



Sample Information

Patient Name: 張黃玉香**Gender:** Female**ID No.:** K201582834**History No.:** 42128938**Age:** 77**Ordering Doctor:** DOC6258D 林益庭**Ordering REQ.:** 0BRCLKW**Signing in Date:** 2022/01/22**Path No.:** S111-98213**MP No.:** MY22002**Assay:** Oncomine Myeloid Assay**Sample Type:** Bone Marrow**Bone Marrow Aspirating Date:** 2022/01/13**Reporting Doctor:** DOC5466K 葉奕成 (Phone: 8#5466)**Note:**

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Myelodysplastic Syndrome Variants

Gene	Finding	Gene	Finding
ASXL1	ASXL1 p.(Q733*) c.2197C>T	NPM1	None detected
BCOR	None detected	NRAS	None detected
CBL	None detected	NUP214	None detected
CREBBP	None detected	RUNX1	None detected
ETV6	None detected	SF3B1	None detected
EZH2	None detected	SRSF2	SRSF2 p.(P95L) c.284C>T
FLT3	None detected	STAG2	None detected
GATA2	None detected	TP53	None detected
IDH2	None detected	U2AF1	None detected
KIT	None detected	WT1	None detected
KMT2A	None detected	ZRSR2	None detected
MECOM	None detected		

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
SRSF2 p.(P95L) c.284C>T serine and arginine rich splicing factor 2 Allele Frequency: 24.62% Prognostic significance: NCCN: Poor Diagnostic significance: None	None	None	0
ASXL1 p.(Q733*) c.2197C>T ASXL transcriptional regulator 1 Allele Frequency: 25.90% Prognostic significance: NCCN: Poor Diagnostic significance: None	None	None	0

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

DNMT3A p.(R729G) c.2185C>G

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
DNMT3A	p.(R729G)	c.2185C>G	.	chr2:25463308	38.00%	NM_022552.4	missense	2000
SRSF2	p.(P95L)	c.284C>T	COSM146288	chr17:74732959	24.62%	NM_003016.4	missense	1962
ASXL1	p.(Q733*)	c.2197C>T	.	chr20:31022712	25.90%	NM_015338.6	nonsense	2000

Biomarker Descriptions

ASXL1 (ASXL transcriptional regulator 1)

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation^{1,2}. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3². ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones^{2,3}. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors^{2,4}. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD^{5,6,7}. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1⁸.

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)^{4,9,10,11,12,13,14,15,16}. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies^{6,11,17}. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence¹⁸. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing¹⁹. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation^{9,18,20}.

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic²¹. Mutations in ASXL1 confer poor/adverse risk in AML and are associated with poor

Biomarker Descriptions (continued)

outcomes and adverse risk¹⁶. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML²². Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM^{23,24}.

DNMT3A (DNA methyltransferase 3 alpha)

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA²⁵. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression^{26,27}.

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)^{12,16,28,29,30,31,32}. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer^{12,22}. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported^{12,28}. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations^{33,34}. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation^{35,36}. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity³⁷.

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML^{28,31,32,34}. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)³⁸.

SRSF2 (serine and arginine rich splicing factor 2)

Background: The SRSF2 gene encodes the serine/arginine (SR)-rich splicing factor 2, a member of the SR-rich family of pre-mRNA splicing factors which make up part of the spliceosome. SRSF2 contains an RNA recognition motif (RRM) that recognizes and binds exonic splicing enhancers (ESE) in a sequence-specific manner³⁹. SR proteins are essential regulators of alternative RNA splicing due to their ability to bind RNA and interact with other splicing factors. These proteins can influence the exclusion of cassette exons, a form of alternative splicing also known as exon skipping, which allows for the production of different protein isoforms^{39,40}. SRSF2 is the target of somatic missense mutations and in-frame deletions in hematological malignancies, particularly myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and myeloproliferative neoplasms (MPN)^{41,42,43}. Such mutations in SRSF2 result in a differential gain of function which influences cassette exon exclusion, thereby supporting an oncogenic role in cancer⁴⁴.

Alterations and prevalence: Mutations in SRSF2 are observed in approximately 10% of MDS cases and 30-40% of CMML^{42,45,46}. Missense mutations at P95 are most recurrent, which leads to an amino acid change from proline to histidine (H), leucine (L), or arginine (R)⁴⁶. Specifically, the P95H substitution alters SRSF2 affinity for ESEs and drives preferential recognition of cassette exons containing C- versus G-rich ESEs^{43,44}. Although less prevalent, recurrent in-frame deletions (P95H_R102del) are observed in primary myelofibrosis (PMF)⁴⁷. This mutation results in the deletion of 8 amino acids which has been shown to exhibit greater variation of splicing events relative to the P95 missense mutation alone⁴⁸.

Potential relevance: In CMML, SRSF2 mutations are often enriched and can be used to support diagnosis^{22,49}. SRSF2 mutations confer poor prognosis in MDS and systemic mastocytosis (SM) and are associated with decreased overall survival (OS)^{22,24,50}. In MPN, SRSF2 mutations are considered high-risk mutations and are independently associated with inferior OS as well as leukemia-free survival^{23,51}. Additionally, SRSF2 mutations are predictive of leukemic transformation in patients with PMF²³.

Prognostic Details

Current NCCN Information

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

SRSF2 p.(P95L) c.284C>T

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome

Variant class: SRSF2 P95 mutation

NCCN Recommendation category: 2A

Summary:

- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2022]

ASXL1 p.(Q733*) c.2197C>T

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome

Variant class: ASXL1 truncating mutation

NCCN Recommendation category: 2A

Summary:

- NCCN Guidelines® independently associate the biomarker with poor prognosis in MDS and CMML

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2022]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

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