Clinical Variant Report

This is not a medical product. Use only for research purposes!

Patient:

Name:	Demo patient
Birth date:	1972-02-28
Patient number:	1234
Sex:	M

Sample:

Sample taken:	2019-03-19
Diagnosis:	Demo sample
Comments:	Demo sample

Known Mutations

Mutations within the following regions are known to have therapeutical consequences.

Mutations found

KIT (exons 8, 10, 11, 17)	RUNX1 (exons 3-8)

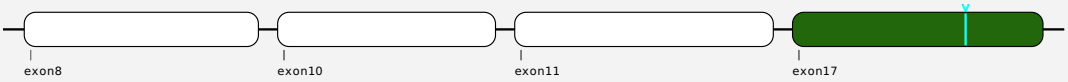
No mutations found, but insufficient coverage

NPM1 (type A)	FLT3_TKD	FLT3_ITD	DNMT3A (R882)	TET2 (exons 3-11)	CEBPA
IDH1_mut	IDH2_mut	ASXL1 (exons 9, 12)	WT1 (rs16754)	MLL_breakpt_clstr	MLL_PTD_coding
ABL1 (exons 4-6)	JAK1_TKD	JAK2 (Y931)	BTK (exon15)	MYD88_mut	PLCG2 (Ser707Tyr)
PML_muts	SRSF2_c95ex1				

KIT (exons 8, 10, 11, 17)

Mutations found in this region

Considered Region



Region evidence

KIT mutations were associated with a **higher cumulative incidence of relapse**, but in multivariate analysis this was only significant for cases with a higher mutant level of 25% or greater. Mutations in exon 8 are usually in-frame insertions or deletions that affect an extracellular domain of the receptor implicated in receptor dimerization (KIT-ECD).

http://www.nature.com/leu/journal/v27/n9/full/leu2013186a.html

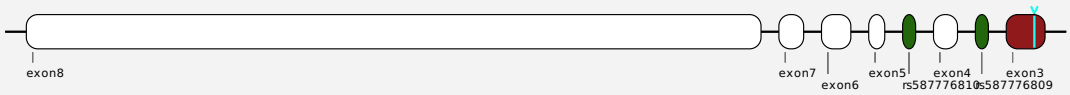
Mutations found

Color	chr	pos	dbSNP	Transcripts	Exons	Codons	Proteins	NRalt	Cvg	Freq	1000G	Provean	ClinVar	Cosmic	CosmicSNP	Category
	4	55599321	rs121913507	ENST00000288135 ENST00000412167	17 17	c.2447A>T c.2435A>T	p.D816V p.D812V	257	558	0.4606		-7.53 -7.53	Uncertain significance			

RUNX1 (exons 3-8)

Mutations found in this region

Considered Region



Region evidence

RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis

http://www.ncbi.nlm.nih.gov/pubmed/21148331

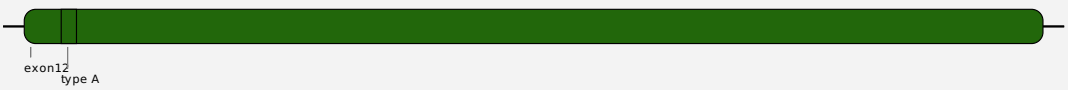
Mutations found

Color	chr	pos	dbSNP	Transcripts	Exons	Codons	Proteins	NRalt	Cvg	Freq	1000G	Provean	ClinVar	Cosmic	CosmicSNP	Category
	21	36259324	rs111527738	ENST00000300305 ENST00000325074 ENST00000344691 ENST00000358356 ENST00000399237 ENST00000399240 ENST00000437180 ENST00000455571 ENST00000486278	3 2 1 1 2 1 4 3 4	c.167T>C c.131T>C c.86T>C c.86T>C c.131T>C c.86T>C c.167T>C c.128T>C c.95T>C	p.L56S p.L44S p.L29S p.L29S p.L44S p.L29S p.L56S p.L43S p.L32S	440	453	0.9713	0.0103834	-0.65 -0.54 -0.08 -0.09 0.4 -0.8 -0.1 0.31	Benign/Likely benign			

NPM1 (type A)

No mutations but low coverage in this region

Considered Region



Region evidence

NPM1 exon 12 mutations are frequently identified in patients with cytogenetically normal acute myeloid leukemia (AML) and often co-occur with FLT3-ITD. FLT3 status should also be evaluated as co-occurence with FLT3-ITD may impact prognosis. Exon 12 mutations have been identified as a predictor of good prognostic outcomes in the absence of FLT3-ITD. Due to their high frequency, NPM1 mutations have been retrospectively analyzed in the context of a number of therapies including variable results following ATRA treatment as well as improved response to high-dose daunorubicin or valproic acid. Additionally, multiple groups have shown increased surface expression of CD33 associated with NPM1 mutation, suggesting these patients may respond to anti-CD33 therapy. Cytoplasmic sequestration of NPM1 (NPM1c) is associated with a good response to induction therapy.

https://civicdb.org/events/genes/35/summary/variants/86/summary#variant

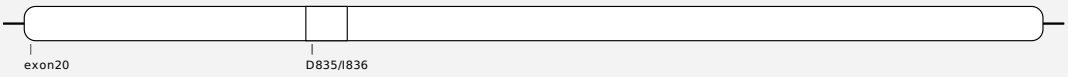
Mutations found

No Mutations

FLT3_TKD

No mutations but low coverage in this region

Considered Region



Region evidence

FLT3-TKD mutations are small mutations in the activation loop of FLT3, mostly representing point mutations in codon D835 or deletions of codon I836 (on exon 20 [Myeloid Leukemia: Methods and Protocols, Iland]). They induce constitutive tyrosine phosphorylation leading to activation of the receptor tyrosine kinase and are supposed to represent gain-of-function mutations.

http://www.bloodjournal.org/content/111/5/2527.long

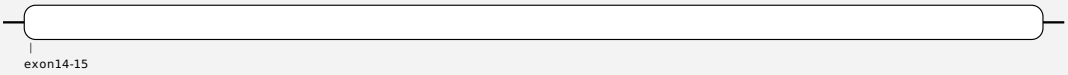
Mutations found

No Mutations

FLT3_ITD

No mutations but low coverage in this region

Considered Region



Region evidence

FLT3-ITD (internal tandem duplications) frequently occur in patients with hematologic malignancies such as chronic myelogenous leukemia, acute myeloid leukemia (AML) and myelodysplastic syndrome, but particularly in cytogenetically normal AML (CN-AML). These duplication events disrupt the juxtamembrane domain of FLT3 and can be the result of a duplication of internal FLT3 sequence or other unrelated sequence resulting in an in-frame duplication event. The length of these duplications can vary widely which may have prognostic consequences, but this has not been conclusively determined. FLT3-ITD mutations overall have generally been associated with poor prognosis. Additional genes associated with CN-AML such as NPM1 may modulate the prognosis associated with this variant.

https://civicdb.org/events/genes/24/summary/variants/55/summary#variant

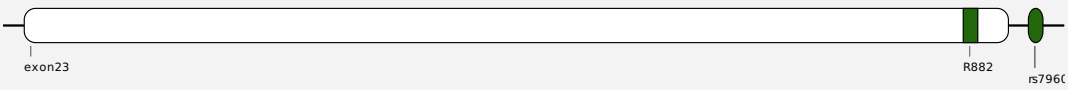
Mutations found

No Mutations

DNMT3A (R882)

No mutations but low coverage in this region

Considered Region



Region evidence

DNMT3A mutations can lead to epigenetic modifications and can cause excessive hypermethylation of tumor suppressor genes resulting in increased tumor growth. Methyltransferase inhibitors including decitabine and azacitidine inhibit the activity of DNMT3A and will decrease DNA methylation and potentially restore regular transcriptional activity of tumor suppressor genes.

https://civicdb.org/events/genes/18/summary/variants/189/summary#variant

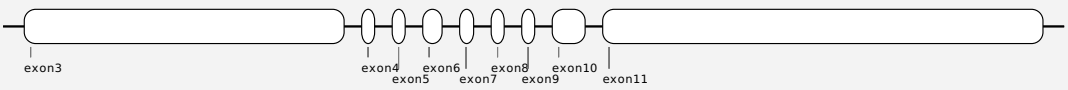
Mutations found

No Mutations

TET2 (exons 3-11)

No mutations but low coverage in this region

Considered Region



Region evidence

In patients receiving intensive therapy, one group found a negative prognostic effect restricted to patients with CN-AML and favourable genetic aberrations (NPM1 mutated/FLT3 no ITD, or CEBPA mutated) (Metzeler et al, 2012b), which could not be confirmed in other analyses (Shen et al, 2011; Gaidzik et al, 2012; Nomdedeu et al, 2012). Another group found TET2 mutations were a negative prognostic factor in patients with intermediate cytogenetic risk (Chou et al, 2011a). However, it lost its independent significance when additional genetic aberrations were considered (Hou et al, 2012). Higher response rate after 5-azacitidine in patients with 20–30% BM blasts [Itzykson et al (2011)]

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12750/full

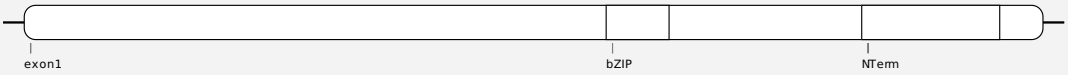
Mutations found

No Mutations

CEBPA

No mutations but low coverage in this region

Considered Region



Region evidence

Importantly, recent studies show that only double, but not single, CEBPA mutations predict for this **favorable outcome**, whereas AML with a single CEBPA mutation is associated with survival similar to that of AML with wild-type CEBPA. Therefore, with regard to disease classification and risk stratification, **only AML with double CEBPA mutations** likely define a distinct entity with **favorable prognosis**

http://jco.ascopubs.org/content/29/5/475.full#sec-3

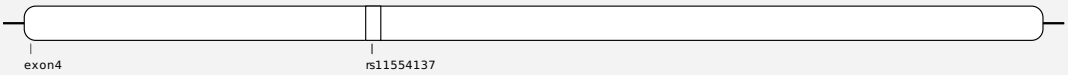
Mutations found

No Mutations

IDH1_mut

No mutations but low coverage in this region

Considered Region



Region evidence

Mutations of the isocitrate dehydrogenase 1 gene (IDH1) have been reported as an adverse prognostic factor only in genetically defined subgroups of patients (Abbas et al, 2010; Boissel et al, 2010; Green et al, 2010b; Marcucci et al, 2010; Paschka et al, 2010; Schnittger et al, 2010; Nomdedeu et al, 2012), while a prognostic impact could not be detected by others (Chou et al, 2010a; Ho et al, 2010; Wagner et al, 2010; Shen et al, 2011; Zhang et al, 2011; Chotirat et al, 2012; Patel et al, 2012; Ravandi et al, 2012)

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12750/full

Mutations found

No Mutations

IDH2_mut

No mutations but low coverage in this region

Considered Region

Region evidence

The prognostic effect of IDH2 mutations is even less clear, with some groups finding **a positive impact on survival** (Chou et al, 2011b; Patel et al, 2012), while others found **a negative impact** in defined subgroups (Paschka et al, 2010; Rockova et al, 2011; Ravandi et al, 2012) or in the total cohort when only the R172 mutation was evaluated (Boissel et al, 2010). One group found divergent results with a favourable impact of the R140 and a nonsignificant unfavourable impact of the R172 mutation (Green et al, 2011). Most groups did not find a prognostic impact of IDH2 mutations (Abbas et al, 2010; Marcucci et al, 2010; Thol et al, 2010; Chotirat et al, 2012; Nomdedeu et al, 2012; Renneville et al, 2012). A recent meta-analysis found a positive prognostic impact of IDH2 mutations on survival (Zhou et al, 2012).

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12750/full

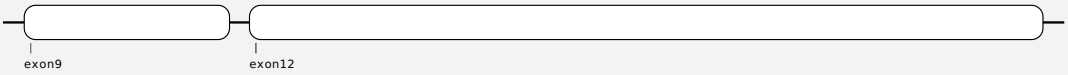
Mutations found

No Mutations

ASXL1 (exons 9, 12)

No mutations but low coverage in this region

Considered Region



Region evidence

ASXL1 mutations were found to be an independent adverse prognostic factor for survival in patients with CN-AML (Schnittger et al, 2013) and in older patients with CN-AML and favourable genetic risk (Metzeler et al, 2011). ASXL1 mutations were an adverse factor for survival in a univariate analysis, but not in a multivariate analysis in a Taiwanese study (Chou et al, 2010b).

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12750/full

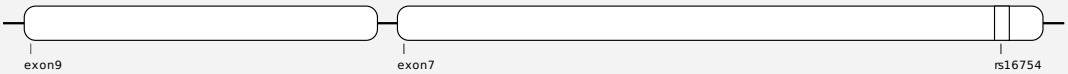
Mutations found

No Mutations

WT1 (rs16754)

No mutations but low coverage in this region

Considered Region



Region evidence

Wilms tumor 1 gene (WT1) mutations are detected in approximately 10–13% of AML and an independent **negative prognostic impact** (Paschka et al, 2008; Virappane et al, 2008), as well as **no prognostic impact** (Gaidzik et al, 2009; Damm et al, 2010) have been reported in CN-AML patients.

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12750/full

Mutations found

No Mutations

MLL_breakpt_clstr

No mutations but low coverage in this region

Considered Region

Region evidence

MLL-PTD have been associated with **inferior CR duration and relapse-free survival**, although **more recent studies show no prognostic impact** in patients with CN-AML intensively treated with autologous HSCT or four cycles of consolidations

http://jco.ascopubs.org/content/29/5/475.full#sec-3

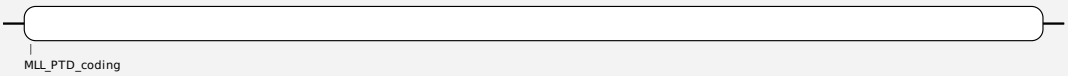
Mutations found

No Mutations

MLL_PTD_coding

No mutations but low coverage in this region

Considered Region



Region evidence

MLL-PTD have been associated with **inferior CR duration and relapse-free survival**, although **more recent studies show no prognostic impact** in patients with CN-AML intensively treated with autologous HSCT or four cycles of consolidations

http://jco.ascopubs.org/content/29/5/475.full#sec-3

Mutations found

No Mutations

ABL1 (exons 4-6)

No mutations but low coverage in this region

Considered Region

Region evidence

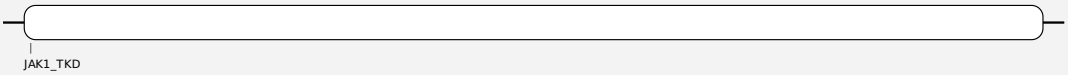
Mutations found

No Mutations

JAK1_TKD

No mutations but low coverage in this region

Considered Region



Region evidence

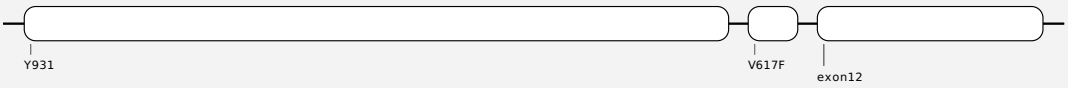
Mutations found

No Mutations

JAK2 (Y931)

No mutations but low coverage in this region

Considered Region



Region evidence

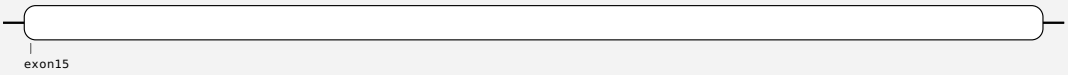
Mutations found

No Mutations

BTK (exon15)

No mutations but low coverage in this region

Considered Region



Region evidence

Mutations found

No Mutations

MYD88_mut

No mutations but low coverage in this region

Considered Region

Region evidence

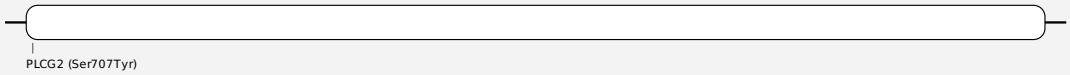
Mutations found

No Mutations

PLCG2 (Ser707Tyr)

No mutations but low coverage in this region

Considered Region



Region evidence

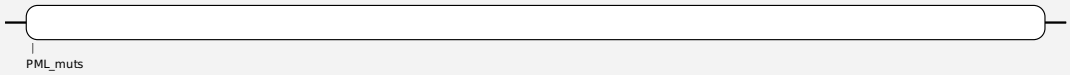
Mutations found

No Mutations

PML_muts

No mutations but low coverage in this region

Considered Region



Region evidence

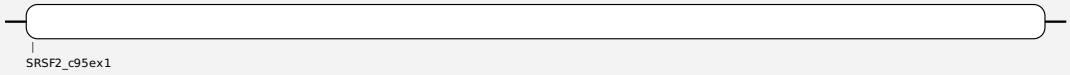
Mutations found

No Mutations

SRSF2_c95ex1

No mutations but low coverage in this region

Considered Region



Region evidence

Mutations found

No Mutations

Coverage color-coding:

Full region meets coverage threshold (default: 20 r... >=99% of region meets coverage thresh... >=98% coverage >=97% coverage >=96% coverage >=95% coverage >=94% coverage <94% coverage

Possible interpretation

Intermediate 1 (no NPM1 mutation, no FLT3_ITD)	Source: Modified ELN-Classification
Adverse (RUNX1 mutation)	Source: Acute Myeloid Leukemia. Döhner H, Weisdorf DJ, Bloomfield CD. N Engl J Med. 2015 Sep 17;373(12):1136-52.
Adverse (c-KIT)	Source: Acute Myeloid Leukemia. Döhner H, Weisdorf DJ, Bloomfield CD. N Engl J Med. 2015 Sep 17;373(12):1136-52.

This sample was sequenced with lab design 0 (Sequencer: Ilumina, Panel: DEMO).
The analysis and report generation was generated on Tue, 19 Mar 19 19:04:43 0100 with AMLVaran configuration version 0.
Detailed information about the processing steps can be obtained from http://amlvaran.uni-muenster.de/doc/Version0.pdf.