is consistent with the genetic diagnosis of autosomal recessive mucopolysaccharidosis type 3A.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
SGSH	c.697C>T; p.Arg233*	Hom	P	Mucopolysaccharidosis type 3A	AR

Incidental Findings

Incidental findings describe actionable variants in gene(s) that are unrelated to the indication for which sequencing was ordered. These findings are reported based on ACMG guidelines and ClinGen recommendations.

Results: A heterozygous likely pathogenic variant was identified in the TTN gene, A-band. This result is consistent with increased risk to develop autosomal dominant dilated cardiomyopathy type 1G.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
TTN	c.107641G>T; p.(Glu35881*)	Het	LP	Dilated cardiomyopathy type 1G (CMD1G)	AD

AD: autosomal dominant; AR: autosomal recessive; XL- X-linked, DR: digenic recessive; Het: Heterozygous; Hom: Homozygous; Hem: Hemizygous; LP: Likely Pathogenic; P: Pathogenic; RF: risk factor VUS: Variant of Uncertain Significance.

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Carrier Status

Carrier Status includes pathogenic or likely pathogenic variants which have a direct impact on reproductive risk (heterozygous variants in a gene associated with a recessive or X-linked disorder).

Results: This proband is found to be a carrier for 3 genetic conditions.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
CEP250	c.6913C>T; p.Arg2305*	Het	LP	Cone-rod dystrophy and hearing loss type 2	AR
DHTKD1	c.1671+1G>A; p.?	Het	LP	Alpha-aminoadipic and alpha-ketoadipic aciduria	AR
TPRN	c.25delT; p.Ser9fs*22	Het	LP	Deafness type 79	AR

RECOMMENDATIONS

- Genetic counselling is recommended to further explain the implications of this test result and assess family health history, which may point to health information that merits additional consideration.
- The medical genetics field is continuously evolving, so updates related to your genetic results, medical recommendations, and potential treatments may be available over time.
- Mucopolysaccharidosis type 3A is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes (i.e. carriers). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once pathogenic variants in the family are known, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing is possible. We will proceed with Sanger sequencing in the family members (affected and unaffected siblings) to establish the genetic diagnosis and further identify at-risk carriers.
- Truncating TTN variants localized in the A-band of titin protein have been associated with dilated cardiomyopathy. The transmission pattern of CMD1G in the families reported by Gerull et al. (2002) was consistent with autosomal dominant inheritance with incomplete penetrance. Cardiovascular screening of asymptomatic first-degree family members of an individual with genetic increased susceptibility risk to develop DCM can allow early detection of DCM, prompt initiation of treatment, and improvement in long-term outcome (Morales & Hershberger 2015). Clarification of the genetic status of first-degree family members of an individual with DCM can inform who is at risk and the recommended frequency of subsequent cardiovascular screening (Hershberger et al 2018).

Signatures

DETAILED INSIGHTS

Primary Findings

A homozygous pathogenic variant was identified in the SGSH gene. This result is consistent with the genetic diagnosis of autosomal recessive mucopolysaccharidosis type 3A.

SGSH (N-Sulfoglucosamine Sulfohydrolase) is a protein coding gene. This gene encodes the enzyme sulfamidase; one of several enzymes involved in the lysosomal degradation of heparan sulfate. Mutations in this gene are associated with the lysosomal storage disease mucopolysaccaridosis 3A, also known as Sanfilippo syndrome A, which results from impaired degradation of heparan sulfate. Transcripts of varying sizes have been reported but their biological validity has not been determined. An important paralog of this gene is ARSA.

	Gene/OMIM	*SGSH/605270*
	Genomic coordinate (GRCh38)	chr17:80213852G>A
	ID Transcript	NM_000199.5
	HGVS nomenclature	c.697C>T
	Protein change	p.Arg233*
	Location	exon 6/8
	Zygosity	Hom
	Function	Nonsense
	Impact	High
	ClinVar	Pathogenic, Likely Pathogenic
Allele Frequency	Local Database	N/A
	gnomAD	0.0000263
In silico Predictors	REVEL	N/A
	CADD (PHRED)	42.0
	Splice-AI	0.04
	Clinical significance	Pathogenic
	ACMG Criteria	PVS1, PM2, PM3

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; ranges from 0 to 1)= higher scores reflect greater likelihood that variant is disease- causing; CADD (PHRED)= Combined Annotation Dependent Depletion scoring, ranging from 1 to 99, Splice-AI= deep neural network that accurately predicts splice junctions from an pre-mRNA transcript (using 0.8 as high-precision cut-off).
**: The ACMG criteria are described under Methods /Variant interpretation section.*

Disease description: Mucopolysaccharidosis type 3 (MPS 3) is a multisystem lysosomal storage disease characterized by progressive central nervous system degeneration manifest as severe intellectual disability (ID), developmental regression, and other neurologic manifestations including autism spectrum disorder (ASD), behavioral problems, and sleep disturbances. Disease onset is typically before age ten years. Disease course may be rapidly or slowly progressive; some individuals with an extremely attenuated disease course present in mid-to-late adulthood with early-onset dementia with or without a history of ID. Systemic manifestations can include musculoskeletal problems (joint stiffness, contractures, scoliosis, and hip dysplasia), hearing loss, respiratory tract and sinopulmonary infections, and cardiac disease (valvular thickening, defects in the cardiac conduction system). Neurologic decline is seen in all affected individuals; however, clinical severity can vary even among members of the same family. The subtypes of MPS 3 (MPS 3A, MPS 3B, MPS 3C, MPS 3D) are distinguished by their associated enzymatic deficiencies rather than phenotypic differences. However, MPS 3A typically have the most severe and rapidly progressing disease course (PMID: 31536183).
Treatment of manifestations is based on supportive therapies for neurodevelopmental delays, hearing loss, and visual impairment; medications (rather than behavioral therapy) for psychiatric/behavioral issues; physical therapy and/or orthopedic management of musculoskeletal manifestations; and management as prescribed by consulting specialists for seizures, cardiac involvement, sleep disorders, feeding difficulties. Surveillance is through routine monitoring of developmental capabilities and educational needs, destructive or disruptive behaviors; musculoskeletal involvement; hearing; cardiac involvement.
Individuals with mucopolysaccharidosis type 3 may participate in the clinical trials: https://clinicaltrials.gov/search?cond=MUCOPOLYSACCHARIDOSIS,%20TYPE%20IIIA

Variant description: This variant creates a premature stop codon at position 233. It is expected to result in a truncated or disrupted protein. The variant is present in gnomAD (allele frequency: 0.0000263) and is absent from the local database. This variant is listed in ClinVar as pathogenic/likely Pathogenic (Accession ID: 370732). This variant is classified as pathogenic based on ACMG/ClinGen recommendations.

John Doe
DOB: dd/mm/yyyy
Order ID:2xxxxx
Requested Test: myLifeExome

Incidental Findings

A heterozygous likely pathogenic variant was identified in the TTN gene. This result is consistent with increased risk to develop autosomal dominant dilated cardiomyopathy type 1G.

The TTN gene encodes a large abundant protein of striated muscle. The product of this gene is divided into two regions, a N-terminal I-band and a C-terminal A-band. The I-band, which is the elastic part of the molecule, contains two regions of tandem immunoglobulin domains on either side of a PEVK region that is rich in proline, glutamate, valine and lysine. The A-band, which is thought to act as a protein-ruler, contains a mixture of immunoglobulin and fibronectin repeats, and possesses kinase activity. An N-terminal Z-disc region and a C-terminal M-line region bind to the Z-line and M-line of the sarcomere, respectively, so that a single titin molecule spans half the length of a sarcomere. Titin also contains binding sites for muscle associated proteins so it serves as an adhesion template for the assembly of contractile machinery in muscle cells. It has also been identified as a structural protein for chromosomes. Alternative splicing of this gene results in multiple transcript variants. Considerable variability exists in the I-band, the M-line and the Z-disc regions of titin. Variability in the I-band region contributes to the differences in elasticity of different titin isoforms and, therefore, to the differences in elasticity of different muscle types.

	Gene/OMIM	*TTN*/ 602851
	Genomic coordinate (GRCh38)	Chr2:178527485 C>T
	ID Transcript	NM_001267550.2
	HGVS nomenclature	c.107641G>T
	Protein change	p.(Glu35881*)
	Location	exon 179 / 360
	Zygosity	Het
	Function	stop_gained
	Impact	HIGH
	ClinVar	-
Allele Frequency	Local Database	-
	gnomAD	-
In silico Predictors	REVEL	-
	CADD (PHRED)	-
	Splice-AI	-
	Clinical significance	Likely pathogenic
	ACMG Criteria*	PVS1, PM2_SUP

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; ranges from 0 to 1)= higher scores reflect greater likelihood that variant is disease- causing; CADD (PHRED)= Combined Annotation Dependent Depletion scoring, ranging from 1 to 99, Splice-AI= deep neural network that accurately predicts splice junctions from an pre-mRNA transcript (using 0.8 as high-precision cut-off).
**: The ACMG criteria are described under Methods /Variant interpretation section.*

Disease Disease description: Dilated cardiomyopathy type 1D. Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by left ventricular dilation and systolic dysfunction, and typically it presents with heart failure with symptoms of congestion (edema, orthopnea, paroxysmal nocturnal dyspnea) and/or reduced cardiac output (fatigue, dyspnea on exertion)], arrhythmias and/or conduction system disease, and thromboembolic disease including stroke. Patients with DCM are at risk of premature death (ORPHA:217604. DCM may be asymptomatic with only mild ventricular dilation and DCM may be asymptomatic with only mild ventricular dilation and dysfunction for years. Patients with severe heart failure, severe reduction of the functional capacity and depressed left ventricular ejection fraction have a low survival rate and may require heart transplant.
The management of DCM aims at reducing symptoms of heart failure and improving cardiac function. Clinical management of a patient with symptomatic DCM starts with standard heart failure medications. Specific recommendations regarding DCM for individuals involved in sports can be found in the relevant guidelines (PMID: 32860412, PMID: 32845299).
Individuals with DCM my participate in the clinical trials: https://clinicaltrials.gov/ct2/show/NCT04572893 https://www.clinicaltrialsregister.eu/ctr-search/search?query=Dilated+cardiomyopathy

Variant description: This changes the amino acid from a Glu to a stop codon within coding exon 179. This exon is in the A-band region of the N2-B isoform of the titin protein and is constitutively expressed in TTN transcripts (percent spliced in or PSI 100%). This alteration is expected to result in loss of function by premature protein truncation or nonsense-mediated mRNA decay. This variant is rare based on population cohorts in the Genome Aggregation Database (gnomAD). While truncating variants in TTN are present in 1-3% of the general population, truncating variants in the A-band are the most common cause of dilated cardiomyopathy (DCM) (Herman DS et al. N. Engl. J. Med., 2012 Feb;366:619-28; Roberts AM et al. Sci Transl Med, 2015 Jan;7:270ra6). This variant is classified as likely pathogenic based on ACMG and ClinGen recommendations.

Carrier Status Findings

Carrier status determines the proband's risk for passing inherited genetic condition(s) to the children. Carriers are typically healthy/ asymptomatic. When an individual is found to be a carrier of a genetic condition, his or her relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. If an individual is found to be a carrier of a specific condition, the patient's reproductive partner should be offered testing to receive informed genetic counseling about potential reproductive outcomes. If both partners are found to be carriers of a genetic condition, genetic counseling should be offered.

This proband is found to be a carrier for 3 genetic conditions.

Gene	Variant details	Zygosity	Annotations	Related disease (OMIM)- MOI Clinical assessment	Clinical significance (ACMG criteria*)
CEP250	chr20:35508949C>T NM_007186.6 c.6913C>T p.Arg2305* Exon/Intron rank:33/35 Nonsense Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: N/A -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):48.0 -Splice-AI:0.21	Cone-rod dystrophy and hearing loss type 2 AR Carrier	Likely pathogenic PVS1, PM2
DHTKD1	chr10:12097997G>A NM_018706.7 c.1671+1G>A p.? Exon/Intron rank:8/17 Intron, Splice site donor Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: 0.0000167 -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):33.0 -Splice-AI:1.0	Alpha-aminoadipic and alpha-ketoadipic aciduria AR Carrier	Likely pathogenic PVS1, PM2
TPRN	chr9:137200686GA>G NM_001128228.3 c.25delT p.Ser9fs*22 Exon/Intron rank:1/4 Frameshift Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: N/A -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):N/A -Splice-AI:0.0	Deafness type 79 AR Carrier	Likely pathogenic PVS1, PM2

**: The ACMG criteria are described under Methods /Variant interpretation section.*

TECHNICAL INFORMATION

Methods	**Whole exome sequencing and primary analysis.** Whole exome libraries were generated at Cegat (https://www.cegat.de), using Twist Human Core Exome kit with RefSeq and Mitochondrial Panel enrichment. The libraries are 100nt paired end sequenced on an Illumina platform to obtain 20x depth of coverage for >98% of the autosome target region and at least 300x coverage of the mitochondrial genome. Read alignment to reference genome GRCH38 and variant calling, including single nucleotide substitutions (SNVs), small insertions/deletions (Indels) and copy number variants (CNVs) with default parameters were performed using DRAGEN (version 4.2.4, Illumina). SNV and indel annotation was performed by geneyx® (https://geneyx.com). CNVs were annotated with ANNOTSV3.1 and an in-house CNV database to obtain allele frequencies. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org).
	Incidental genes: The gene panel is based on the ACMG (American College of Medical Genetics and Genomics) SF v.3.2 recommendations (https://www.gimjournal.org/article/S1098-3600(23)00879-1/fulltext). ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1.
	Variant interpretation: All candidate variants were evaluated with respect to their pathogenicity and causality significance, which are categorized following ACMG guidelines (PMID: 25741868) and ClinGen recommendations (https://www.clinicalgenome.org). Only those variants with evidence for causing or contributing to disease are reported as primary findings. All variants are visually inspected in IGV prior to reporting. The variants are classified following the 5-tier classes: pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign and benign. Likely benign and benign variants are not reported. VUSs are classified as "strong variants of unclear significance" when there is limited supporting evidence of pathogenicity (e.g., rare or absent from general population databases BUT in silico tools predict a deleterious effect on the protein consistent with the mechanism of disease; AND the gene has already been confirmed to be associated with the patient's observed phenotype). Incidental findings that do not correlate with the provided phenotype(s) are reported according to ACMG recommendations for reporting of incidental findings in using clinical exome and genome sequencing (PMID: 37347242), if consented. Only variants classified as pathogenic, likely pathogenic or uncertain (variants of unknown significance or VUS) according to the ACMG guidelines and associated with the patient's phenotype are listed among the primary findings. Variants of uncertain significance are categorized as strong candidates when they are extremely rare or absent in external and internal databases, are predicted to be deleterious, and the respective gene matches patient's phenotype (i.e. insufficient evidence available). Variants like risk factors (or risk alleles) and genetic modifiers, impacting the disease severity are reported ONLY when extensive scientific and clinical evidence is established. **ACMG criteria for classifying SNV/ Indels pathogenic variants:** PVS1- Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease; PS1- Same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2- De novo (both maternity and paternity confirmed) in a patient with the disease and no family history; PS3- Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product; PS4- The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls; PM1- Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation; PM2- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; PM3- For recessive disorders, detected in trans with a pathogenic variant; PM4-Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants; PM5- Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before at the acid/protein level; PM6- Assumed de novo, but without confirmation of paternity and maternity; PP1- Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease; PP2- Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease; PP3- Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc); PP4- Patient's phenotype or family history is highly specific for a disease with a single genetic etiology. ACMG criteria for classifying benign variants: BA1- Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; BS1- Allele frequency is greater than expected for the disorder; BS2- Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age; BS3- Well-established in vitro or in vivo functional studies shows no damaging effect on protein function or splicing; BS4- Lack of segregation in affected members of a family; BP1- Missense variant in a gene for which primarily truncating variants are known to cause disease; BP2- Observed in trans with a pathogenic variant for a fully penetrant

	dominant gene/disorder; or observed in cis with a pathogenic variant in any inheritance pattern; BP3- In-frame deletions/insertions in a repetitive region without a known function; BP4- Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc); BP5- Variant found in a case with an alternate molecular basis for disease; BP7- A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved. **ACMG criteria for classifying CNV/ SV pathogenic variants: LOSS** 1A. Contains protein-coding or other known functionally important elements; 1B. Does NOT contain protein-coding or any known functionally important elements; 2A. Complete overlap of an established HI gene/genomic region; 2B. Partial overlap of an established HI genomic region; 2C. Partial overlap with the 5' end of an established HI gene (3' end of the gene not involved); 2D. Partial overlap with the 3' end of an established HI gene (5' end of the gene not involved); 2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant); 2F. Completely contained within an established benign CNV region; 2G. Overlaps an established benign CNV but includes additional genomic material; 2H. Two or more HI predictors suggest that AT LEAST ONE gene in the interval is haploinsufficient (HI); 3A. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (0-24 genes); 3B. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (25-34 genes); 3C. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (35+ genes); 4A-4C. Individual case evidence – de novo occurrences; 4D. Individual case evidence – inconsistent phenotype; 4E. Individual case evidence – unknown inheritance; 4F-4H. Individual case evidence – segregation among similarly affected family members; 4I-4K. Individual case evidence - Non-Segregations; 4L-4O. Case-control and population evidence; 5A. Observed copy number loss is DE NOVO; 5B-5D. Observed copy number loss is INHERITED; 5E. Observed copy number loss – NON-SEGREGATIONS; 5F-5H Other. **GAIN**: 1A. Contains protein-coding or other known functionally important elements; 1B. Does NOT contain protein-coding or any known functionally important elements; 2A. Complete overlap; the TS gene or minimal critical region is fully contained within the observed copy number gain; 2B. Partial overlap of an established TS region; 2C. Identical in gene content to the established benign copy number gain; 2D. Smaller than established benign copy number gain, breakpoint(s) does not interrupt protein-coding genes; 2E. Smaller than established benign copy number gain, breakpoint(s) potentially interrupts protein-coding gene; 2F. Larger than known benign copy number gain, does not include additional protein-coding genes; 2G. Overlaps a benign copy number gain but includes additional genomic material; 2H. HI gene fully contained within observed copy number gain; 2I. Both breakpoints are within the same gene (gene-level sequence variant, possibly resulting in loss of function (LOF)); 2J. One breakpoint is within an established HI gene, patient's phenotype is either inconsistent with what is expected for LOF of that gene OR unknown; 2K. One breakpoint is within an established HI gene, patient's phenotype is highly specific and consistent with what is expected for LOF of that gene; 2L. One or both breakpoints are within gene(s) of no established clinical significance; 3A. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (0-34 genes); 3B. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (35-49 genes); 3C. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (50+ genes); 4A-4C. Individual case evidence – de novo occurrences; 4D. Individual case evidence – inconsistent phenotype; 4E. Individual case evidence – unknown inheritance; 4F-4H. Individual case evidence – segregation among similarly affected family members; 4I-4K. Individual case evidence - Non-Segregations; 4L-4O. Case-control and population evidence; 5A. Observed copy number loss is DE NOVO; 5B-5D. Observed copy number loss is INHERITED; 5E. Observed copy number loss – NON-SEGREGATIONS; 5F-5H Other. Point- based scoring framework: Pathogenic for 0.99 or more points; Liley pathogenic for 0.90 to 0.98 points; Variant of Uncertain Significance for scores between -0.89 to 0.89 points; Likely benign for scores between -0.90 to - 0.98; Benign for -0.99 or fewer points.
Limitations	The interpretation of genetic results is strongly dependent on the clarity of privided clinical information and the family history. Misinterpretation may occur if this data is provided incorrectly or incompletely. The variant frequency may change over time due to identification of new variants, addition of new datasets and frequent update of databases. Therefore, reclassification of previously reported variants may occur. Variants with this assay are detected across the whole exome; and possibly also within (intragenic) and beyond (intergenic) genes. The detectable variant types include nucleotide substitution, small insertions/deletions and copy number variants (CNVs). Variants may not be detected in low complexity genomic regions due to high sequence homology, pseudogenes, or highly repetitive sequences. This methodology detects events of mosaicism of single nucleotide variants (SNVs) with a minor allele fraction of at least 5%. It is possible that a particular genetic variant may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the biological function of all the genes in the human genome and/or due to the unclear impact of the variant on the expression and/or the function of the genes.

Test Performance

Total number of reads: 167,284,024 Percentage of reads mapping to hg38: 98.15% Median coverage: 120.16x

Annotation Datasets:

1kGenome:2019-02	ACMG:2024-12	AcmgSv:2024-12	AlphaMissense:v2-t113	CADD:1.6
CamouflagedGenes:v1	ClinGen:2024-12	ClinVar:2024-12	CoLoRSdb:v1.0.0	Cytogenetic:2022-10

DarkGenes:v1	DbNsfp:4.4a	DbscSNV:1.1	DbSnp:1405	DGVGold:v107_2020-03-02
DGVSV:v107_2020-02-25	ESP6500:2	GeneEnhancerSv:v6.1	GeneYX Version :v6.1	GeneyxRepeats:v1.1
Gerp:2010	gnomAD-exomes:2.1.1	gnomAD-genomes:3.1.2	gnomAD-mit:2.1.1	GnomADSV:v2.1
GnomADv4-exomes:4.1.0	GnomADv4-genomes:4.1.0	LitVar2:2024-12	MANE:v1.4	MasterMind:2024-07
MitoMap:2021-10	OMIM:2024-12	Phylop:2015-05	Revel:2016-03	Rmsk:2022-10
SnpEff:v5.2-2024-12	SpliceAI:1.3			

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