Patient Details

Name	: Mr. KARTIK PRATAP KATHURIYA	**Sex / Age**	: Male / 19 Years	**Case ID**	: 40307406155
Ref By	: Dr. Manoj Toshniwal	**PT. ID**	:	**Test Name**	: ORION Focus
Bill. Loc.	: Jeevan Amrut Hematology Center India Pvt. Ltd - Aurangabad				

Sample Details

Registration Date & Time	: 2024-03-31 04:26:29 PM	**Sample Type**	: Whole Blood EDTA	**Sample Date & Time**	: 2024-03-31 04:26:00 PM
Ref ID 1.	: -	**Report Date & Time**	: 2024-04-30 06:56:42 PM		

Clinical History

Clinical symptoms: H/O leuco thrombocytopenia, G6PD deficiency
Investigations done: PHN Workup, cytogenetics- normal
Clinical suspicion: Aplastic anemia

Test Results and Interpretation

HEMIZYGOUS PATHOGENIC VARIANT IN G6PD GENE, CONSISTENT WITH PHENOTYPE DETECTED.

HETEROZYGOUS VARIANT OF UNCERTAIN SIGNIFICANCE (VUS) IN TERT GENE DETECTED: CLINICAL CORRELATION RECOMMENDED.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
G6PD (NM_001360016.2)	Exon 6	c.563C>T p.Ser188Phe [56x/57x]	Hemizygous	Pathogenic	Hemolytic anemia, G6PD deficient (favism)	X-linked
TERT (NM_198253.3)	Exon 3	c.1691C>T p.Thr564Met [31x/81x]	Heterozygous	Uncertain significance	Dyskeratosis congenita	Autosomal dominant, Autosomal recessive

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Variant Details

TERT

Variant Nomenclature	c.1691C>T (p.Thr564Met)
Genomic Nomenclature	chr5:g.1282622G>A
Zygosity	Heterozygous

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references
Missense variant	Absent	**SIFT**: Damaging **Polyphen**: Probably damaging **MutationTaster**: Disease causing **CADD Phred**:26.7000	GERP++ PhyloP	Uncertain significance	Yes (Heterozygous)	(Ley B et al., 2019)

The amino acid Thr at position 564 is changed to a Met changing protein sequence and it might alter its composition and physico-chemical properties. This missense variant has not been reported in literature. Same variant has been previously reproted in heterozygous state with the chronic hypersensitivity pneumonitisit (Ley B et al., 2019). **Heterozygous variants in the TERT gene** has previously been reproted in patients affected with **Aplastic anemia** (Yamaguchi H et al., 2005), **dyskeratosis congenita** (Du HY et al., 2008, Armanios M et al., 2005, Basel-Vanagaite L et al., 2008). Biallelic variants in TERT gene has been reported in individuals swith more severe featurs (Çepni E et al., 2022). Additional literature and functional evidence will be required to prove the pathogenicity. For these reasons, this variant has been classified as Uncertain Significance.

Disease

DYSKERATOSIS CONGENITA

Dyskeratosis congenita is a multisystem disorder caused by defective telomere maintenance. Features are variable and include **thrombocytopenia**, **aplastic anemia,,** bone marrow failure, pulmonary and liver fibrosis, premature graying of the hair, immunodeficiency and gastrointestinal disease and pulmonary and hepatic fibrosis (Armanios M et al., 2005).

References

1. Ley B et al., Rare Protein-Altering Telomere-related Gene Variants in Patients with Chronic Hypersensitivity Pneumonitis. Am J Respir Crit Care Med. 2019 Nov 1;200(9):1154-1163.
2. Yamaguchi H et al., Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. N Engl J Med. 2005 Apr 7;352(14):1413-24.
3. Du HY et al., Complex inheritance pattern of dyskeratosis congenita in two families with 2 different mutations in the telomerase reverse transcriptase gene. Blood. 2008 Feb 1;111(3):1128-30.
4. Armanios M et al., Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci U S A. 2005 Nov 1;102(44):15960-4.
5. Basel-Vanagaite L et al., Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. Haematologica. 2008 Jun;93(6):943-4.
6. Çepni E et al., Biallelic TERT variant leads to Hoyeraal-Hreidarsson syndrome with additional dyskeratosis congenita findings. Am J Med Genet A. 2022 Apr;188(4):1226-1232.

G6PD

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Variant Details

Variant Nomenclature	c.563C>T (p.Ser188Phe)
Genomic Nomenclature	chrX:g.153762634G>A
Zygosity	Hemizygous

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references
Missense variant	0.14%	**SIFT**: Damaging **MutationTaster**: Disease causing **CADD Phred**: 23.6000	GERP++ PhyloP	Yes Pathogenic/Likely pathogenic (Multiple submissions)	Yes (Hemizyous/Heterozygous)	Errigo et al., 2023

The missense variant c.563C>T (p.Ser188Phe) in G6PD gene has been observed in individual with G6PD deficiency (Al-Jaouni SK et al., 2011; Jamornthanyawat N et. al., 2014). Experimental studies have shown that this missense change affects G6PD function (Molou E et. al., 2014). It is commonly reported in individuals of Mediterranean, Middle Eastern, or Indian ancestry. This variant is located in a mutational hot spot and/or critical and well-established functional domain without benign variation. For these reasons, this variant has been classified as Pathogenic.

Disease

ANEMIA, NONSPHEROCYTIC HEMOLYTIC, DUE TO G6PD DEFICIENCY

G6PD deficiency is the most common genetic cause of chronic and drug-, food-, or infection-induced hemolytic anemia. G6PD catalyzes the first reaction in the pentose phosphate pathway, which is the only NADPH-generation process in mature red cells; therefore, defense against oxidative damage is dependent on G6PD. Most G6PD-deficient patients are asymptomatic throughout their life, but G6PD deficiency can be life-threatening. The most common clinical manifestations of G6PD deficiency are neonatal jaundice and acute hemolytic anemia, which in most patients is triggered by an exogenous agent, e.g., primaquine or fava beans. Acute hemolysis is characterized by fatigue, back pain, anemia, and jaundice. Increased unconjugated bilirubin, lactate dehydrogenase, and reticulocytosis are markers of the disorder. The striking similarity between the areas where G6PD deficiency is common and Plasmodium falciparum malaria (see 611162) is endemic provided evidence that G6PD deficiency confers resistance against malaria (summary by Cappellini and Fiorelli, 2008).

References

1. Errigo et al., Relationship between Glucose-6-Phosphate Dehydrogenase Deficiency, X-Chromosome Inactivation and Inflammatory Markers. Antioxidants (Basel). 2023 Jan 31;12(2):334
2. Al-Jaouni SK et al., 2011 Moradkhani K. Molecular characterization of glucose-6-phosphate dehydrogenase deficiency in Jeddah, Kingdom of Saudi Arabia. BMC Res Notes. 2011 Oct 24;4:436.
3. Jamornthanyawat N et al., A population survey of the glucose-6-phosphate dehydrogenase (G6PD) 563C>T (Mediterranean) mutation in Afghanistan. PLoS One. 2014 Feb 21;9(2):e88605.
4. Molou E et. al., Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency in Greek newborns: the Mediterranean C563T mutation screening. Scand J Clin Lab Invest. 2014 Apr;74(3):259-63.

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Recommendations

1. **Please correlate clinically.**
2. **Variant depth/Total depth has been mentioned in summary of the variants.**
3. **Genetic counseling for accurate interpretation of test results is recommended.**
4. **The reported findings are based on NGS analysis.**
5. **Parental/Maternal testing as applicable is recommended for variants when detected and/or to confirm if variants are in trans (if applicable).**
6. **Segregation analysis (testing of multiple affected as well as unaffected members) of detected variants (if any) is recommended. Variant classification is subject to change after segregation.**
7. **CNV confirmation via MLPA or Exon array is recommended for copy number variants involving a single gene as well as for CNV <400kb. Only large constitutional CNV can be tested via other array platforms.**
8. **If the above results do not correlate completely with patient phenotype, additional testing is advised based on clinician's discretion.**

Technical Notes

Methodology - Massively Parallel Sequencing (Next Generation Sequencing): Genomic DNA from the submitted specimen was enriched for the complete coding regions and splice site junctions of genes listed below using a custom bait- capture system. Paired End Sequencing was performed with 2x100/2x150 chemistry. Reads were assembled and were aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Data was filtered and analyzed to identify variants of interest and interpreted in the context of a single most damaging, clinically relevant transcript for the purpose of the report, indicated as a part of variant details. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 5-10bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Deletion and duplication analysis is performed in cases when indicated but detected variations need to be confirmed by an alternate methodology. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS).

Laboratory reporting protocol: The analysis is based on the provided phenotype: relevant HPO terms, curated gene panels and relevant literature is assessed for phenotype based analysis. Variant reporting is limited to exon regions and upto 10 basepairs within exon intron boundaries. Previously reported deep intronic and non coding variants will be included when detected at a depth more than 10X . Variant reporting is performed at a minimum depth of 10X.

For Mitochondrial Genome Sequencing (if requested): Only phenotype-related Pathogenic and Likely Pathogenic variations reported in the MitoMap database as well as literature are reported. Haplogroups are not analyzed. A list of variants other than the above are available on request. Analyzed genes include:MT-ND1, MT-ND2, MT-ND3, MT-ND4L, MT-ND4, MT-ND5, MT-ND6, MT-CYB, MT-CO1, MT-CO2, MT-CO3, MT-ATP6, MT-ATP8, MT-RNR2, MT-RNR1, MT-RNR2, MT-TA, MT-TR, MT-TN, MT-TD, MT-TC, MT-TE, MT-TQ, MT-TG, MT-TH, MT-TI, MT-TL1, MT-TL2, MT-TK, MT-TM, MT-TF, MT-TP, MT-TS1, MT-TS2, MT-TT, MT-TW, MT-TY, MT-TV.

Tools and Databases employed for analysis: Clinvar, OMIM, HGMD, UCSC genome browser, Uniprot, Ensembl, dbSNP, gnomAD, ExAC, Pubmed, Dgap, icgc, Kaviar, various bioinformatics analysis, predictive tools and disease specific databases used as available and appropriate. Such tools/databases would be mentioned wherever used.

Bioinformatics pipeline version: 12.0.1.

Gene Coverage

Indication Based Analysis:

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
ABCG5	100%	ABCG8	100%	ACTN1	100%	ADA2	100%
ADAMTS13	98.1%	ALDH1A1	100%	ANKRD26	99.4%	ARPC1B	100%

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Gene Coverage

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
ARTN	100%	ATM	99.8%	BLM	100%	BRCA1	100%
BRCA2	100%	BRIP1	100%	CDC42	100%	CXCR4	100%
CYCS	100%	DIAPH1	100%	DKC1	100%	EPO	100%
EPX	100%	ERCC4	99.5%	ERCC6L2	100%	ETV6	100%
FANCA	100%	FANCB	100%	FANCC	99.4%	FANCD2	100%
FANCE	100%	FANCF	98.4%	FANCG	100%	FANCI	100%
FANCL	100%	FANCM	98.9%	FLI1	100%	FLNA	100%
FYB1	97.9%	G6PD	100%	GALE	100%	GATA1	100%
GFI1B	100%	GNE	100%	GP1BA	100%	GP1BB	100%
GP9	100%	HAX1	100%	HOXA11	100%	ITGA2	98.9%
ITGA2B	100%	ITGB3	100%	KDSR	100%	MAD2L2	100%
MASTL	100%	MECOM	100%	MPIG6B	100%	MPL	100%
MRPL36	100%	MYH9	100%	NBEAL2	100%	NBN	100%
NOP10	100%	PALB2	100%	PRKACG	100%	PTPRJ	100%
RAD51	100%	RAD51C	100%	RAP1B	100%	RBM8A	100%
RPL11	100%	RPL15	100%	RPL18	100%	RPL27	100%
RPL31	100%	RPL35	100%	RPL35A	100%	RPL5	100%
RPS10	100%	RPS15A	100%	RPS17	100%	RPS19	100%
RPS24	100%	RPS26	100%	RPS27	100%	RPS28	100%
RPS29	100%	RPS7	100%	RUNX1	100%	SBDS	100%
SLC35A1	100%	SLFN14	100%	SLX4	100%	SRC	99.9%
STIM1	100%	TADA2A	100%	TERT	100%	THBD	100%
THPO	100%	TIMP1	100%	TOP3A	100%	TP53	100%
TPM4	100%	TRPM7	100%	TSR2	100%	TUBB	100%
TUBB1	100%	UBE2T	100%	UBL4A	96%	VWF	100%
WAS	85.3%	WIPF1	100%	WRN	99.5%	XRCC2	100%

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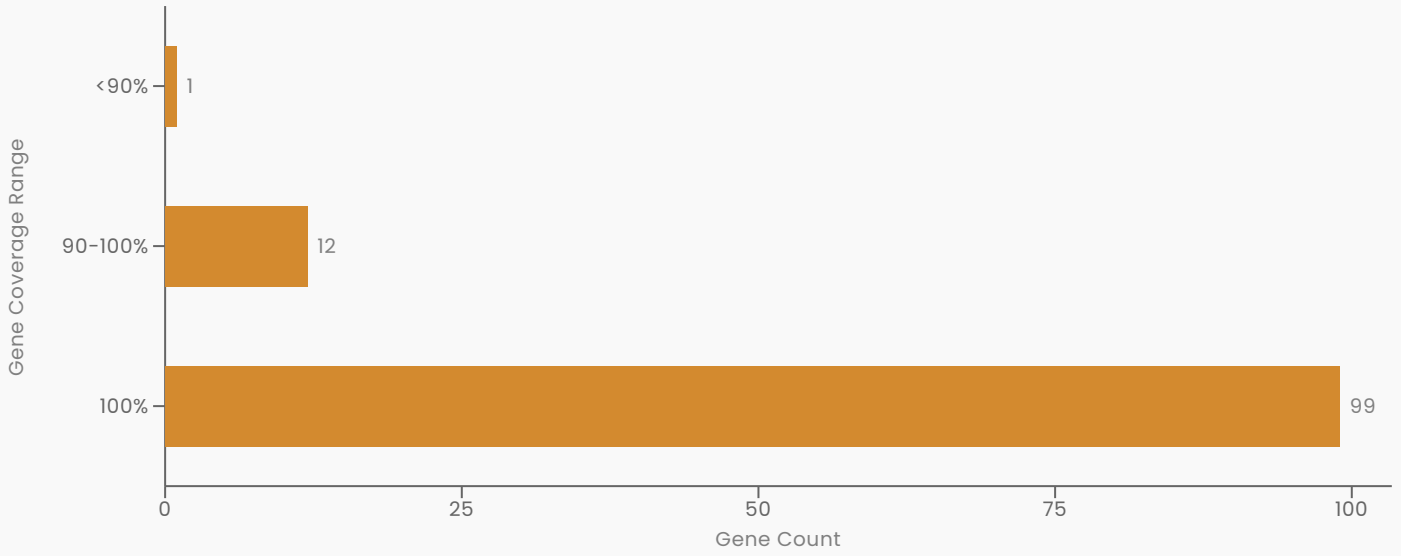
Gene Coverage

Gene Coverage Distribution



QC Metrics

Total Aligned Reads	99.95 %
Total Reads	47.25 (M)
Total data generated	7.06 (Gb)
Total reads which passed mapping quality cut-off	6.20 (Gb)

Test Limitations

- Testing has been performed assuming that the sample received belongs to the above named individual(s) and any stated relationships between individuals are accepted as true. It is also assumed that consent for the same was provided after pre-test counseling at the point of collection/referral.
- The current results are based on analysis of coding regions (exons) as well as certain intron padding regions on patient's genomic DNA with respect to patient phenotype as defined in the target regions (link available below). However, due to inherent technology limitations, coverage is not uniform across all regions. Hence pathogenic variants present in areas of insufficient coverage as well as those variants which currently do not co-relate with the provided phenotype may not be analyzed/ reported. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity.
- The reported findings are based on NGS analysis.
- The test methodology currently does not detect large deletions/duplications, triplet repeat expansions and epigenetic changes. The test also does not include analysis of predictors for multifactorial, polygenic and/or complex diseases. Novel synonymous

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Test Limitations

changes as well as intronic mutations (excluding those affecting invariant splice nucleotides) are not routinely reported.

- Phenotype variability may be due to modifying genetic/non-genetic factors and is not a part of the current analysis.
- The classification and interpretation of all the variants in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information comes to light. We recommend re- analysis of this report yearly, in order to take advantage of any new scientific data that may become available. Please contact laboratory in case re-analysis of the report is desired. It is the lab's policy to perform re-analysis once on a complimentary basis. However, this re-analysis is performed only when requested.

Accreditation

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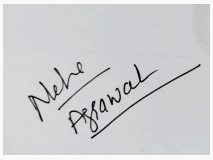

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