MAYO CLINIC

1-800-533-1710

Autoinflammatory Gene Panel

AUTOG

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**N022000305**
PATIENT ID X100420055	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY ATLAS TEST
COLLECTED 5/22/2023, 6:33 AM	RECEIVED 5/22/2023, 12:20 PM	REPORTED 5/24/2023, 10:21 AM		
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TEST DESCRIPTION

Evaluation of 117 genes associated with autoinflammatory disorders

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
IL36RN (NM_012275.2)	c.338C>T p.Ser113Leu (p.S113L) Chr2(GRCh37):g.113820124C>T	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected:
IL36RN (NM_012275.2), chr2(GRCh37):g.113820124C>T, c.338C>T, p.Ser113Leu (p.S113L)

No additional reportable variants were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by this assay.

INTERPRETATION

IL36RN c.338C>T (p.Ser113Leu), PATHOGENIC
The heterozygous c.338C>T (p.Ser113Leu) missense variant in the IL36RN gene (MIM:605507) is classified as pathogenic. The IL36RN gene (previously known as IL1F5) encodes IL-36Ra, a member of the IL-1 family of cytokines and cell surface receptors that mediate inflammation. IL-36Ra blocks the proinflammatory cytokine IL-36. Biallelic pathogenic loss-of-function variants in IL36RN have been primarily associated with generalized pustular psoriasis (GPP) due to elevated proinflammatory response following stimulation with IL-36. This variant has been reported in the homozygous and compound heterozygous state in association with GPP and other overlapping phenotypes (1-10). While IL36RN-associated GPP is typically associated with autosomal recessive inheritance, it has been suggested that the p.Ser113Leu variant may be associated with clinical symptoms even in the heterozygous state with no other variants in IL36RN (2,4,6,11). Heterozygotes for p.Ser113Leu may have additional genetic and/or environmental factors that contribute to the development of GPP. Functional studies demonstrate that the p.Ser113Leu variant is associated with an increase in the production of proinflammatory cytokines after IL-36 stimulation in patient cells, and reduced expression and decreased inhibitory function in vitro (1,8). This variant has been reported in large multi-ethnic population cohorts at frequencies ranging from 0.02% to 0.66% (12,13). Taken together, these findings suggest that the identified IL36RN p.Ser113Leu variant is pathogenic. This result is consistent with, at a minimum, carrier status for autosomal recessive

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IL36RN-associated GPP due to the presence of the IL36RN c.338C>T (p.Ser113Leu) variant. However, as noted above, heterozygous carriers of this IL36RN variant have been reported to present with GPP. Of note, in some affected individuals with this variant, anakinra and/or infliximab were reported to have a markedly positive effect on GPP (4,11). Appropriate screening and/or management procedures should be considered.

This result decreases the likelihood but does not rule out the involvement of the genes evaluated in this panel.

Individuals may have a pathogenic variant in one of the interrogated genes that is not detectable by the methods utilized. Additionally, the clinical phenotype that is observed in this individual and/or family may be due to a pathogenic variant or variants in another gene not targeted by this test.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

A genetic consultation may be of benefit.

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METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. NGS and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID AUTOG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACP5, ADA, ADA2, ADAM17, ADAR, AIRE, ALPI, AP3B1, AP3D1, ARPC1B, ASAH1, C1QA, C1QB, C1QC, C1R, C1S, C2, CARD11, CARD14, CASP10, CASP8, CD3G, CD40LG, CD48, CD55, CDC42, COPA, CTLA4, DDX58, DNASE1, DNASE1L3, DNASE2, DOCK8, FADD, FOXP3, GATA2, HAVCR2, ICOS, IFIH1, IKBKG, IL10, IL10RA, IL10RB, IL1RN, IL2RA, IL2RB, IL2RG, IL36RN, ISG15, ITCH, ITGB2, ITK, JAK1, LACC1, LIG4, LPIN2, LRBA, LSM11, LYN, LYST, MEFV, MVK, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OAS1, OTULIN, PIK3CD, PIK3R1, PLCG2, POLA1, POMP, PRF1, PRKCD, PSMA3, PSMB10, PSMB4, PSMB8, PSMB9, PSMG2, PSTPIP1, RAB27A, RBCK1, RIPK1, RNASEH2A, RNASEH2B, RNASEH2C, RNF31, RNU7-1, SAMD9L, SAMHD1, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC37A4, STAT1, STAT2, STAT3, STIM1, STING1, STX11, STXBP2, TLR7, TNFAIP3, TNFRSF1A, TPP2, TREX1, TRNT1, UNC13D, USP18, WAS, WDR1, XIAP and ZAP70

DISCLAIMER

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Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Autoinflammatory Disorders Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID AUTOG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional

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clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

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