Patient name: example report
HN: 123456789
Date of birth: 02/01/1985
Sex: Male

Sample type: EDTA Blood
Specimen id: 12345678-1
Date of collection: 01/03/2022
Date of receive: 01/03/2022

Date of result: 28/04/2023
Physician order: Dr. Examplereport Test

RESULT : Positive

TEST INFORMATION

Additional finding includes 78 genes as shown in the section "condition associated gene" below.

TEST RESULTS

One Likely pathogenic variant in LDLR was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

VARIANTS FINDING

Gene	Transcript	Chromosome position	Variant	Allele State	Inheritance	Classification
LDLR	NM_000527.5	Chr19:11227576	p.His583Tyr	Heterozygous	Dominant	Likely pathogenic

INTERPRETATION SUMMARY

A single likely pathogenic variant, c.1747C>T (p.His583Tyr) was identified in the LDLR gene, which is associated with familial hypercholesterolemia.

RECOMMENDATIONS

The interpretation of these results should be done in the context of a patient's medical record and family history. Please note that interpretation and classification of the variants reported here may change over time. Please see a genetic counselor for services regarding the implications of these results in the context of understanding the implications of incidental findings, family planning and the informing of family members of potentially shared genetic outcomes.

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DETAILED GENETIC VARIANT INFORMATION

- ### VARIANTS FINDING

LDLR NM_000527.5

Gene summary
The low density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. The encoded protein is normally bound at the cell membrane, where it binds low density lipoprotein/cholesterol and is taken into the cell. Lysosomes release the cholesterol, which is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. At the same time, a reciprocal stimulation of cholesterol ester synthesis takes place. Mutations in this gene cause the autosomal dominant disorder, familial hypercholesterolemia. Alternate splicing results in multiple transcript variants.[provided by RefSeq, May 2022]

Variants summary
The missense variant NM_000527.5(LDLR):c.1747C>T (p.His583Tyr) causes a change at the same amino acid residue as a previously established pathogenic variant. Additionally, the variant has been reported to ClinVar as Conflicting interpretations of pathogenicity with a status of (1 star) criteria provided, conflicting interpretations (Variation ID 200921 as of 2023-04-06). There is a moderate physicochemical difference between histidine and tyrosine. 24 variants within 6 amino acid positions of the variant p.His583Tyr have been shown to be pathogenic, while none have been shown to be benign. The p.His583Tyr missense variant is predicted to be damaging by both SIFT and PolyPhen2. The histidine residue at codon 583 of LDLR is conserved in all mammalian species. The nucleotide c.1747 in LDLR is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Likely Pathogenic.

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METHODOLOGY

Genomic DNA is extracted from an individual at Bumrungrad Hospital. DNA sample is sent to the Macrogen, Korea to process Whole Exome Sequencing (WES). Library preparation, clustering and sequencing are processed on the Illumina platform to cover the coding regions of targeted genes ± ~10 bases of non-coding DNA flanking each exon. Raw data in an average at 6 Gb were generated. Reads from the sequence output were aligned to the human reference genome (GRCh37) using BWA. Variants are called using GATK pipeline. The tertiary analysis is performed at Bumrungrad Hospital. The variants were annotated and filtered using the Golden Helix VarSeq analysis workflow implementing the ACMG guidelines for the interpretation of sequence variants. This includes a comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact.

Coverage Statistics for additional finding

Target region / Coverage	WES Target region	Additional finding target region
Mean depth (X)	**40.4X**	**39.0X**
Mean depth ≥ 10X	**92.8%**	**94.6%**

VARIANT ASSESSMENT PROCESS

The following databases and in-silico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB RefSeq Genes, ExAC Gene Constraints, VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Analysis was reported using the to HGVS nomenclature (www.hgvs.org/mutnomen) as implemented by the VarSeq transcript annotation algorithm. The reported transcript matches that used most frequently by the clinical labs submitting to ClinVar.

LIMITATIONS

It should be noted that the test result is limited to a set of genes indicated in the panel and might not cover all possible variants related to the particular condition. For some target regions, the depth covered for analysis may be variable, However, any targeted gene that fails to meet the acceptance criteria (Mean depth ≥ 10X) will be noted. Due to these limitations, ruling out the diagnosis of a genetic disorder should not be made based on negative results. An evaluation by alternative methods should be considered if a specific clinical disorder is suspected. This report only includes variants that meet a level of evidence threshold for cause or contribute to disease/condition. Reported variants are not confirmed by Sanger sequencing. Certain classes of genomic variants are also not covered using the NGS testing technology, including repeat expansions, large deletion or large duplication (≥50 kb), translocations and gene fusions or other complex structural rearrangements.

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DISCLAIMER

The result interpretation is based on the most current scientific and analytical standards. However, more evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically. There is also a possibility of an error in the result due to contaminants in the sample, rare technical errors, a rare genetic variant that could interfere with the analysis. This test should be used in compliance with the other diagnostic test. Note that this test cannot exclude the possibility of variants in genes not analyzed or assayed with incomplete coverage. Even though this test is not designed to distinguish between somatic and germline variants, if variant of somatic is detected, supplementary testing may be compulsory to clarify the significance of results. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

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CONDITION ASSOCIATED GENE

The table shows the list of 78 genes related to additional conditions analyzed in this test. Gene-Phenotype relationship information is retrieved from http:/www.omim.org and ACMG SF v3.1[1]

Gene	Transcript	Gene MIM number	Gene associated condition
ACTA2	NM_001613.4	102620	Familial thoracic aortic aneurysm
ACTC1	NM_005159.5	102540	Hypertrophic cardiomyopathy
ACVRL1	NM_000020.3	601284	Hereditary hemorrhagic telangiectasia
APC	NM_000038.6	611731	Familial adenomatous polyposis
APOB	NM_000384.3	107730	Familial hypercholesterolemia
ATP7B	NM_000053.4	606882	Wilson disease
BAG3	NM_004281.4	603883	Dilated cardiomyopathy, Myofibrillar myopathy
BMPR1A	NM_004329.3	601299	Juvenile polyposis syndrome
BRCA1	NM_007294.4	113705	Hereditary breast and ovarian cancer
BRCA2	NM_000059.4	600185	Hereditary breast and ovarian cancer
BTD	NM_001370658.1	609019	Biotinidase deficiency
CACNA1S	NM_000069.3	114208	Malignant hyperthermia
CASQ2	NM_001232.4	114251	Catecholaminergic polymorphic ventricular tachycardia
COL3A1	NM_000090.4	120180	Ehlers-Danlos syndrome, vascular type
DES	NM_001927.4	125660	Dliated cardiomyopathy, Myofibrillar myopathy
DSC2	NM_024422.6	125645	Arrhythmogenic right ventricular cardiomyopathy
DSG2	NM_001943.5	125671	Arrhythmogenic right ventricular cardiomyopathy
DSP	NM_004415.4	125647	Arrhythmogenic right ventricular cardiomyopathy, Dilated cardiomyopathy
ENG	NM_000118.3	131195	Hereditary hemorrhagic telangiectasia
FBN1	NM_000138.5	134797	Marfan syndrome
FLNC	NM_001458.5	102565	Dilated cardiomyopathy, Myofibrillar myopathy
GAA	NM_000152.5	606800	Pompe disease
GLA	NM_000169.3	300644	Fabry disease
HFE	NM_000410.4	613609	Hereditary hemochromatosis
HNF1A	NM_000545.8	142410	Maturity-Onset of Diabetes of the Young
KCNH2	NM_000238.4	152427	Long-QT syndrome type 2
KCNQ1	NM_000218.3	607542	Long-QT syndrome type 1
LDLR	NM_000527.5	606945	Familial hypercholesterolemia
LMNA	NM_170707.4	150330	Dilated cardiomyopathy
MAX	NM_002382.5	154950	Hereditary paraganglioma-pheochromocytoma syndrome
MEN1	NM_130799.2	613733	Multiple endocrine neoplasia type 1
MLH1	NM_000249.4	120436	Lynch syndrome
MSH2	NM_000251.3	609309	Lynch syndrome
MSH6	NM_000179.3	600678	Lynch syndrome

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Gene	Transcript	Gene MIM number	Gene associated condition
MUTYH	NM_001128425.2	604933	MUTYH-associated polyposis
MYBPC3	NM_000256.3	600958	Hypertrophic cardiomyopathy
MYH11	NM_002474.3	160745	Familial thoracic aortic aneurysm
MYH7	NM_000257.4	160760	Hypertrophic cardiomyopathy, Dilated cardiomyopathy
MYL2	NM_000432.4	160781	Hypertrophic cardiomyopathy
MYL3	NM_000258.3	160790	Hypertrophic cardiomyopathy
NF2	NM_000268.4	607379	Neurofibromatosis type 2
OTC	NM_000531.6	300461	Ornithine transcarbamylase deficiency
PALB2	NM_024675.4	610355	Hereditary breast cancer
PCSK9	NM_174936.4	607786	Familial hypercholesterolemia
PKP2	NM_004572.4	602861	Arrhythmogenic right ventricular cardiomyopathy
PMS2	NM_000535.7	600259	Lynch syndrome
PRKAG2	NM_016203.4	602743	Hypertrophic cardiomyopathy
PTEN	NM_000314.8	601728	PTEN hamartoma tumor syndrome
RB1	NM_000321.3	614041	Retinoblastoma
RBM20	NM_001134363.3	613171	Dliated cardiomyopathy
RET	NM_020975.6	164761	Familial medullary thyroid cancer, Multiple endocrine neoplasia type 2A, Multiple endocrine neoplasia type 2B
RPE65	NM_000329.3	180069	RPE65-related retinopathy
RYR1	NM_000540.3	180901	Malignant hyperthermia
RYR2	NM_001035.3	180902	Catecholaminergic polymorphic ventricular tachycardia
SCN5A	NM_198056.3	600163	Long QT syndrome type 3, Brugada syndrome, Dilated cardiomyopathy
SDHAF2	NM_017841.4	613019	Hereditary paraganglioma-pheochromocytoma syndrome
SDHB	NM_003000.3	185470	Hereditary paraganglioma-pheochromocytoma syndrome
SDHC	NM_003001.5	602413	Hereditary paraganglioma-pheochromocytoma syndrome
SDHD	NM_003002.4	602690	Hereditary paraganglioma-pheochromocytoma syndrome
SMAD3	NM_005902.4	603109	Loeys-Dietz syndrome
SMAD4	NM_005359.6	600993	Juvenile polyposis syndrome, Hereditary hemorrhagic telangiectasia
STK11	NM_000455.5	602216	Peutz-Jeghers syndrome
TGFBR1	NM_004612.4	190181	Loeys-Dietz syndrome
TGFBR2	NM_003242.6	190182	Loeys-Dietz syndrome
TMEM127	NM_017849.4	613403	Hereditary paraganglioma-pheochromocytoma syndrome
TMEM43	NM_024334.3	612048	Arrhythmogenic right ventricular cardiomyopathy
TNNC1	NM_003280.3	191040	Dilated cardiomyopathy
TNNI3	NM_000363.5	191044	Hypertrophic cardiomyopathy
TNNT2	NM_001001430.3	191045	Dilated cardiomyopathy, Hypertrophic cardiomyopathy
TP53	NM_000546.6	191170	Li-Fraumeni syndrome
TPM1	NM_001018005.2	191010	Hypertrophic cardiomyopathy

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Gene	Transcript	Gene MIM number	Gene associated condition
TRDN	NM_006073.4	603283	Catecholaminergic polymorphic ventricular tachycardia, Long QT syndrome
TSC1	NM_000368.5	605284	Tuberous sclerosis complex
TSC2	NM_000548.5	191092	Tuberous sclerosis complex
TTN	NM_001267550.2	188840	Dilated cardiomyopathy (truncating variants only)
TTR	NM_000371.4	176300	Hereditary transthyretin-related amyloidosis
VHL	NM_000551.4	608537	Von Hippel-Lindau syndrome
WT1	NM_024426.6	607102	WT1-related Wilms tumor

[1]Miller, David T., et al. "ACMG SF v3. 1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG)." Genetics in Medicine (2022).

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