MAYO CLINIC

1-800-533-1710

Hyper-IgE Syndrome Gene Panel

HIESG

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**M702000277**
PATIENT ID X100407762	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY ATLAS TEST
COLLECTED 2/2/2023, 8:33 AM	RECEIVED 2/7/2023, 3:05 PM	REPORTED 2/24/2023, 4:30 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location. 7028846 MCL RochesterCampus Rochester MN 55901				CLIENT ORDER NUMBER X100407762 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 21 genes associated with Hyper-IgE Syndrome

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
AIRE (NM_000383.3)	c.1A>G p.Met1Val (p.M1V) Chr21(GRCh37):g.45705890A>G	Homozygous	Pathogenic

The following homozygous PATHOGENIC variant was detected:
AIRE (NM_000383.3), chr21(GRCh37):g.45705890A>G, c.1A>G, p.Met1Val (p.M1V)

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

AIRE c.1A>G (p.Met1Val), PATHOGENIC
The homozygous c.1A>G (p.Met1Val) missense variant in the initiation codon of the AIRE gene (MIM:607358) is classified as pathogenic. The AIRE gene encodes for a transcription factor that is critical for preventing autoimmunity by regulating the expression of tissue-specific self-antigens. Pathogenic variants in this gene cause autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type-1 (APS-1). APECED is generally inherited in an autosomal recessive manner. However, some cases of autosomal dominant inheritance have been reported. This variant has been reported as a homozygous variant in several individuals with APECED (1-4). This variant has also been detected in the compound heterozygous state with a different pathogenic variant in three affected individuals from the same family (2). This variant affects the translation initiation (start) codon of the AIRE gene. In some cases, an alternate methionine (ATG) or non-ATG site further downstream may be used to initiate translation, which may impact pathogenicity. However, the next ATG nucleotide sequence in the protein coding portion of this gene is located in the first codon of exon 3. This variant is absent from large control databases (5,6). Taken together, this evidence supports a pathogenic classification for this AIRE gene variant.

The finding of a homozygous pathogenic AIRE variant is supportive of a diagnosis of APECED for this individual but should be correlated with clinical findings. Appropriate screening and/or management procedures should be considered.

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

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

1) Faiyaz-Ul-Haque M, Bin-Abbas B, Al-Abdullatif A, et al. Novel and recurrent mutations in the AIRE gene of autoimmune polyendocrinopathy syndrome type 1 (APS1) patients. Clin Genet. 2009;76(5):431-440. doi:10.1111/j.1399-0004.2009.01278.x (PMID 19758376)
2) Zaidi G, Bhatia V, Sahoo SK, et al. Autoimmune polyendocrine syndrome type 1 in an Indian cohort: a longitudinal study. Endocr Connect. 2017;6(5):289-296. doi:10.1530/EC-17-0022 (PMID 28446514)
3) Monies D, Abouelhoda M, Assoum M, et al. Lessons Learned from Large-Scale, First-Tier Clinical Exome Sequencing in a Highly Consanguineous Population [published correction appears in Am J Hum Genet. 2019 Oct 3;105(4):879]. Am J Hum Genet. 2019;104(6):1182-1201. doi:10.1016/j.ajhg.2019.04.011 (PMID 31130284)
4) Turro E, Astle WJ, Megy K, et al. Whole-genome sequencing of patients with rare diseases in a national health system. Nature. 2020;583(7814):96-102. doi:10.1038/s41586-020-2434-2 (PMID 32581362)
5) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
6) gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

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 HIESG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

AIRE, CARD11, CARD9, CARMIL2, DOCK8, ERBIN, IL6R, IL6ST, IL17RA, IL17RC, IL17F, PGM3, SPINK5, STAT1,

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STAT3, TGFBR1, TGFBR2, TRAF3IP2, TYK2, WAS and ZNF341

DISCLAIMER

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 Hyper-IgE Syndrome Gene 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 HIESG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation

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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 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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