MAYO CLINIC

1-800-533-1710

# Congenital Neutropenia GenePanel

# SCCNP

| PATIENT NAME | | | | ORDER NUMBER |
|---|---|---|---|---|
| **TESTRNV, IMPLEMENTATION** | | | | **M702000278** |
| PATIENT ID<br>X100407767 | DATE OF BIRTH<br>02/19/1968 | AGE<br>54 Y | SEX<br>Male | REQUESTED BY<br>ATLAS TEST |
| COLLECTED<br>2/2/2023, 8:33 AM | RECEIVED<br>2/7/2023, 3:06 PM | REPORTED<br>2/24/2023, 4:41 PM | | |
| The collected, received, and reported dates and times on the report are in the time zone of the performing location.<br>7028846<br>MCL RochesterCampus<br>Rochester MN 55901 | | | | CLIENT ORDER NUMBER<br>X100407767<br>CLIENT MRN<br>321 |

## TEST DESCRIPTION

Evaluation of 30 genes associated with severe congenital neutropenia and cyclic neutropenia

## SPECIMEN

WB Whole Blood

## RESULT SUMMARY

Pathogenic Variant Detected

## RESULT

| Gene (Transcript) | Variant | Zygosity | Classification |
|---|---|---|---|
| GATA2<br>(NM_001145661.1) | c.1017+572C>T<br>p.?<br>Chr3(GRCh37):g.128202131G>A | Heterozygous | Pathogenic |

The following heterozygous PATHOGENIC variant was detected:
GATA2 (NM_001145661.1), chr3(GRCh37):g.128202131G>A, c.1017+572C>T, p.?

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

GATA2 c.1017+572C>T, p.?, PATHOGENIC
The heterozygous c.1017+572C>T intronic variant in the GATA2 gene (MIM:137295) is classified as pathogenic. The GATA2 gene encodes GATA binding protein 2, a transcription factor that plays an essential role in development and proliferation of hematopoietic and endocrine cell lineages. Pathogenic variants in this gene cause autosomal dominant GATA2 deficiency, which may present clinically as Emberger syndrome, immunodeficiency 21, susceptibility to acute myeloid leukemia or myelodysplastic syndrome, WILD syndrome (warts, immunodeficiency, lymphedema), MonoMAC or DCML (dendritic cells, monocytopenia, and lymphopenia) deficiency. The c.1017+572C>T variant has been previously reported in several unrelated individuals in association with GATA2 deficiency, myelodysplastic syndrome, and MonoMAC (1-5). This variant segregated with disease in at least two families (1,6). Functional studies demonstrate that the c.1017+572C>T variant, which disrupts the conserved ETS motif in the GATA2 intron 5 enhancer region, reduces the intron 5 enhancer activity, decreases GATA2 transcription from the affected allele, and results in profound NK cell dysfunction (1,7,8). This variant is absent from large control databases (9,10). Taken together, this evidence supports a pathogenic classification for this GATA2 gene variant.

The finding of a pathogenic GATA2 variant is supportive of a diagnosis of GATA2 deficiency or other GATA2-related condition 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) Hsu AP, Johnson KD, Falcone EL, et al. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. Blood. 2013;121(19):3830-S7. doi:10.1182/blood-2012-08-452763 (PMID 23502222)
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3) Koegel AK, Hofmann I, Moffitt K, Degar B, Duncan C, Tubman VN. Acute lymphoblastic leukemia in a patient with MonoMAC syndrome/GATA2 haploinsufficiency. Pediatr Blood Cancer. 2016;63(10):1844-1847. doi:10.1002/pbc.26084 (PMID 27232273)
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5) Saettini F, Coliva T, Vendemini F, et al. When to suspect GATA2 deficiency in pediatric patients: from complete blood count to diagnosis. Pediatr Hematol Oncol. 2021;38(5):510-514. doi:10.1080/08880018.2020.1863536 (PMID 33726626)
6) Churpek JE, Pyrtel K, Kanchi KL, et al. Genomic analysis of germ line and somatic variants in familial myelodysplasia/acute myeloid leukemia. Blood. 2015;126(22):2484-2490. doi:10.1182/blood-2015-04-641100 (PMID 26492932)
7) Mace EM, Hsu AP, Monaco-Shawver L, et al. Mutations in GATA2 cause human NK cell deficiency with specific loss of the CD56(bright) subset. Blood. 2013;121(14):2669-2677. doi:10.1182/blood-2012-09-453969 (PMID 23365458)
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9) 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)
10) 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

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

## GENES ANALYZED

AK2, AP3B1, AP3D1, CD40LG, CEBPE, CLPB, CSF3R, CXCR2, CXCR4, DNAJC21, EFL1, ELANE, G6PC3, GATA2, GFI1, GINS1, HAX1, JAGN1, LYST, RAC2, SBDS, SLC37A4, SMARCD2, SRP54, TAZ(TAFAZZIN), USB1, VPS13B, VPS45, WAS, and WIPF1

## 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.

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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 Severe Congenital and Cyclic Neutropenia 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 SCCNP) 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 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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