MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

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Date: 16.03.2023

Report to:

Requesting Physician Name

Address

Contact Information

Order Number	**20 2009 1234**
Born	DD/MM/YYYY
Sex	
Date test requested:	27.02.2023
Sample collected:	27.02.2023
Sample / Specimen:	DNA from EDTA blood

Order: molecular genetic analysis of Hypertrophic cardiomyopathy - teen and adult_2.11
Additional Information /patient phenotype: Clinical diagnosis of hypertrophic cardiomyopathy.

RESULT SUMMARY:

POSITIVE – Consistent with familial hypertrophic cardiomyopathy (HCM) – heterozygous for a likely pathogenic variant

Result

The missense variant p.(Lys351Glu) in *MYH7* has been reported in several individuals affected with hypertrophic cardiomyopathy (ClinVar; Mohiddin et al. 2003, Genet Test 7:21; Lopes et al. 2015, Heart 101:294; Walsh et al. 2017, Genet Med 19:192). It is located within a region of *MYH7* between codons 181 and 937 that contains the majority of the myosin head domain. Missense variants in this region have been shown to be significantly overrepresented in individuals with hypertrophic cardiomyopathy (Walsh et al. 2017, Genet Med 19:192).

The *MYH7* gene encodes Myosin-7, which is an actin-based motor molecule with ATPase activity essential for muscle contraction. It forms regular bipolar thick filaments that, together with actin thin filaments, constitute the fundamental contractile unit of skeletal and cardiac muscle. Pathogenic *MYH7* variants can be causal for severeal forms of myopathies or cardiomyopathies (CM) like dilated CM, hypertrophic CM, and left ventricular noncompaction CM.

Conclusion

The detected variant in *MYH7* is consistent with the clinical diagnosis of HCM and may with a high probability be regarded as causative for the patient's phenotype.

Offspring inherit variants with a probability of 50%, each.

Recommended action

- Offer genetic counselling.
- Offer variant-specific genetic testing of biological relatives.
- Offer segregation analysis to enable further evaluation of pathogenicity of the likely pathogenic variant.

VARIANT DETAILS

Gene	Variant	Classification	Exon	Location on GRCh38
MYH7	NM_000257.4:c.1051A>G p.(Lys351Glu)	Likely pathogenic	12	Chr14:g.23899071T>C
Consequence	**Zygosity**	**Inheritance**	**ACMG/AMP criteria (Richards et al.; Ellard et al.)**	**Disorder**
Missense	Heterozygous	Autosomal Dominant	PM2,PM1,PP3,PS4_Moderate	Cardiomyopathy, Familial Hypertrophic, 1
GeneID	**#OMIM**	**ClinVarID**	**dbSNP ID**	**Allele Frequency**
4625	192600	181335	rs730880864	

Report released by

John Doe 16.03.2023

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TEST METHODOLOGY

Sequencing	Enrichment	SNV and CNV Data analysis	data evaluation	Reference genome
Next Generation Sequencing (Illumina)	Twist Human Core Exome plus RefSeq SpikeIn	Illumina Dragen Bio-IT Platform VarSeq by GoldenHelix	VarSeq by GoldenHelix	hg38, NCBI GR38
Quality criteria	**SNV detection sensitivity**	**Classification of variants**	**in silico algorithms**	**Databases**
>30 (precision >99,9%) in min. 75% of bases	99.92 - 99.93 %; confirmation of reported SNV with Sanger sequencing, data analysis with SeqPilot	Richards et al. 2015, Genet Med 17:405; Ellard et al. "ACGS Best Practice Guidelines for Variant Classification 2020“	MaxEntScan, SpliceSiteFinder-like, REVEL	HGMD Professional release, ClinVar, gnomAD

PERCENTAGE OF SEQUENCED BASES WITH COVERAGE >20X

97.957%

ANALYZED GENES

ACTC1(NM_005159.5), ACTN2(NM_001103.3), CACNA1C(NM_000719.7), CSRP3(NM_003476.5), FHL1(NM_001159699.2), FHOD3(NM_001281740.3), FLNC(NM_001458.4), GLA(NM_000169.2), JPH2(NM_020433.4), LAMP2(NM_002294.3), MYBPC3(NM_000256.3), MYH7(NM_000257.4), MYL2(NM_000432.3), MYL3(NM_000258.3), PLN(NM_002667.5), PRKAG2(NM_016203.4), TNNC1(NM_003280.3), TNNI3(NM_000363.5), TNNT2(NM_001276345.2), TPM1(NM_001018005.2), TTR(NM_000371.3)

LIST OF EXONS WITH COVERAGE <20X

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TECHNICAL LIMITATIONS

mosaics (<20%); indels >21bp; repeat expansions; repetitive regions; variants in: homopolymeric regions or regions of high sequence homology, unenriched regions (untranslated regions, introns, promoter and enhancer regions) or enriched but insufficiently covered regions; variants in mt-DNA (VAF<20%); determination of the phase of multiple variants in one gene; balanced genomic rearrangements

CLASSES OF VARIANTS

Class 5: pathogenic variant – are reported, posterior probability >99 %
Class 4: likely pathogenic variant – are reported, posterior probability >90 %
Class 3: uncertain significance – only be listed in the report if posterior probability is >67.5 %
Class 2: likely benign – not reported, posterior probability <10 %
Class 1: benign – not reported, posterior probability <0,1 %

ACMG CRITERIA

1. Criteria for pathogenic evidence
PVS1: Null variant 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/PM6: de novo in a patient with the disease and no family history; PS3: well-established 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 with the prevalence in controls/was identified in unrelated affected individuals; PM1: missense variant located in a mutational hot spot and/or critical and well-established functional domain; PM2: absent from controls (or at extremely low frequency) in Genome Aggregation Database (gnomAD); PM3: for recessive disorders, detected in homozygous state or together with another (not benign or likely benign) variant; PM4: protein length changes as a result of in-frame deletions/insertions in a non- repeat region or stop-loss variants; PM5: missense change at an amino acid residue where a different missense change determined to be (likely) pathogenic has been seen before; PP1: co-segregation with disease in multiple affected family members; PP2: missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease; PP3: multiple lines of computational evidence support a deleterious effect on the gene or gene product; PP4: patient's phenotype or family history is (highly) is specific for variations in the affected gene; PP5: reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

2. Criteria for benign evidence
BA1: allele frequency is >5% if recessive and 0.5% if dominant in gnomAD; 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 functional studies show no damaging effect on protein function or splicing; BS4: lack of segregation with disease; BP1: missense variant in a gene for which primarily truncating variants are known to cause disease OR for loss-of-function variants in a gene where the disease is caused by gain-of-function variants; 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; BP5: variant found in a case with an alternate molecular basis for disease; BP6: reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation; 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.

According to Ellard et al. 2020, the strength level of criteria PVS1, PS1, PS2, PS3, PS4, PM1, PM3, PM4, PM5, PP1, PP4, BP2, and BP4 can be modified depending on the cogency of the evidence.

ALLELE FREQUENCIES

This value corresponds to the maximum frequency of all reference populations (POPMAX).

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