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: Carrier

TEST INFORMATION

Additional finding includes 14 genes as shown in the section "condition associated gene" below

TEST RESULTS

One Likely pathogenic variant in SERPINA1 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
SERPINA1	NM_000295.5	Chr14:94849388	p.Arg63Cys	Heterozygous	Recessive	Likely pathogenic

INTERPRETATION SUMMARY

A single clinically significant genetic change was found in the SERPINA1 gene, which is associated with being a carrier for a hereditary condition.

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.

Patient name: example report **HN:** 123456789

DETAILED GENETIC VARIANT INFORMATION

- ### VARIANTS FINDING

SERPINA1 NM_000295.5

Gene summary

The protein encoded by this gene is a serine protease inhibitor belonging to the serpin superfamily whose targets include elastase, plasmin, thrombin, trypsin, chymotrypsin, and plasminogen activator. This protein is produced in the liver, the bone marrow, by lymphocytic and monocytic cells in lymphoid tissue, and by the Paneth cells of the gut. Defects in this gene are associated with chronic obstructive pulmonary disease, emphysema, and chronic liver disease. Several transcript variants encoding the same protein have been found for this gene. [provided by RefSeq, Aug 2020]. If a person carries two clinically significant genetic changes, one in each copy of the SERPINA1 gene, this may increase the risk for a condition known as alpha-1-antitrypsin deficiency (AATD). This result is associated with being a carrier of autosomal recessive AATD. Carries typically do no have symptoms of the condition, but may be at risk to have a child with the condition.

Variants summary

The missense variant NM_000295.5(SERPINA1):c.187C>T (p.Arg63Cys) causes the same amino acid change as a previously established pathogenic variant. There is a large physicochemical difference between arginine and cysteine, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size and/or other properties. This variant is present in population database (rs28931570). The p.Arg63Cys missense variant is predicted to be damaging by both SIFT and PolyPhen2. This variant is also known as Arg39Cys and the I allele in the literature. 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 Genome Sequencing (WGS). Library preparation, clustering and sequencing are processed on the Illumina platform. Data in a mean depth of 30X were generated. Reads from the sequence output were aligned to the human reference genome (GRCh37) and processed for variant calling (SNP/Indel) using the Illumina pipeline (Isaac.v4). Manta is performed to identify structural variants and large indels while copy number variant is identified by Control-FREEC. 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	WGS Target region	Additional finding target region
Mean depth (X)	**29.9X**	**29.22X**
Mean depth ≥ 10X	**99%**	**99.59%**

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, translocations and gene fusions or other complex structural rearrangements.

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. Genetic counseling is recommended to help understand the test result and explain the implications of this result for the patients and other family members. 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.

Patient name: example report **HN:** 123456789

CONDITION ASSOCIATED GENE

The table shows the list of 14 genes related to additional conditions analyzed in this test. Gene-Phenotype relationship information is retrieved from http://www.omim.org

Gene	Transcript	Gene MIM number	Condition associated gene
ATP7B	NM_000053.4	606882	Wilson disease
BTD	NM_001370658.1	609019	Biotinidase deficiency
CACNA1S	NM_000069.3	114208	Malignant hyperthermia
GAA	NM_000152.5	606800	Pompe disease
HAMP	NM_021175.4	606464	Hereditary hemochromatosis
HFE	NM_000410.4	613609	Hereditary hemochromatosis
HJV	NM_213653.4	608374	Hereditary hemochromatosis
HNF1A	NM_000545.8	142410	Maturity-Onset of Diabetes of the Young
OTC	NM_000531.6	300461	Ornithine transcarbamylase deficiency
RPE65	NM_000329.3	180069	RPE65-related retinopathy
RYR1	NM_000540.3	180901	Malignant hyperthermia
SERPINA1	NM_000295.5	107400	Alpha-1-antitrypsin deficiency
SLC40A1	NM_014585.6	604653	Hereditary hemochromatosis
TFR2	NM_003227.4	604720	Hereditary hemochromatosis