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Name: **Wayne Kearns**
URN: PMEX347746
DOB: 04-Dec-1994
Sex: F

Clinical Indication Ploycythaemia

Correlative Morphology Not provided

TEST DETAILS
Lab No: 19277020
Ext Ref: 7950601669
Collected: 04-Jun-2022
Received: 04-Oct-2023
Specimen: Muscle biopsy test
TEST ORDERED BY
Requester: DrJoan Lewis
Referral Lab: Alpha Pathology

HAEMATOLOGICAL MALIGNANCY GENE PANEL REPORT

Test Description Somatic variant analysis of 22 genes with clinical significance in myeloproliferative neoplasms. Referto Panel Summary for gene list.

Result Summary: **ASSUMED SOMATIC VARIANTS DETECTED. See Reportable Variants table below for details.**

Test Results

ASSUMED ORIGIN	GENE	VARIANT	VRF(%)	CLINICAL SIGNIFICANCE IN AML
Eukaryotic	**FOXP2**	**c.2842del, p.(Glu948Argfs*3)**	**15**	**PROGNISTIC**
Germ	**TP53**	**c.2645G>A, p.(Arg882His)**	**6**	**DIAGNOSTIC**

VRF – variant read frequency

Clinical Interpretation Variants in DNMT3A and SH2B3 were detected in this bone marrow aspirate sample consistent witha diagnosis of a myeloproliferative neoplasm (MPN) or idiopathic erythrocytosis. No typical MPNdriver variants (JAK2/CALR/MPL) were detected in this sample. Please correlate with morphological, immunophenotypic and cytogenetic features. Refer to final page of report for further information regarding the clinical utility of genomic testing inthis context.

FLT3-ITD Analysis FLT3-ITD DETECTED BY SEPARATE ASSAY (see Reportable Variants table for details)

Reportable Variants Please note, variant origin (somatic or germline) cannot be determined by this assay. Variant origin is assumedhere based on ancillary information (e.g. population databases, literature, variant read frequency) for the purposeof clinical interpretation however testing of a germline sample may be recommended in some circumstances.

Test Methodology

DNA is analysed by targeted gene sequencing of coding regions and flanking splice sites (within 2 bp) of the genes listed below. Libraries areprepared using a custom QIAGEN QIAseq single primer extension-based panel (Peter MacCallum Cancer Centre AllHaem v1) and sequencedon an Illumina NextSeq500 with 150 bp paired end reads. A customised CLC bioinformatics pipeline including QIAGEN CLC enterprise solutionsis used to generate aligned reads and call variants (single nucleotide variants and short insertions or deletions) against the hg19 human referencgenome. Variants are analysed using PathOS software (Peter Mac) and described according to HGVS nomenclature version 19.01(http://varnomen.hgvs.org/) with minor differences in accordance with Peter MacCallum Cancer Centre Molecular Pathology departmental policy.The following population variation and cancer or genetic disease databases are commonly used in addition to literature review to assist withvariant interpretation: the Genome Aggregation Database (gnomAD; gnomad.broadinstitute.org), the Catalogue of Somatic Mutations in Cancer(COSMIC; cancer.sanger.ac.uk), ClinVar (ncbi.nlm.nih.gov/clinvar) and the IARC TP53 Database (p53.iarc.fr). Variant origin (i.e. somatic orgermline) is assumed based on ancillary information (e.g. population databases, literature, variant read frequency) for the purpose of clinicalinterpretation. All assumed somatic variants are reported (and generally considered clinically significant). Variants of uncertain origin are alsoreported, as are likely benign germline polymorphisms if sufficiently rare and otherwise

undescribed. Testing of a non-haematological specimenmay be recommended to evaluate variant origin. Recurrent population variants are not reported. Somatic variant categorisation (modified fromAMP/ASCO/CAP guidelines1) – Variants are curated and categorised according to the clinical context of the patient and categorised asDIAGNOSTIC (the variant either defines a diagnostic category or is sufficiently specific for the clinical context to contribute to diagnosticsubcategorisation), PROGNOSTIC (the variant has been associated in large trials/series with inferior or superior outcomes in either the contextof a specific therapy or independent of therapy. Note this does not take into account interaction between prognostic variants present in theindividual patient. Relevant pairwise interactions are presented in the clinical summary), DRUG TARGET (the variant or variant class is specificallytargeted by a therapeutic agent, this category only includes therapeutic agents that are clinically advanced and generally available through eitherreimbursement or clinical trials [i.e. not early stage investigational agents]), DRUG RESISTANCE (the variant is specifically associated withresistance to a targeted agent [i.e. does not include non-specific resistance to non-targeted therapies]), MRD MARKER (the variant is anestablished biomarker for which assessment at MRD sensitivity after therapy is accepted practice). If the variant is not categorised into any of the above categories it is assigned CLONAL MARKER indicating its utility in defining the presence of a clonal haematopoietic process in thespecimen. These categorisations are general in nature and may not be applicable to the specific clinicopathological context of the patient.

Test Limitations

The detection limit of this assay for specimens sequenced to the target read depth of 500x is a variant allele frequency (VAF) of approximately2% with the exception of ASXL1 c.1934dup;p.Gly646Trpfs*12 (detection limit ~ 5%). This assay is primarily qualitative however, the variant readfrequency (VRF) is provided to assist with variant interpretation and is assumed to approximate VAF in most instances (noting that the VAF ofsome insertions/deletions may be underrepresented due to assay-based allele bias). The measurement of uncertainty provided as a percentagerelative standard uncertainty (i.e. CV%) for variants with VAFs of 5%, 10%-20%, 30%-40% and 50% are on average, 10.2%, 10.4%, 3.5% and4.4%, respectively. Copy number variations, loss of heterozygosity, structural rearrangements or aneuploidies are not reported. Insertions ordeletions (particularly those > 25 bp in length), including FLT3-ITDs, are not reliably detected by this assay. Genes are analysed using thereference transcripts listed below; coding exons found in alternative transcripts are not assessed by this assay. This assay does not distinguishbetween somatic and germline variants. In addition, the clonal origin of somatic variants (i.e. disease compartment or cell lineage) cannot bedetermined. Synonymous variants are not routinely reported. Please note Peter Mac assumes sample identification, family relationships, andclinical diagnoses are as stated on the request. Our clinical recommendations may be based on evidence from third-party data sources and shouldbe interpreted in the context of all other clinical and laboratory information for this patient.

Panel Summary

Please note variants may not be optimally detected in genes with less than 100% coverage. The gene coverage above is considered acceptablegiven the available information about the clinical context, however please contact the laboratory for further advice should specific genes coveredat less than 100% require full coverage. A list of regions with suboptimal coverage is available upon request.

Gene	Transcript	Targeted exons	Coverage at >500x (%)
ABL1	NM_005157.4	4-10	100
ARAF	NM_001654.4	7,10,15	100
ASXL1	NM_015338.5	10-12	100
BCL2	NM_000633.2	All coding	100
BIRC3	NM_001165.4	6-9	100
BRAF	NM_004333.4	15	100
BTK	NM_000061.2	11,15-16	100
CALR	NM_004343.3	9	100
CARD11	NM_032415.4	4-9,15,20	100
CBL	NM_005188.3	8-9	100
CD274	NM_014143.3	All coding,3'UTR	100
CD79B	NM_000626.2	5,6	100
CEBPA	NM_004364.3	All coding	100
CSF3R	NM_156039.3	14,17	100
CXCR4	NM_003467.2	2^	100
DDX41	NM_016222.2	All coding	100
DNMT3A	NM_022552.4	All coding	100
ETNK1	NM_018638.4	3	100
EZH2	NM_004456.4	All coding	100
FLT3*	NM_004119.2	14-15,17,20	100
FYN	NM_002037.5	7	100
GATA1	NM_002049.3	2-6	100
GATA2	NM_032638.4	All coding	100
ID3	NM_002167.4	All coding	100
IDH1	NM_005896.2	4,7	100
IDH2	NM_002168.2	4,7	100
IRF8	NM_002163.2	3	100
JAK2	NM_004972.3	12-14,16	100
JAK3	NM_000215.3	11,13,15	94.9
KIT	NM_000222.2	8,10-11,17	100
KRAS	NM_033360.2	2-4	100
MAP2K1	NM_002755.3	2-3	100
MPL	NM_005373.2	1-11	100
MYD88	NM_002468.4	4-5	100
NOTCH1	NM_017617.3	26-28,34,3'UTR^	100
NPM1	NM_002520.6	11	100
NRAS	NM_002524.4	2-4	97.4
PDCD1LG2	NM_025239.3	All coding,3'UTR	100
PHF6	NM_001015877.1	7-10	95
PIGA	NM_002641.3	All coding	100
PLCG1	NM_002660.2	11	100
PLCG2	NM_002661.3	16,19-20,24	100
RHOA	NM_001664.2	2	100
RUNX1	NM_001754.4	All coding	100
SETBP1	NM_015559.2	4	100
SF3B1	NM_012433.2	14-16	100
SH2B3	NM_005475.2	All coding	98.6
SRSF2	NM_003016.4	1	100
STAT3	NM_139276.2	6,13,15,18-21	100
STAT5B	NM_012448.3	16	100
STAT6	NM_001178078.1	10,13,16	100
TCF3	NM_001136139.2	17	100
TET2	NM_001127208.2	All coding	100
TP53	NM_000546.5	All coding	100
U2AF1	NM_006758.2	2,6	100
XPO1	NM_003400.3	15-16	100
ZRSR2	NM_005089.3	All coding	100

* Please note FLT3-ITDs are not detected with this assay. A separate assay may have been performed, result included in Test Results if sample tested.
^ Partial coverage of region

Please note variants may not be optimally detected in genes with less than 100% coverage. The gene coverage above is considered acceptablegiven the available information about the clinical context, however please contact the laboratory for further advice should specific genes coveredat less than 100% require full coverage. A list of regions with suboptimal coverage is available upon request.

Please contact the laboratory on 03 8559 7284 if you wish to discuss this report further.

Reported by	**Dr Ing Soo Tiong (Consultant Haematologist)**
Authorised by	**A/Prof Piers Blombery (Consultant Haematologist)**
Reported	**16-Mar-2023**

References

1. 1. Li MM, Datto M, Duncavage EJ, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer:A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College ofAmerican Pathologists. J Mol Diagn 2017; 19(1): 4-23.