Case SH2017-0281

Acute Myeloid Leukemia with RUNX1 and Several Co-mutations

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Clinical History

Chief Complaint: 72 year old man presented with worsening dyspnea, poor appetite and weight loss.

Past Medical History: Hypertension, Diverticulosis

Social History: Retired mill worker, non-smoker, occasional drinks

Family History: Father- heart disease, Mother- gastric cancer

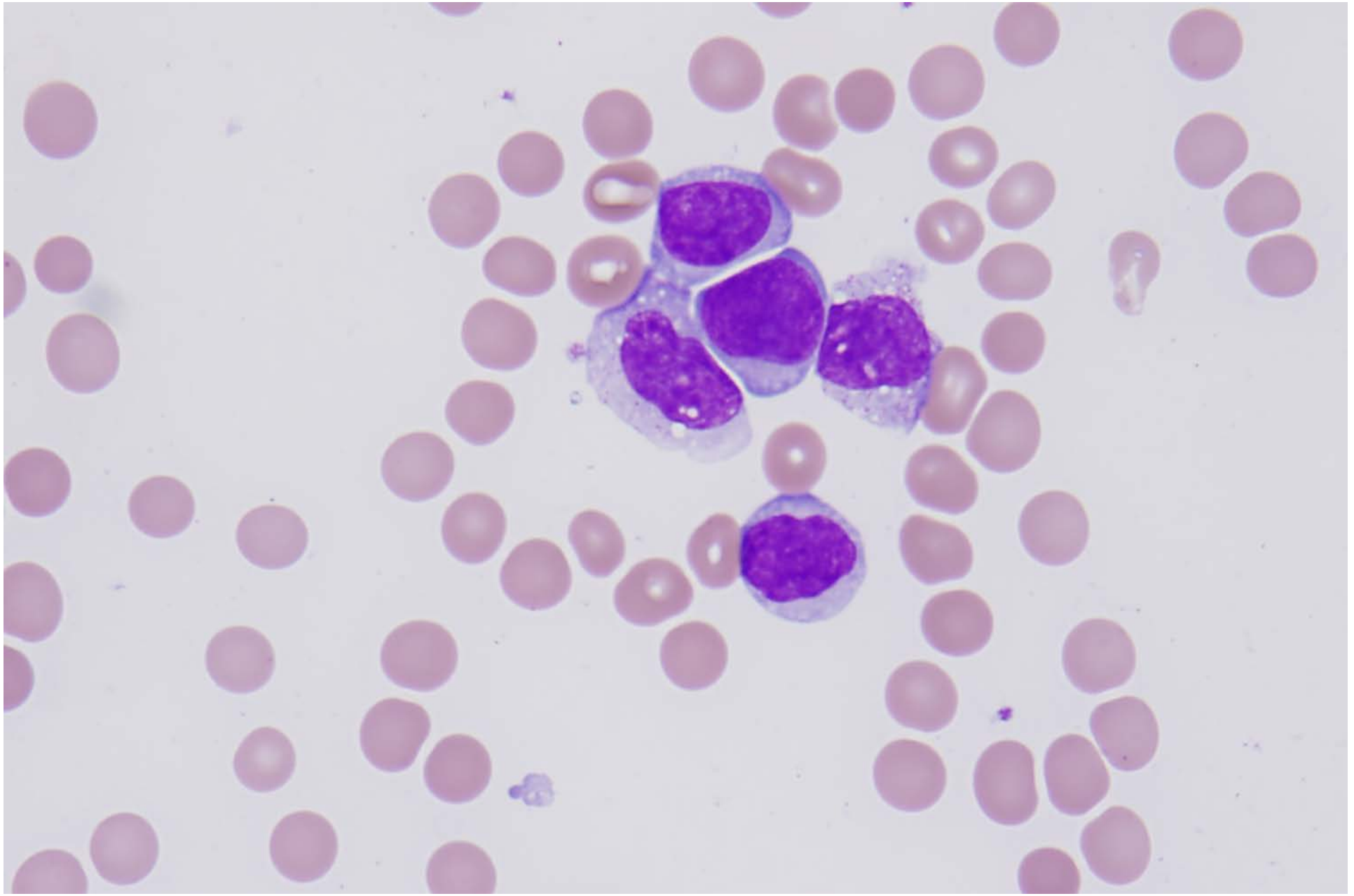
Physical exam: No lymphadenopathy, no hepatosplenomegally

Peripheral Smear:

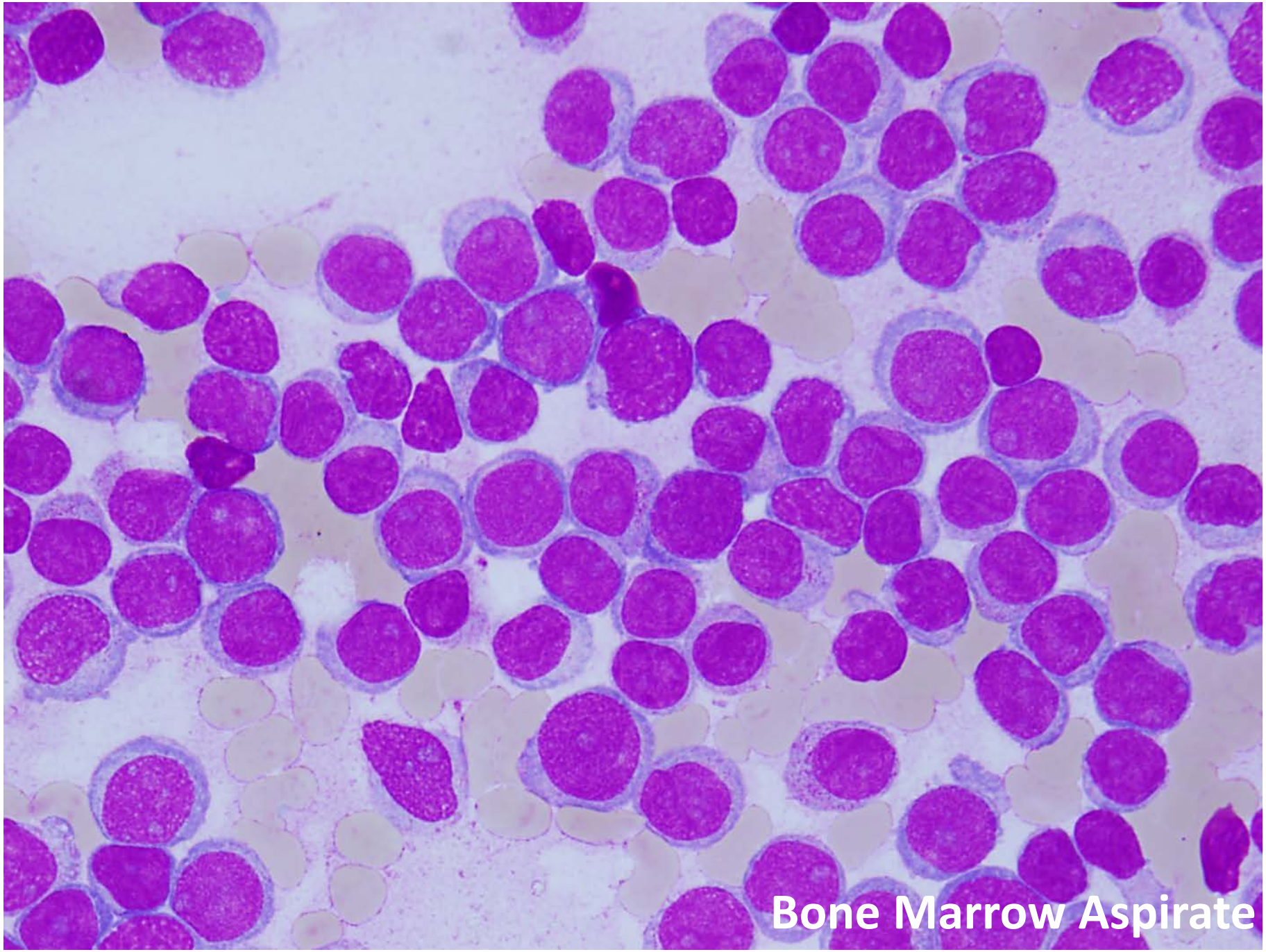
CBC:

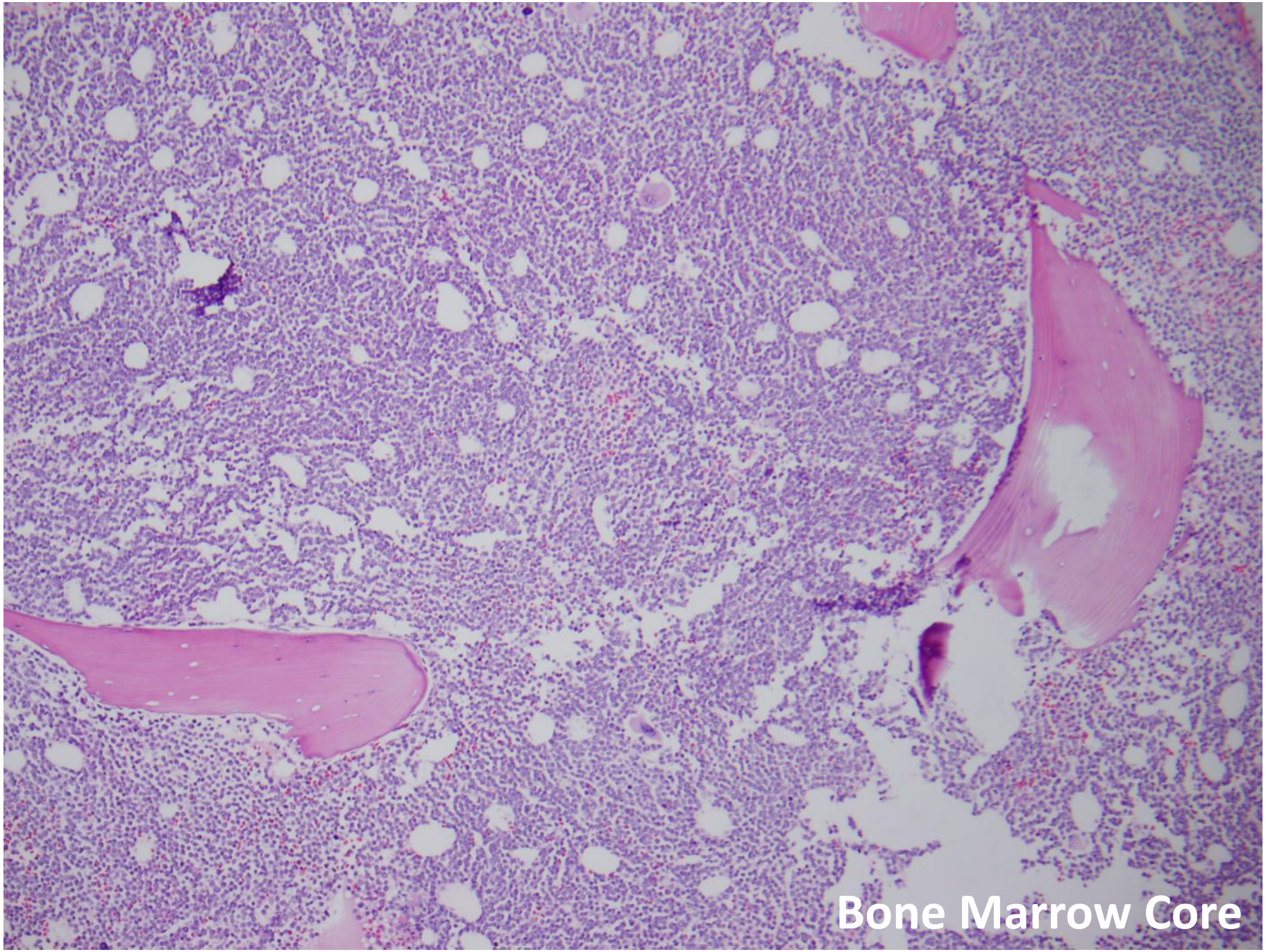
WBC	119	K/uL
Hgb	6.7	g/dL
Hct	20	%
Plt	102	K/uL

Neut	1190	/uL
Lymph	8340	/uL
Mono	2380	/uL
Blast	107190	/uL



Peripheral Smear


Bone Marrow Aspirate


Bone Marrow Core

Flow Cytometry:

CD45 dim blasts comprise 90% of the nucleated cells. The blasts express CD34, CD117, CD33, and dim TdT. A subset of blasts show a monocytic phenotype with expression of CD11b, CD14, bright CD64, CD33 and dim CD34 without CD117.

Cytogenetics/FISH:

Karyotype:

46~47, XY, add(4)(q21), inc[2]/46, XY[15]

FISH for CBFB rearrangement in 16q22 was negative

Illumina based Targeted NGS (ARUP Myeloid Malignancies Mutation Panel):

Tier 1 Variants:

1. RUNX1 c.601C>T, p.Arg201* (NM_001754.4) VAF: 91.1%
2. U2AF1 c.101C>T, p.Ser34Phe (NM_006758.2) VAF: 45.9%
3. WT1 c.1138delinsGG, p.arg380fs (NM_024426.4) VAF: 34.7%
4. PHF6 c.903delinsGT, p.TYR301* (NM_001015877.1) VAF: 7.8%
5. FLT3 c.2039C>T, p.Ala680Val (NM_004119.2) VAF: 31.3%

Tier 2 Variants: None detected

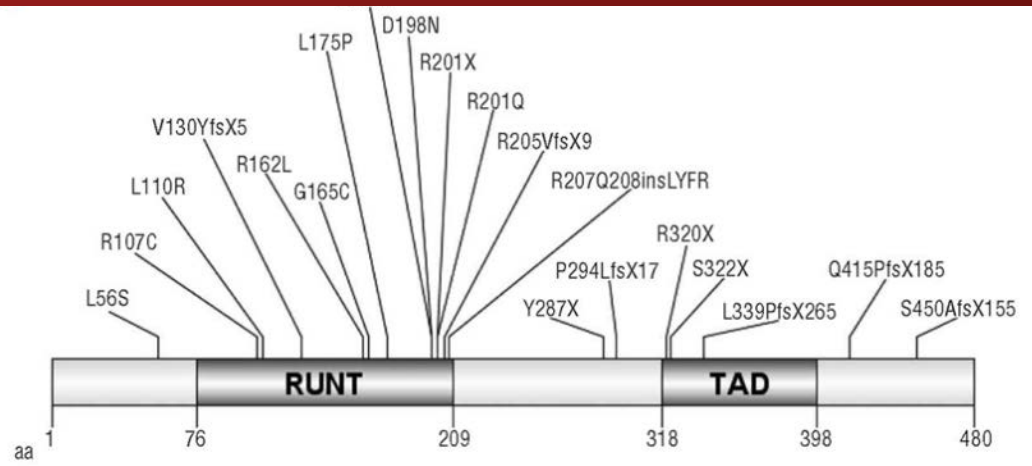
Tier 3 Variants: None detected

Final Diagnosis:

- AML with mutated RUNX1

(*provisional entity*, WHO acute leukemia classification 2016 revision)

Runx1 Biology



- Transcription factor essential for hematopoiesis
- 261 kb gene on the long arm of chromosome 21
- Most point mutations within the 2 major functional domains:
  - Runt-homology domain (RHC, RUNT)- DNA binding, interaction with CBFβ
  - Transactivation domain (TAD)

Philipp A. Greif et al. Haematologica 2012;97:1909-1915

RUNX1 in Hematologic Malignancy

Recurrent chromosomal translocations:

- t(8;21)(q22;q22) *RUNX1-RUNX1T1* } AML
- t(3;21)(q26.2;q22) *MCOM(EVI1)-RUNX1* } AML

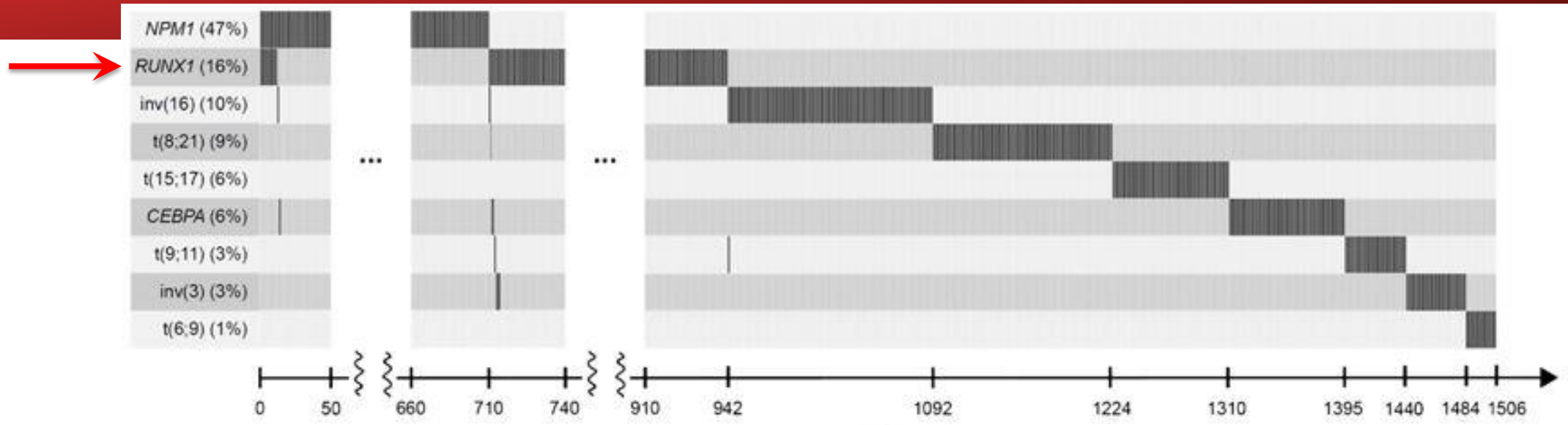
- t(12;21)(p13;q22) *ETV6-RUNX1* } B-lymphoblastic leukemia

Point mutations:

- Missense
- Nonsense
- Frameshift

} AML, MDS, Therapy-related MDS/AML, CMML, T-lymphoblastic leukemia, Congenital bone marrow failure syndromes (Fanconi anemia and congenital neutropenia), Familial platelet disorder with associated myeloid malignancy

RUNX1 Point Mutations in AML

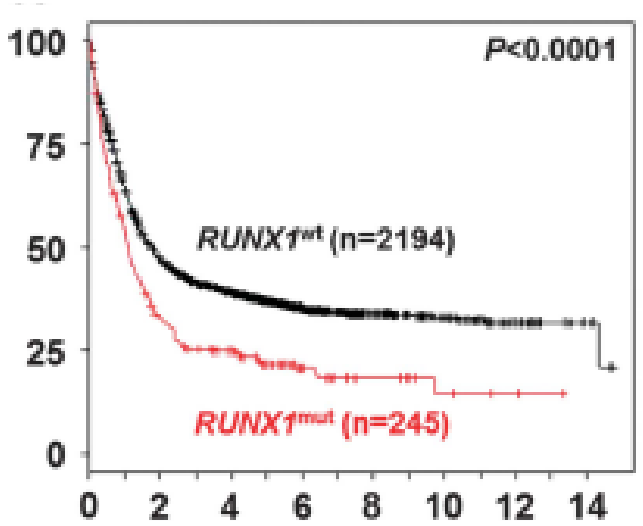


- RUNX1 point mutations found in 10% of patients with AML
  - 9% in de novo AML and 24% in secondary AML
- AML with RUNX1 point mutations were almost exclusive of AML with recurrent genetic abnormalities
- Associated with older age, male sex, and secondary AML evolving from MDS
- Predominantly inactivating mutations in the RHD domain

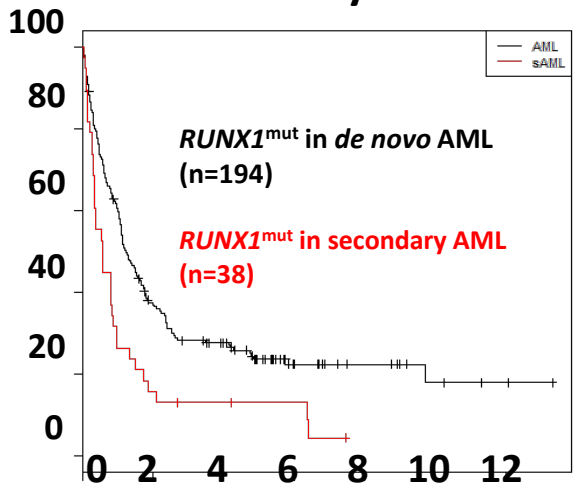
Gaidzik VI et al. Leukemia 2016;30:2160-2168

Effect of RUNX1 Point Mutations in AML

AML: RUNX1^{wt} vs RUNX1^{mut}



RUNX1^{mut}: *de novo* AML vs secondary AML



- RUNX1 mutated AML are associated with inferior overall survival
- RUNX1 mutated secondary AML (AML from MDS) had inferior outcome compared to RUNX1 mutated de novo AML

Gaidzik VI et al. Leukemia 2016;30:2160-2168

RUNX1 Mutations in MDS

- RUNX1 mutations can be found in up to 20% of MDS cases including:
  - Primary MDS
  - MDS arising from congenital bone marrow failure syndromes
    - Fanconi anemia, 20%
    - Congenital neutropenia, 68%
  - Therapy-related MDS/AML
    - Frequently associated with monosomy 7/del 7q
  - AML arising from progression of MDS
    - AML with myelodysplasia related changes

Harada H et al Blood 2004;103:2316-2324
Christiansen DH et al Blood 2004;104:1474-1481
Quentin S et al Blood 2011;117:e161-e170
Skokowa J et al Blood 2014;123:2229-2237

AML with myelodysplasia related changes

- Morphologic detection of dysplasia in at least 50% of cells in 2 lineages

  or

- History of MDS

  or

- Presence of MDS-related cytogenetic abnormality

Cytogenetic abnormalities sufficient to diagnose AML with MRC

Complex karyotype (3 or more abnormalities)	
Unbalanced abnormalities	
-7/del(7q) del(5q)/t(5q) i(17q)/t(17p) -13/del(13q)	del(11q) del(12p)/t(12p) idic(X)(q13)
Balanced abnormalities	
t(11;16)(q23.3;p13.3) t(3;21)(p26.3;q21.2) t(1;3)(p36.3;q21.2) t(2;11)(p21;q23.3) t(5;12)(q32;p13.2)	t(5;7)(q32;q11.2) t(5;17)(q32;p13.2) t(5;10)(q32;q21.2) t(3;5)(q25.3;q35.1)

Familial platelet disorder with predisposition to acute myeloid leukemia

- Rare autosomal dominant disorder with germline RUNX1 mutation
- Clinical symptoms:
  - Mild to moderate thrombocytopenia
  - Platelet dysfunction
  - Bleeding propensity
  - 40% lifetime risk for development of MDS and AML, average age of onset 33 years
- Over 70 families identified, most with unique RUNX1 mutations

Sood R et al. Blood 2017;129:2070-2082

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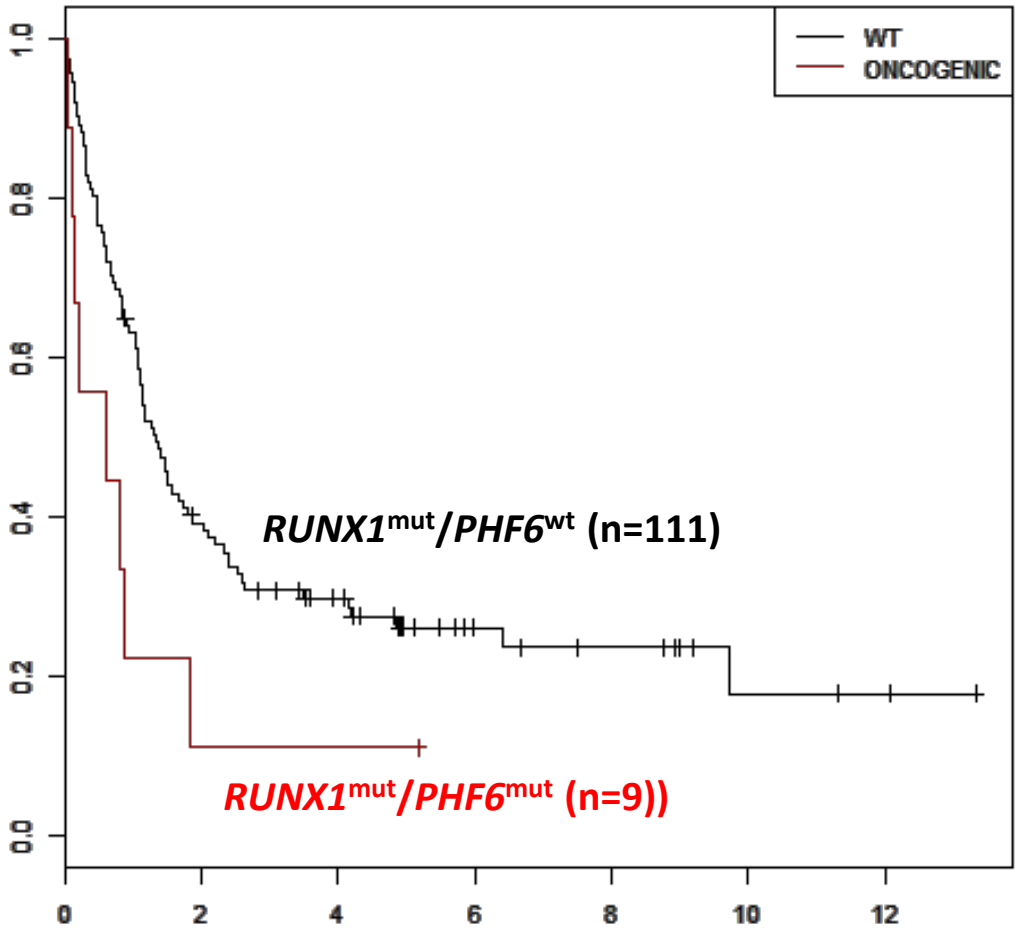
RUNX1 somatic mutations in AML: Biallelic mutations and co-mutations

- Over 50% of RUNX1 mutations in undifferentiated AML (M0) are biallelic
- RUNX1 mutations co-occur with:
  - Epigenetic modifiers (ASXL1, IDH2, KMT2A, EZH2)
  - Spliceosome components (SRSF2, SF3B1)
  - FLT3-ITD and FLT3-TKD
  - STAG2, PHF6, and BCOR
- Some co-mutations (ASXL1, SRSF2, PHF6) are associated with inferior prognosis



Osato M. Oncogene 2004;23:4284-4296
Gaidzik VI et al. Leukemia 2016;30:2160-2168