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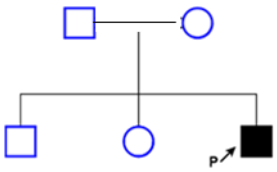
Add genetics to your health

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:	11/12/2023
Specimen type:	Buccal swab		
Specimen arrival date:	dd/mm/yyyy		

Requested Test: myLifeExome
Indication for test: Abnormal heart morphology, Abnormal nasal bridge morphology, Delayed speech and language development, Growth delay, Hepatosplenomegaly, Kyphoscoliosis, Low-set ears, Micrognathia, Scoliosis, Short stature.



Consanguineous parents: No
Consent for evaluation: Primary findings: Yes
Incidental findings: Yes

SUMMARY OF GENETIC FINDINGS

PRIMARY	INCIDENTAL	CARRIER STATUS
Positive	Negative	Positive

Primary Findings

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

Results: A heterozygous pathogenic variant was identified in the PTPN11 gene. This result is consistent with the genetic diagnosis of autosomal dominant Noonan syndrome type 1, under the assumption that variant arose de novo.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
PTPN11	c.218C>T; p.Thr73Ile	Het	P	Noonan Syndrome type 1	AD

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: No incidental finding detected.

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.

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

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
TPRN	c.25delT; p.Ser9fs*22	Het	LP	Deafness type 79	AR
DHTKD1	c.1671+1G>A; p.?	Het	LP	Alpha-aminoadipic and alpha-ketoadipic aciduria	AR
CEP250	c.6913C>T; p.Arg2305*	Het	LP	Cone-rod dystrophy and hearing loss type 2	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.
- Noonan syndrome (NS) is inherited in an autosomal dominant manner. Most affected individuals have the condition as the result of a de novo pathogenic variant. Therefore, it is recommended to clarify the origin of PTPN11 variant (de novo or inherited) by analyzing the parents via Sanger sequencing.
- The family history of some individuals diagnosed with NS may appear to be negative because of failure to recognize the disorder in affected family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Signatures

Medical Advisor

Lab Director

Clinical Genomics Scientist

DETAILED INSIGHTS

Primary Findings

A heterozygous pathogenic variant was identified in the PTPN11 gene. This result is consistent with the genetic diagnosis of autosomal dominant Noonan syndrome type 1, under the assumption that variant arose de novo.

PTPN11 (Protein Tyrosine Phosphatase Non-Receptor Type 11) is a protein coding gene. The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This PTP contains two tandem Src homology-2 domains, which function as phospho-tyrosine binding domains and mediate the interaction of this PTP with its substrates. PTP is widely expressed in most tissues and plays a regulatory role in various cell signaling events that are important for a diversity of cell functions, such as mitogenic activation, metabolic control, transcription regulation, and cell migration.

	Gene/OMIM	*PTPN11/176876*
	Genomic coordinate (GRCh38)	chr12:112450398C>T
	ID Transcript	NM_002834.5
	HGVS nomenclature	c.218C>T
	Protein change	p.Thr73Ile
	Location	exon 3/16
	Zygosity	Het
	Function	Missense
	Impact	High
	ClinVar	Conflicting interpretations of pathogenicity
Allele Frequency	Local Database	N/A
	gnomAD	N/A
In silico Predictors	REVEL	0.954
	CADD (PHRED)	25.6
	Splice-AI	0.0
	Clinical significance	Pathogenic
	ACMG Criteria	PS3, PS4, PM1, PM2, PM5, PP2, PP3

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; rages 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: Noonan syndrome is characterized by characteristic facies, short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one fourth of affected individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population.
Affected individuals may participate in the clinical trials:
https://clinicaltrials.gov/ct2/results?cond=Noonan+Syndrome
https://clinicaltrials.gov/ct2/results?cond=Noonan+Syndrome+with+Multiple+Lentigines
https://www.clinicaltrialsregister.eu/ctr-search/search?query=Noonan+Syndrome

Variant description: This sequence change replaces threonine, which is neutral and polar, with isoleucine, which is neutral and non-polar, at codon 73 of the PTPN11 protein (p.Thr73Ile). The variant is not present in gnomAD and is absent from the local database. This variant is listed in ClinVar as conflicting interpretations of pathogenicity (Accession ID: 13334). Experimental studies have shown that this missense change affects PTPN11 function (PMID: 15987685, 24718990). This variant is classified as pathogenic based on ACMG 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*)
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
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
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

**: 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, and these are categorized following ACMG guidelines (PMID: 25741868) and ClinGen recommendations (https://www.clinicalgenome.org). All variants are verified to have good quality, and only those variants with evidence for causing or contributing to disease are reported as primary findings. 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. VUS 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 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 very rare or absent in external and internal databases, are predicted to be deleterious, and the respective gene matches patient's phenotype (i.e. insufficient evidences available). Variants like risk factors (or risk alleles) and genetic modifiers, impacting the disease severity are included ONLY when extensive scientific and clinical evidence is established. ACMG criteria for classifying 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 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 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.
Limitations	The interpretation of genetic results is strongly dependent on the clinical information (preferably based on HPO) 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 this may result in reclassification of previously reported variants. 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 in the expression and/or the function of the genes.

GeneYX Version set 45

1kGenome:2019-02	ACMG:2023-10	CADD:1.6	ClinGen:2023-10	ClinVar:2023-10
Cytogenetic:2022-12	DbNsfp:4.4a	DbscSNV:1.1	DbSnp:1405	DGVGold:v107_2016-05-15
DGVSV:v107_2020-02-25	ESP6500:2	GeneEnhancerSv:v5.15	GeneyxRepeats:v1.1	Gerp:2010
gnomAD-exomes:2.1.1	gnomAD-genomes:3.1.2	gnomAD-mit:2.1.1	GnomADSV:v2.1	LitVar2:2023-10
MANE:v1.1				

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