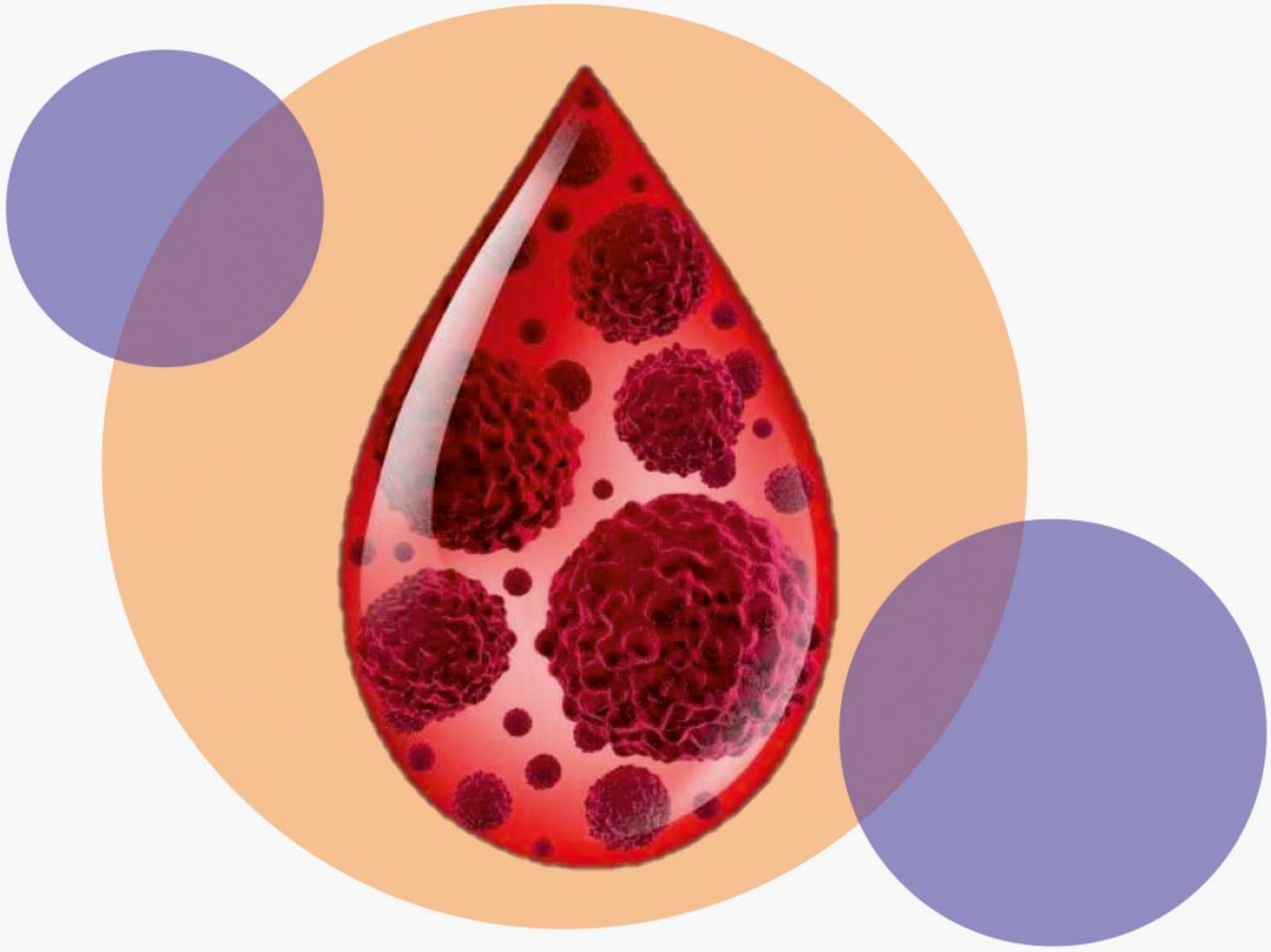
Unipath
SPECIALTY LABORATORY Ltd.

Oncomine Myeloid V2 GX Assay

INTRODUCING

Oncomine Myeloid V2 GX assay

is the most Rapid, Accurate, Automated & Complete Myeloid Genomic Profiling NGS GX Assay



For the First Time in India Updated Complete Myeloid Gene Panel by NGS

Test Overview

- Oncomine Myeloid V2 GX assay is a comprehensive targeted next-generation sequencing (NGS) assay designed for sensitive detection of myeloid disorder-associated DNA mutations and fusion transcripts in blood and bone marrow samples.

- The panel is comprised of 40 key genes while the RNA panel includes a broad fusion panel of 30 driver genes, covering the most relevant targets associated with major myeloid disorders, including…

  - Acute myeloid leukemia (AML)
  - Myeloproliferative neoplasms (MPN)
  - Chronic myelomonocytic leukemia (CMML)
  - Myeloid dysplastic syndrome (MDS)
  - Chronic myeloid leukemia (CML)
  - Juvenile myelomonocytic leukemia (JMML)

- This broad fusion panel allows you to detect over 700 unique fusion isotypes along with the commonly involved gene like DNMT3A.

- With a single assay, you can profile key targets such as…

  - FLT3 (FMS- Like Tyrosine Kinase 3)
  - NPM1 (Necleophosmin)
  - BCR-ABL
  - TP53 (Tumor Protein)
  - IDH1/2
  - PML-RARA

  Along with many other biomarkers in myeloid malignancies

Key Advantages

- Updated version of the commonly used myeloid panel with inclusion of additional genes and fusions like ANKRD26, DDX41, PPM1D, PTPN11, SMC1A, SMC3, NUP98.

- Accurately detect variants and SNV in genes with long homopolymers like CEBPA, ASLX1
  All common fusions detected in a single assay.

- Detection of challenging insertions and deletions in problematic gene like CALR, FLT3

- Fastest turnaround time with almost complete myeloid information for all diseases like AML, MPN, CMML, JMML, MDS

The genes covered in the panel

- **05** Expression Genes
- **17** Full Genes
- **28** Hotspot Genes
- **30** Fusion Drivers
- **700** Fusion Isotypes

List of genes covered in this Assay

DNA panel: Hotspot genes (28)		DNA panel: Full genes (17)		RNA panel: fusion driver genes (30)			RNA panel: Expression genes (5)	RNA panel: Expression control genes (5)
ANKRD26	KRAS	ASXL1	PRPF8	ABL1	HMGA2	NUP98	BAALC	EIF2B1
ABL1	MPL	BCOR	RBI	ALK	JAK2	NUP214	MECOM	FBXW2
BRAF	MYD88	CALR	RUNX1	BCL2	KMT2A	PDGFRA	MYC	PSMB2
CBL	NPM1	CEBPA	SH2B3	BRAF	(MLL PDTs)	PDGFRB	SMCIA	PUM1
CSF3R	NRAS	ETV6	STAG2	CCND1	MECOM	RARA	WT1	TRIM27
DDX41	PPM1D	EZH2	TET2	CREBBP	MET	RBM15		
DNMT3A	PTPN71	IKZF1	Tp53	EGFR	MLLT10	RUNX1		
FLTS (ITD,TKD)	SMCIA	NF1	ZRSR	ETV6	MLLT3	TCF3		
GATA2	SMC3	PHF6		FGFR1	MYBL1	TFES3		
HRAS	SETBP1			FGFR2	MYH11			
IDH1	SF3B1			FUS	NTRK3			
IDH2	SRSF2							
JAK2	U2AF1							
KIT	WT1							

Specimen Requirements

- Sample type: Peripheral blood sample /bone marrow aspirate in an EDTA (lavender) tube.
  Amount: 4-5 ml

Platform

- The Ion Torrent **Genexus** Integrated Sequencer

Turnaround time (TAT)

- 7-10 Days from receiving the sample in the laboratory

Limitations of the Assay

- This test is a targeted next-generation sequencing (NGS) (panel) assay that encompasses 40 genes with variable full exon, partial region (including select intronic or non-coding regions), or hot spot coverage (depending on specific locus).

- Therefore, this test will not detect other genetic abnormalities in genes or regions outside the specified target areas.

- The test detects single base substitutions (i.e., point mutations), as well as small insertion or deletion type events, but it does not detect gene large deletions, complex deletions and insertions.

- This assay does not distinguish between somatic and germline alterations in analyzed gene regions, particularly with variant allele frequencies (VAF) near 50% or 100%.

- If nucleotide alterations in genes associated with germline mutation syndromes are present and there is also a strong clinical suspicion or family history of malignant disease predisposition, additional genetic testing and appropriate counseling may be indicated.

- Variants near the edge of ampl-icons, locations susceptible to strand-specific error, variants located in homopolymers regions larger than 7bp, or complex variants (indels) can cause difficulty for variant calling software and lead to potential false positives results.

- Mutation cells detected between 5% and 10% VAF may indicate low-level (i.e., subclonal) tumor populations, although the clinical significance of these findings may not be clear.

- Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results.

Figure1: Role of various genes in myeloid neoplasms

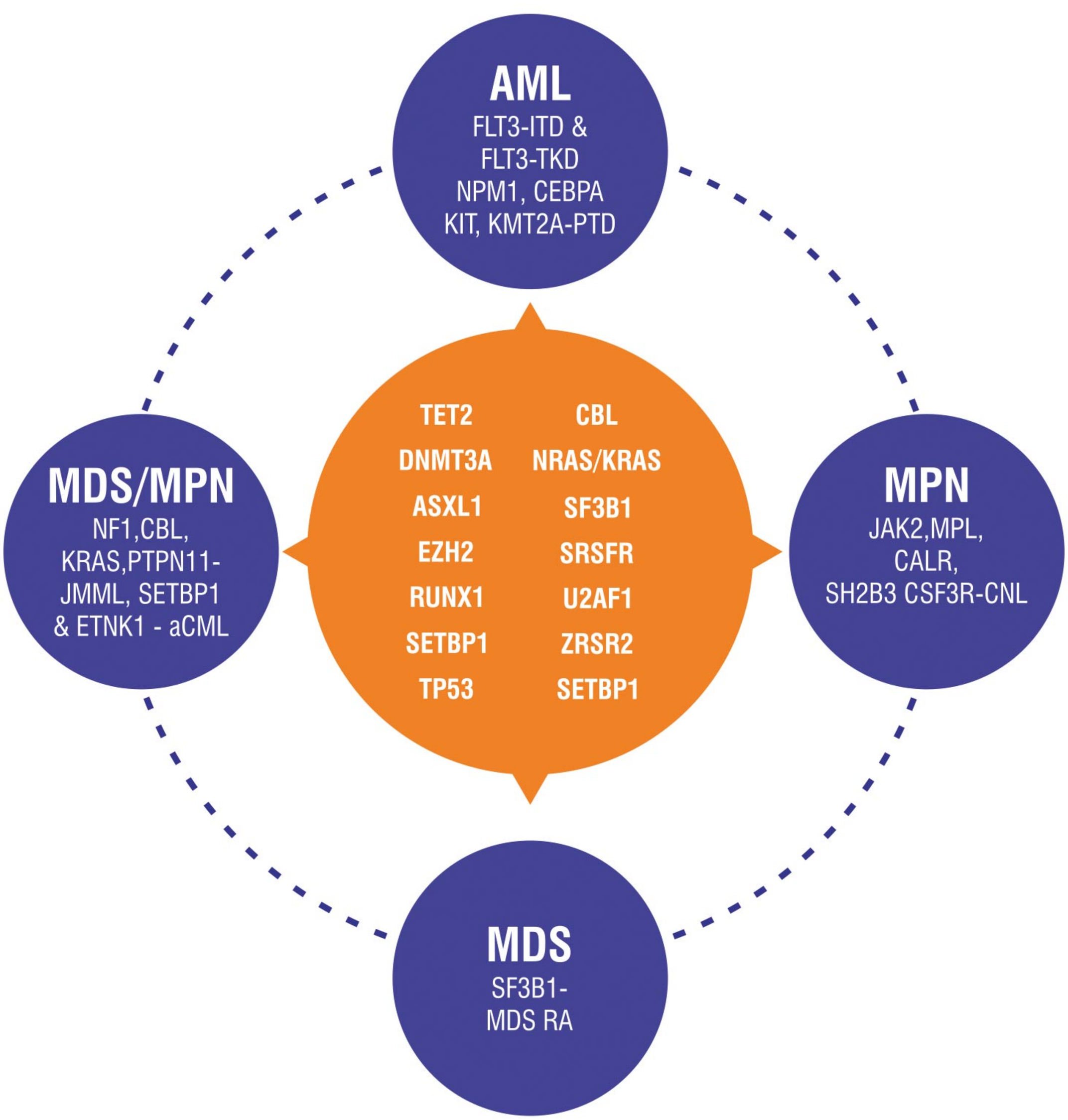


Table 1: Common Gene Mutations in Myeloproliferative Neoplasms

			Estimated Frequency (%)				
Class of Gene	**Chromosome Location**	**Mutation Location Typical Mutation Types**	**PV**	**ET**	**PMF**	**Post-MPN AML**	**Clinical Significance in PMF**
Signal Transduction (JAK/STAT Signaling)							
JAK2	9p24.1	Exon 14 (JAKA/ 617F; missense	95-97	50-60	55-60	40-50	The high JAK2 allelic burden in PV is associated with a greater risk of myelofibrotic transformation
JAK2 exon 12°	9p24.1	Exon 12: missense, deletions, insertions, and duplications	2	Rare	Rare	Not seen	Intermediate prognosis and greater risk of thrombosis compared with CALR mutation
MPL®	1p24.2	Exon 10; missense	<1	3-5	5-10	5-8	Intermediate prognosis and greater risk of thrombosis compared with CALR mutation
CALR®	19p13.13	Exon 9; insertion or deletions	<1	20-250 (~70% AK2 non mutated ET)	25-30 (~90% in JAK2 mutated	25	Favorable prognosis compared with JAK2 and triple-negative PMF; better OS of type 1/type 1-like CALR mutation compared with type2/type2-like
SH2B3	12q24	Exon 2; missense and deletion	Rare	Rare	Rare	10-13	Mostly seen in blast phase MPN (13%), suggesting its role in leukemic transformation
CBL	11q23	Exon 8-9; missense in any codons 366-420	Rare	0-2	5-10	5-9	Might be involved in leukemic transformation
Epigenetic Modification							
TET2	4q24	All exons; insertions or deletions, nonsense and missense	10-20	5	10-20	20-25	No prognostic effect
IDH1/IDH2°	2q33/1 5q26	Exon 4: IDH1: missense R132; IDH2: missense R1400, R172	2	<1	3-5	8-25	Independently associated with inferior OS
DNMT3A	2p23	Exons 7-23; most frequently seen is missense mutation in codon R882; nonsense, frameshift, or splice site		1-5	5-12	10-20	Might be associated with adverse outcome and greater risk of AML transformation
ASXL1°	20q11	Exon 13; frameshift or nonsense		5-10	15-35	15-20	TET2/ASXL1 mutations precede JAK2 mutation in MPN; independently associated with inferior OS and LFS
EZH2”	7q35-q36	All exons; nonsense or frameshift	2	2	5-10	Not seen	independently associated with inferior OS
Splicing Factors							
SF3B1°	2q33	Exon 12-16; missense in codons from 622-781	1	1	5-10	<5	Shows presence of ringed sideroblasts in BM with fibrosis
SRSF2	17q25	Exon 1; missense	Rare	Rare	10-17	19-33	Can co-occur with JET2, RUNX1, or ASXL1 mutations; associated independently with shorter LFS and OS
U2AF1	21q22	Exon 2-7; missense	<1	<1	5-16	5	Seen during progression and suggest advanced disease stage
DNA Repair/Tumor Suppressor Gene							
Tp53	17p13.1	Exons 4-9; nonsense or	<1	<1	5-10	2-4	Associated with disease progression

Table 2: Common Gene Mutations in AML

Gene	Location	Estimated Frequency (%)	Clinical Significance
FLT3-ITD	13q12.2	20-30	Common in NK-AML (35%); adverse outcome mainly in patients with high mutant FLT3-ITD ratio, FLT3 inhibitors are in clinical trials
CEBPA	19q13.11	6-15	Frequent with NK-AML; only AML with biallelic mutation included in recent 2016 WHO 6-15 Classification; favorable outcome
NPM1	5q35.1	30-35	AML with NPM17 is a 2016 WHO-defined entity in classification of myeloid neoplasms; frequently seen in NK-AML and tends to co-occur with FLT3-ITD, DNMT3A, IDH, and TET2 mutations; favorable prognosis with NPM1™ᵒᴵᴵ/FLT3™”
KIT	4q12	<5	Frequent in CBF-AML [t(8;21) and inv(16)/t(16;16)]. (20%-30%); adverse prognosis <5 in CBF AML
RUNX1	21q22.12	5-20	AML with RUNX7 mutation included as provisional entity in 2016 WHO classification of 5-20 myeloid neoplasms; frequent with old age, FAB MO morphology, tends to co-occur with ASKL1, SRSF2, IDH, and KMT2A-PTD; adverse outcome; germline mutation associated with familial platelet disorders with high risk of AML transformation
IDH1	2q34	6-15	Associated with NK-AML and NPM7 mutation; prognosis is controversial: 6-15 IDH1 mutation when combined with /DH2 showed no prognostic effect, although ome studies showed IDH1 mutation in NK-AML or favorable-risk AML (NPM1 mutation without FL73-ITD) had negative prognostic effect.
IDH2	15q26.1	8-20	Prognostic effect is not clear; in 1 study, /DH2 mutation showed poor prognosis in 8-20 patients with NK-AML and favorable-risk AML (NPM1 mutation without FLT3-ITD), and another study showed R140 /DH2 was associated with improved OS with younger patients (age < 60 y) with normal and abnormal karyotypes
TET2	4q24	7-25	Associated with NK-AML; mutually exclusive with /DH1 and /DH2 mutations; prognosis 7-25 is not clear
DNMT3A	2p23	18-22	Early genetic event; frequent in NK-AML; adverse outcome 18-22
ASXL1	20q11	5-17	Early genetic event; frequent in AML arising from previous myeloid neoplasm; mutually xclusive with NPM7 but often co-occurs with RUNX1, SRSF2 and IDH2. adverse outcome
KMT2A-PTD	11q23	3-7	Associated with trisomy 11 and/or >1 additional gene mutation in 90% cases 3-7 (eg, IDH2, DNMT3A, U2AF1, TET2
Tp53	17p13.1	5-18	Associated with complex karyotype and usually shows deletion of other TP53 locus; 5-18 resistance to therapy and adverse outcome

Abbreviations: AML = acute myeloid leukemia; CBF = core binding factor; FAB = French-American-British; ITD = internal tandem duplications; NK = normal karyotype; PTD = partial tandem duplication; WHO = World Health Organization.

Table 3: Common Gene Mutations in MDS & MDS/MPN

		MDS		MPN/MDS	
Class of Gene	**Gene Locus**	**Estimated Frequency (%)**	**Clinical Significance**	**Estimated Frequency (%)**	**Clinical Significance**
DNA Methylation					
TET2	4q24	10-25	Associated with normal karyotypes; no Prognosis Significance	50-60, CMML	No independent effect on LFS or OS
DNMT3A	2p23	2-8	Shorter OS and adverse outcome	<5	No effect on OS
Chromatin'/Histone modification					
ASXL1	20q11	14-25	Independently associated with poor prognosis	40-50	Associated with leukocytosis and monocytosis, and independently with poor prognosis in CMML
EZH2	7q35-7q36	6-12	Associated with loss of heterozygosity 7q and adverse outcome	5-10	No independent prognostic effects
Transcription factors					
RUNX1	21q22.3	10-15	Independently associated with poor	40-50	Associated with shorter LFS but no independent effect on OS
SETBP1	18q21.1	<5	Frequently seen with leukocytosis, monosomy 7, isochromosome 17q, and ASKL1, EZH2, and SRSF2 mutations ;associated with disease progression and shorter OS	5-10, CMML; 7,JMML; 25, aCML	Associated with leukocytosis, disease progression and poor prognosis
DNA repair					
Tp53	17p13.1	8-12	More frequent in complex karyotypes (50%) and del(5)q (20%): shows resistance to chemotherapy and independently with adverse outcome	Rare	
RNA splicing					
SF3B1	21q33.1	20-30	Most frequent mutation in MDS; more common in MDS-RS (80%); associated with favorable outcome	6(CMML) Greater in RARS-T(60-80)	
SRSF2	17q25.1	10-15	Shortern LFS and OS	35-50 (CMML)	Associated with old age, higher Hb, and normal karyotype; no independent prognostic effect in CMML
SRSF2	17q25.1	10-15	High risk of leukemic transformation and shorter OS	35-50 (CMML)	No independent prognostic effect in CMML

Abbreviations: aCML= atypical chronic myeloid leukemia; CMML= chronic myelomonocytic leukemia; CNL = chronic neutrophilic leukemia;Hb= hemoglobin ;JMML= juvenile myelomonocytic leukemia; LFS —jeukemia-freesurvival;MDS—myelody splastic syndromes ;MPN= myelo proliferative neoplasms;OS —overall survival ;RARS-T= refractory anemia with ringed sideroblasts and thrombocytosis..

Other Similar Assays:

Oncomine Myeloid V2 GX DNA only Assay

Oncomine Myeloid V2 GX RNA only Assay

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