WHO SINIFLAMASINDA AKAN HÜCRE ÖLÇER ile AML

TANISAL YAKLAŞIMDA İNCE NOKTALAR

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YEDİTEPE ÜNİVERSİTESİ HASTANESİ

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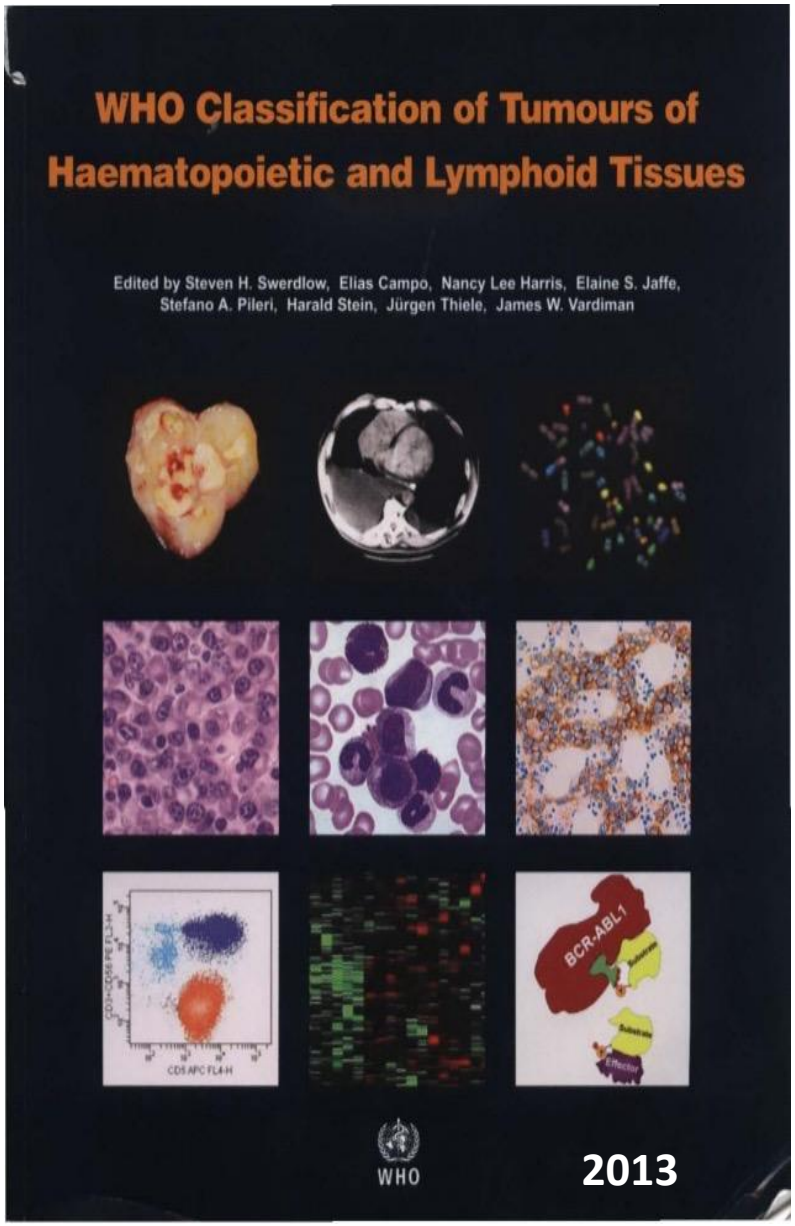
SUNUM AKIŞI

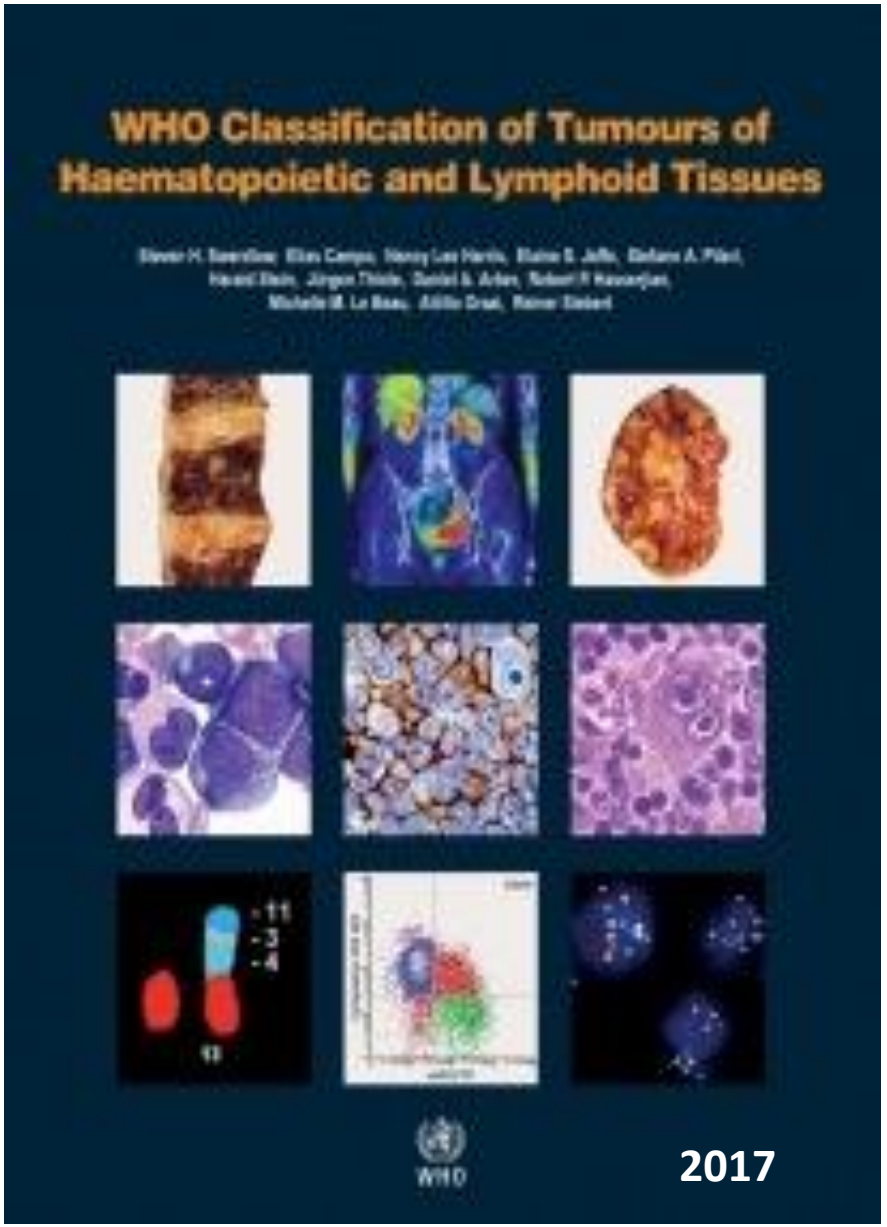
- AML - laboratuvarda tanı
- WHO Sınıflaması - genişletilmiş 4. basım
- FAB Sınıflaması
- İmmünfenotipleme
- Akan hücre ölçerle mutasyonların incelenmesi
- Gelecekte laboratuvar
- Sonuç/Yorum

AML TANISI İÇİN NE GEREKİYOR?

Tanı aracı	Test	Beklenen bulgular
1. Mikroskopi	*Morfoloji*	*% blast* *% displastik hücre*
2. Flow Cytometry Mikroskopi/Floresan mikroskopi	*İmmünfenotipleme*	*Myeloid dizin hücreleri doğrulama* *Blast belirteçlerini belirleme (CD13, CD33, CD34, CD117, MPO)*
3. Mikroskopi/Floresan mikroskopi	*Sitogenetik*	*AML tanımlayıcı karyotip belirlenmesi*
4. Moleküler Yöntemler	*FLT3*, NPM1, CEPBA, RUNX, BCR-ABL 1, KIT vb diğer prognostik belirteçler*	*Tanı* *Prognoz* *Prediktif belirteç*

**Tüm AML tiplerinde FLT3 mutasyon analizinin yapılması gerekli*


WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues
Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman
BCR-ABL1
WHO
2013


WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues
WHO
2017

WHO SINIFLAMASI NASIL YAPILIYOR?

Klinik veriler, morfoloji bulguları, immunofenotip ve genetik verileri olan hasta «cohort»ları inceleniyor

Terminoloji ve tanı kriterlerini belirlemek üzere bir fikirbirliği sürecinden geçerek farklı hastalık tiplerinin belirlenmesi

Daha önceden belirlenen tanı kriterlerine uygun olarak hangi hastanın hangi sınıfta olduğunun belirlenmesi

WHO MYELOİD NEOPLAZİ ve AKUT LÖSEMİ SINIFLANDIRMASI

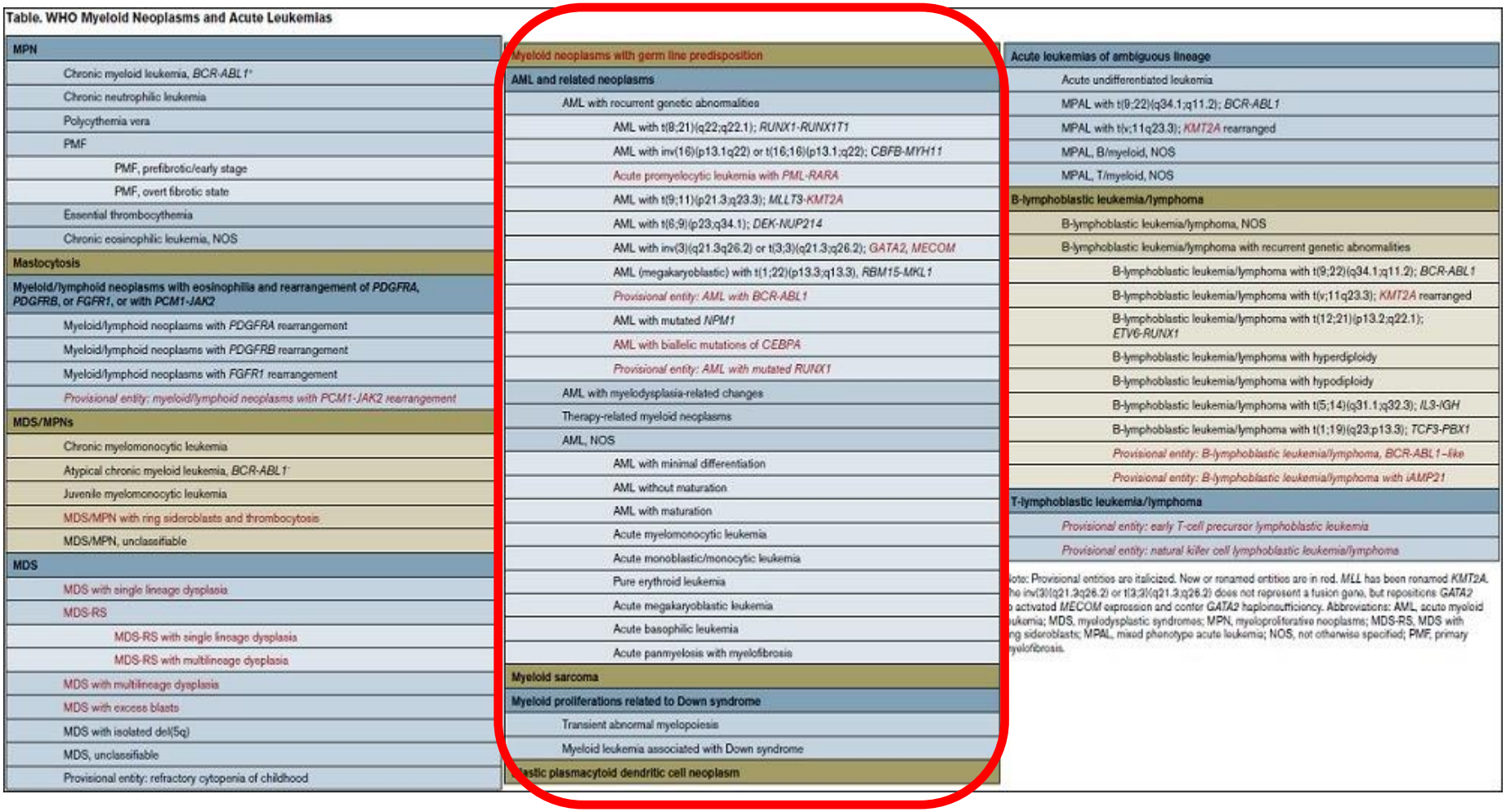


Table. WHO Myeloid Neoplasms and Acute Leukemias

MPN
Chronic myeloid leukemia, *BCR-ABL1*+
Chronic neutrophilic leukemia
Polycythemia vera
PMF
PMF, prefibrotic/early stage
PMF, overt fibrotic state
Essential thrombocythemia
Chronic eosinophilic leukemia, NOS
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: myeloid/lymphoid neoplasms with PCM1-JAK2 rearrangement
MDS/MPNs
Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia, *BCR-ABL1*-
Juvenile myelomonocytic leukemia
MDS/MPN with ring sideroblasts and thrombocytosis
MDS/MPN, unclassifiable
MDS
MDS with single lineage dysplasia
MDS-RS
MDS-RS with single lineage dysplasia
MDS-RS with multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: refractory cytopenia of childhood

Myeloid neoplasms with germ line predisposition
AML and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
Acute promyelocytic leukemia with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3), *RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
...lastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: early T-cell precursor lymphoblastic leukemia
Provisional entity: natural killer cell lymphoblastic leukemia/lymphoma

...ote: Provisional entities are italicized. New or renamed entities are in red. *MLL* has been renamed *KMT2A*. ...he inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) does not represent a fusion gene, but repositions *GATA2* ...o activated *MECOM* expression and confer *GATA2* haploinsufficiency. Abbreviations: AML, acute myeloid ...ukemia; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; MDS-RS, MDS with ...g sideroblasts; MPAL, mixed phenotype acute leukemia; NOS, not otherwise specified; PMF, primary ...yelofibrosis.

George TI, Czuchlewski DR. Blood, 2016 13(5):Mini review

FAB SINIFLAMASI

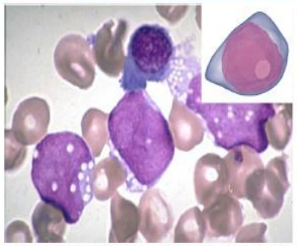


Photo courtesy of: *Acute myeloid leukemia pathophysiology, 2012*

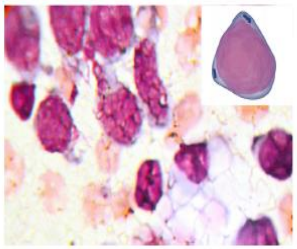
M0 Acute myeloblastic leukaemia with minimal differentiation

Morphology:

Can resemble LLA-L2 blasts. Medium-sized blasts, rounded nucleus, fine chromatin, basophilic non-granular cytoplasm, prominent nucleoli.

Immunophenotype

- CD13 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD15 +



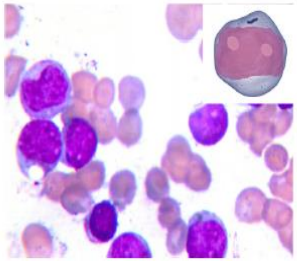
M1 Acute myeloblastic leukaemia without maturation

Morphology:

Medium-sized blasts with high nucleo:cytoplasm (n:c) ratio, rounded nuclei with immature, dispersed chromatin with one or more prominent nucleoli. Blasts can show fine azurophilic granulation or isolated Auer rods in the cytoplasm in 5% to 10% of cases

Immunophenotype

- MPO +
- CD13 +
- CD33 +
- CD117+
- CD34 +/-



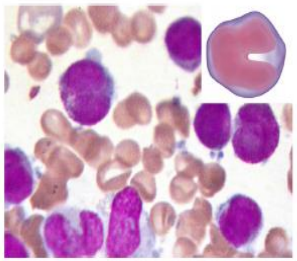
M2 Acute myeloblastic leukaemia with maturation

Morphology:

Small to medium-sized blasts with high nucleo: cytoplasm (n:c) ratio and rounded nuclei sometimes located in a corner of the cytoplasm. The nucleus shows dispersed, immature chromatin with one or more nucleoli. The cytoplasm is basophilic and can contain traces of primary azurophilic granulation or isolated Auer rods.

Immunophenotype

- MPO +
- CD34 +/-
- CD13 +
- CD15 +
- HLA-DR +/-
- Sudan black +
- CD117 +/-



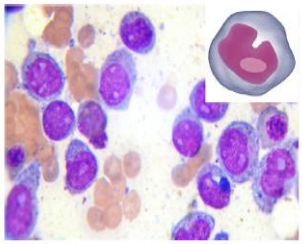
M3 Promyelocytic leukaemia

Morphology:

Abundant, intensely azurophilic granulation. The nucleus is usually monocytic in appearance (reniform) and is either irregular or bilobed with a deep cleft. Scarcely basophilic cytoplasm due to the proliferation of azurophilic granulation. Some atypical promyelocytes also contain elongated or splinter-shaped crystalline cytoplasmic inclusions specific to this type of leukaemia.These usually form clumps, but differ from Auer rods in that they show a tubular substructure on electronic microscopy.

Immunophenotype

- CD13 +
- CD33 +
- HLA-DR -
- CD34 -



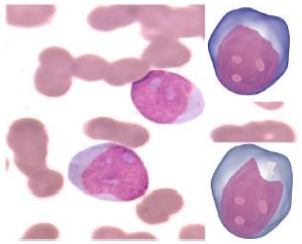
M4 Acute myelomonocytic leukaemia

Morphology:

Large blasts, moderate nucleo:cytoplasm (n:c) ratio and variable basophilia. The nucleus may be rounded, kidney-shaped or irregular. Nucleoli are usually prominent.

Immunophenotype

- CD13 +
- CD15 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD64 +
- CD4 +

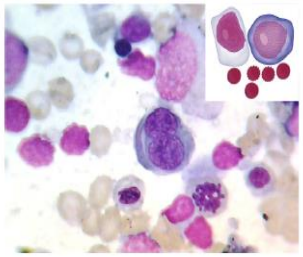


M5 Acute monocytic leukaemia

M5a acute monoblastic leukaemia:
Large blasts with rounded nucleus and dispersed, immature chromatin (1-3 nucleoli) and moderately large and intensely basophilic cytoplasm. The cytoplasm may show some Auer rods and/or prolongations and granulations.
M5b acute monocytic leukaemia
Promonocytes have a rounded or kidney-shaped nucleus with a less basophilic cytoplasm that is more highly granulated than monoblasts and contains some vacuoles. A findings of erythrophagocytosis together with monocytic blasts suggests a t(8;16) translocation.

Immunophenotype

- CD14 +
- CD68 +
- CD4 +
- CD11c +
- HLA-DR +
- CD64 +

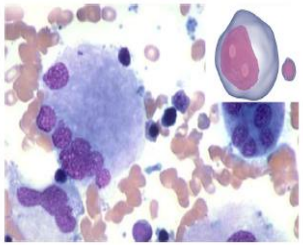


M6 Acute erythroid leukaemia

M6a erythroid leukaemia with proliferation of mixed blasts:
Over 50% erythroid precursors and around 30% myeloblasts. Morphology of erythrocytes in peripheral blood is greatly changed, with schistocytes, "pincered" or mushroom-shaped cells, and spiculated echinocyte and acanthocyte cells.
M6b pure erythroid leukaemia:
Erythroids make up 80% of bone marrow cells, with less than 3% myeloid cells. Erythrocytes in peripheral blood consist of macrocytes, basophilic stippling, Howell-Jolly bodies or Cabot rings.

Immunophenotype

- CD13 +
- CD33 +
- CD15 +
- Glycophorin A +
- Glycophorin C +



M7 Acute megakaryocytic leukaemia

Morphology:

Highly immature, polymorphic blasts. The nucleus is eccentric with dispersed, reticulated chromatin and 1-3 prominent nucleoli. The cytoplasm is non-granular, basophilic, and very similar in appearance to platelets, with pseudopods or granulations. Micromegakaryocytes and fragments of megakarioblasts are seen in peripheral blood (giant platelets, some highly degranulated).

Immunophenotype

- CD41 +
- CD61 +
- CD42 +
- CD13 +
- CD33 +
- CD34 +

LÖSEMİDE NEDEN LAB TESTLERİ YAPIYORUZ?

- Tanı amaçlı
- Prognostik faktör belirleme
- Prediktif faktör belirleme
- Hastalık tanımlayıcı lezyon belirleme

WHO SINIFLAMASINA GÖRE AML

- Tekrarlayan genetik anomaliler gösteren AML
- Myelodisplazi ile ilgili değişiklikler gösteren AML
- Tedavi ilintili myeloid neoplaziler
- AML NOS (“Not Otherwise Specified”)

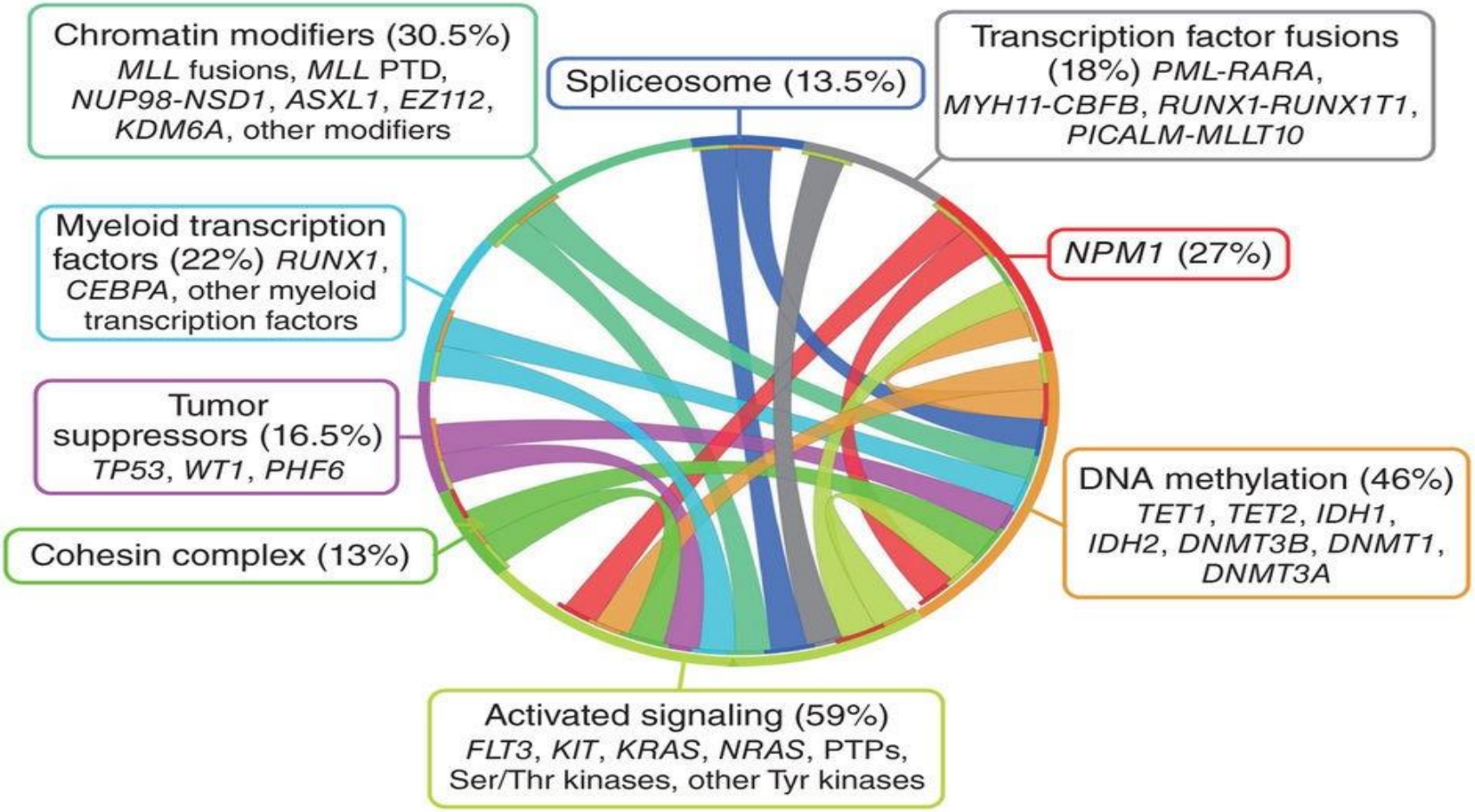
2016 WHO SINIFLAMASINDA NE DEĞİŞTİ?

- **25 alt tip; 3 yeni genetik alt tip**
  - **Prognostik faktörlerde değişiklikler (yeni genetik mutasyonlar eklendi)**
  - **Blast sayısında değişiklikler (kemik iliğinde eritroid seri hücrelerinin yüzde oranına göre blast belirlenmesi, total hücrelerin >%20 oranında blast olması halinde lösemi, <%20 ise MDS)**
  - **Yeni ailesel AML kategorisi**

YENİ AML ALT TİPLERİ

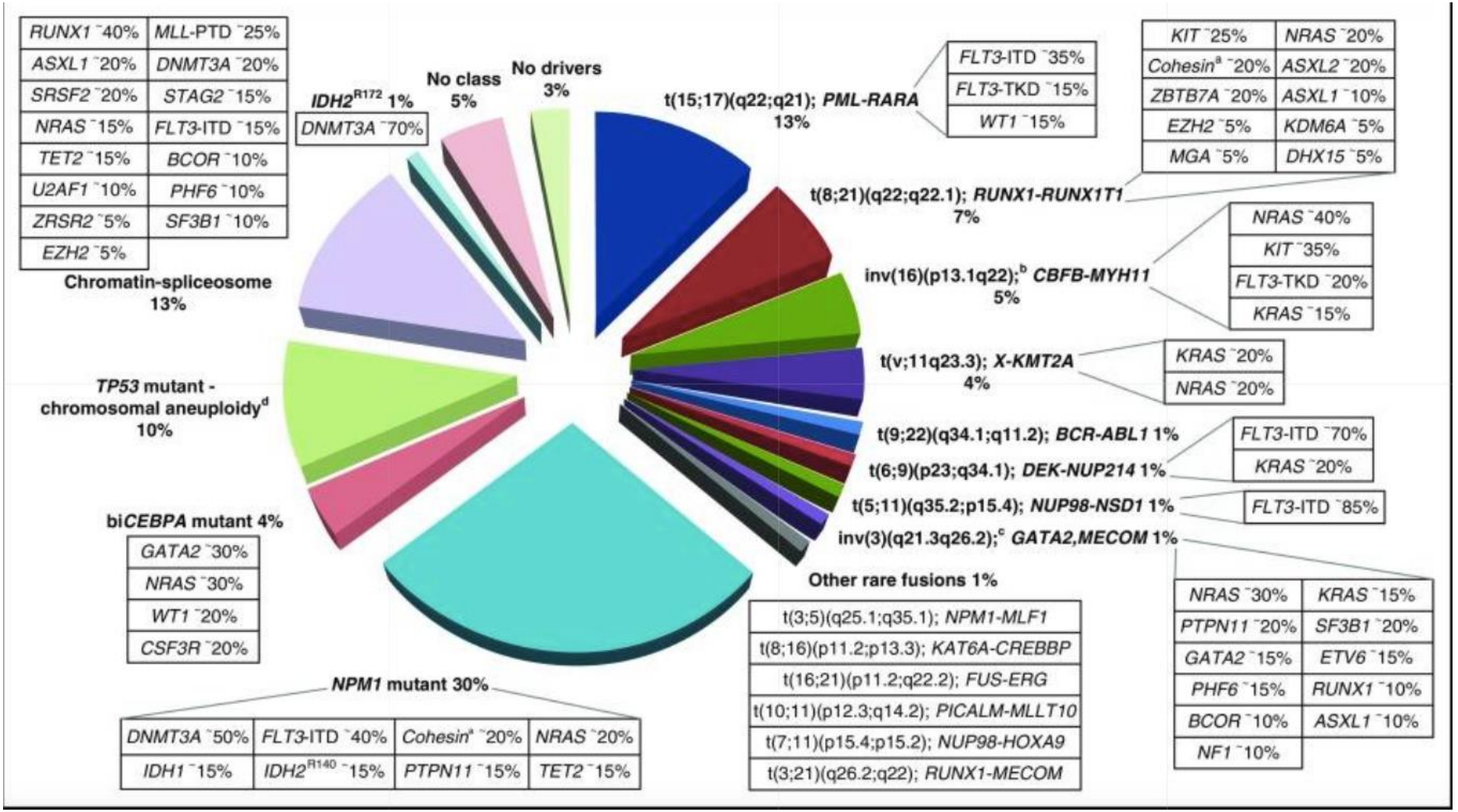
- RUNX1 mutasyonu taşıyan AML (provisional)
- BCR-ABL 1 görülen AML (provisional)
- Biallelik CEBPA mutasyonları görülen AML ($CEBPA^{dm}$)
- Ailesel AML/MDS (farklı tiplerde)
- Tam kategoriye alınan alt tipler
  - NPM1 mutasyonu taşıyan AML
  - $CEBPA^{dm}$ mutasyonu taşıyan AML

AML PATOGENEZİNE YOL AÇAN GENETİK DURUMLAR



Chen ve ark. Nature Genetics 45, 586–587 (2013)

AML'de GENETİK DEĞİŞİKLİKLER



**65 yaşa dek görülen AML olgularında genetik değişiklikler*
Döhner H ve ark. Blood 2017 129(4): 424–447.

WHO SINIFLAMASININ FAB ALT TİPLERİNE UYUMU

AML with recurrent genetic abnormalities	
AML with t(8;21)(q22;q22); *AML1-ETO*	M2>M1>M4>M0
AML wth abnormal marrow eosinophilia and inv(16)(p13q22) or t(16;16)(p13;q22): *CBFβ-MYH11*	M4Eo>M4>M2>M1
Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARα*	M3>M2>M1
AML with 11q23 abnormalities; *MLL* rearrangements	M5>M4>M2>M1>M0
AML with multilineage dysplasia	
Following a myelodysplastic syndrome or myeloproliferative disorder or without antecedent myelodysplastic syndrome	M2>M4>M6
AML and myelodysplastic syndrome, therapy-related	
Alkylating agent-related	M2>M4>M6
Topoisomerase type II inhibitor-related	M5>M4>M2>M1
Other types	
AML not otherwise categorized	
Acute myeloid leukemia minimally differentiated	M0
Acute myeloid leukemia without maturation	M1
Acute myeloid leukemia with maturation	M2
Acute myelomonocytic leukemia	M3
Acute monoblastic leukemia	M4
Acute erythroid leukemia	M5
Acute megakaryoblastic leukemia	M7
Acute basophilic leukemia	—
Acute panmyelosis with myelofibrosis	M7; ? M1; ? MDS
Myeloid sarcoma	—

Behm FG. Classification of acute leukemias, CCO, 2017

ERİTROİD ÖNCÜLLER >%50 OLDUĞUNDA TANI YAKLAŞIMI ve SINIFLANDIRMA

BM erythroid precursors	Myeloblast % of all cells in BM (or PB)	Prior Therapy ?	Recurring WHO genetic abnormality?	Meets criteria for AML-MRC?	4th edition diagnosis (2008)	Updated 4th edition diagnosis (2016)
≥50%	NA	Yes	NA	NA	Therapy-related myeloid neoplasm	Therapy-related myeloid neoplasm
≥50%	≥20%	No	Yes	NA	AML with recurring genetic abnormality	AML with recurring genetic abnormality
≥50%	≥20%	No	No	Yes	AML with myelodysplasia-related changes	AML with myelodysplasia-related changes
≥50%	≥20%	No	No	No	AML, NOS, acute erythroid leukemia (erythroid/myeloid type)	AML, NOS (non erythroid subtype)
≥50%	<20%, but ≥20% of non-erythroid cells	No	No*	NA	AML, NOS, acute erythroid leukemia (erythroid/myeloid subtype)	MDS**
≥50%	<20%, and <20% of non-erythroid cells	No	No*	NA	MDS**	MDS**
>80% immature erythroid precursors with ≥30% proerythroblasts	<20%	No	No*	NA	AML, NOS, acute erythroid leukemia (pure erythroid type)	AML, NOS, acute erythroid leukemia (pure erythroid type)

Arber DA, et al. Blood 127;2391, 2016

AML İMMÜNFENOTİPLEME

Prekürsörler	CD34, CD117, CD33, CD13, HLA-DR
Granülositik belirteçler	CD65, sitoplazmik MPO
Monositik belirteçler	CD14, CD36, CD64
Megakaryositik belirteçler	CD41 (glycoprotein IIb/IIIa), CD61 (glikoprotein IIIa)
Eritroid belirteçler	CD235a (glikoforin A), CD36

AML İMMÜNFENOTİPLEMESİ

Temel Belirteçler Blast tanımlama belirteçleri + Myeloid dizin belirteçleri

CD45/CD117/CD34/HLA-DR CD33/CD13

(saçınım için FS/SS ve canlılık boyası)

BELİRTECİN DÜŞÜK ORANDA/YÜKSEK ORANDA İFADESİ/ASENKRON OLGUNLAŞMA

Lenfoid belirteçler

CD56/CD7/CD19/CD2/CD22 vb

ÇAPRAZ DİZİN BELİRTEÇLERİ

Myelomonositik olgunlaşma belirteçleri

CD11b/CD15/CD4/CD64/CD36/CD14

ASENKRON OLGUNLAŞMA

Kök hücre/öncül hücre alt grupları

CD34/CD117/CD38/CD45RA/CD123

aberran ya da farklı ifade edilen + belirteçler ($CD34^{+}CD38^{-}$ blastlar üzerinde)

CD33/CD123/CD135 (FLT3)/CD47 (Calcireticulin)/CD96/CD25/çapraz dizin belirteçleri/ TIM3 (T cell Ig Mucin3)

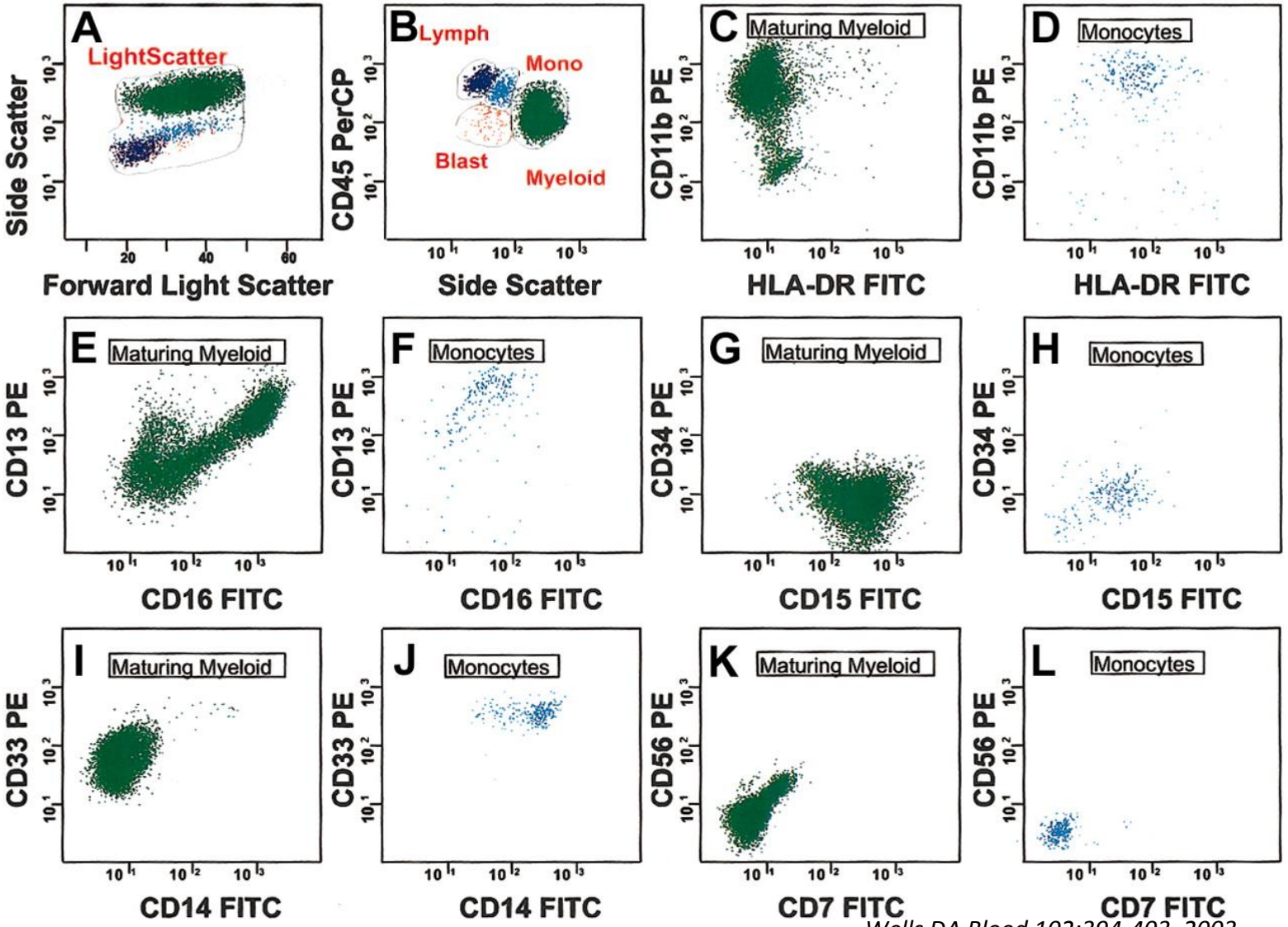
LÖSEMİK KÖK/ÖNCÜL HÜCRELER

AML TANISI İÇİN NE GEREKİYOR?

Tanı aracı	Test	Beklenen bulgular
1. Mikroskopi	*Morfoloji*	*% blast* *% displastik hücre*
2. Flow Cytometry *Mikroskopi/Floresan mikroskopi*	*İmmünfenotipleme*	*Myeloid dizin hücreleri doğrulama* *Blast belirteçlerini belirleme (CD13, CD33, CD34, CD117, MPO)*
3. Mikroskopi/Floresan mikroskopi	*Sitogenetik*	*AML tanımlayıcı karyotip belirlenmesi*
4. Moleküler Yöntemler	*FLT3*, NPM1, CEPBA, RUNX, BCR-ABL 1, KIT vb diğer prognostik belirteçler*	*Tanı* *Prognoz* *Prediktif belirteç*

**Tüm AML tiplerinde FLT3 mutasyon analizinin yapılması gerekli*

NORMAL/ANORMAL AYIRIMI



Wells DA Blood 102:394-403, 2003

MUTASYONLAR/İMMÜNOFENOTİP

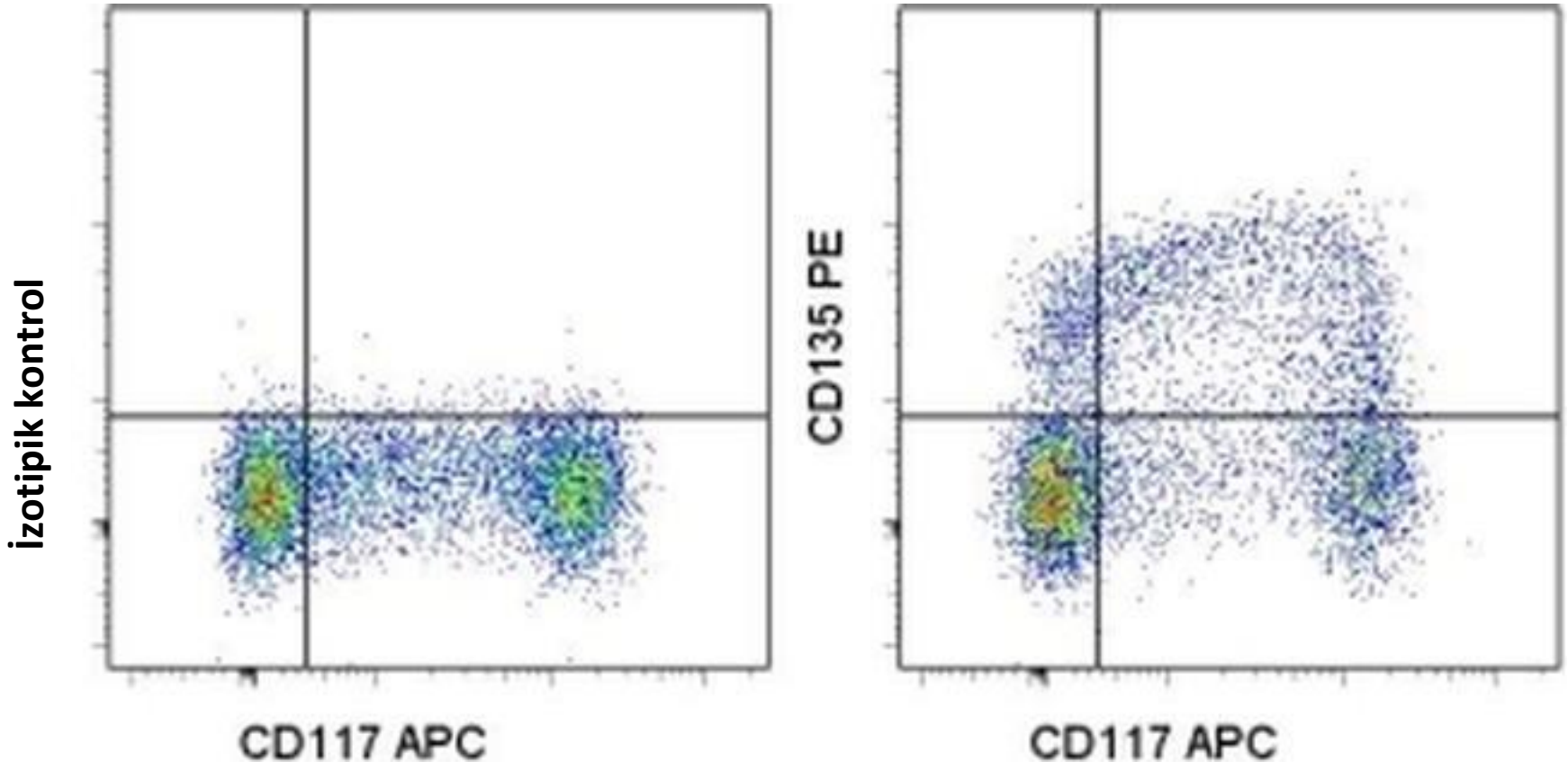
- **t(8;21)(q22;q22) ETO, AML1 AML-M2 (bazı M1 veya M4)**
  $CD45^{+}/CD34^{+}/HLA\text{-}DR^{+}/CD19^{+}/CD13^{low}/CD33^{low}/CD56^{+/-}$

- **t(15;17)(q22;q11) PML, RARalfa AML-M3 (nadiren M1/M2)**
  $CD45^{+}/CD34^{-}/HLA\text{-}DR^{-}/CD19^{-}/CD2^{+}/CD13^{4}/CD33^{+}$

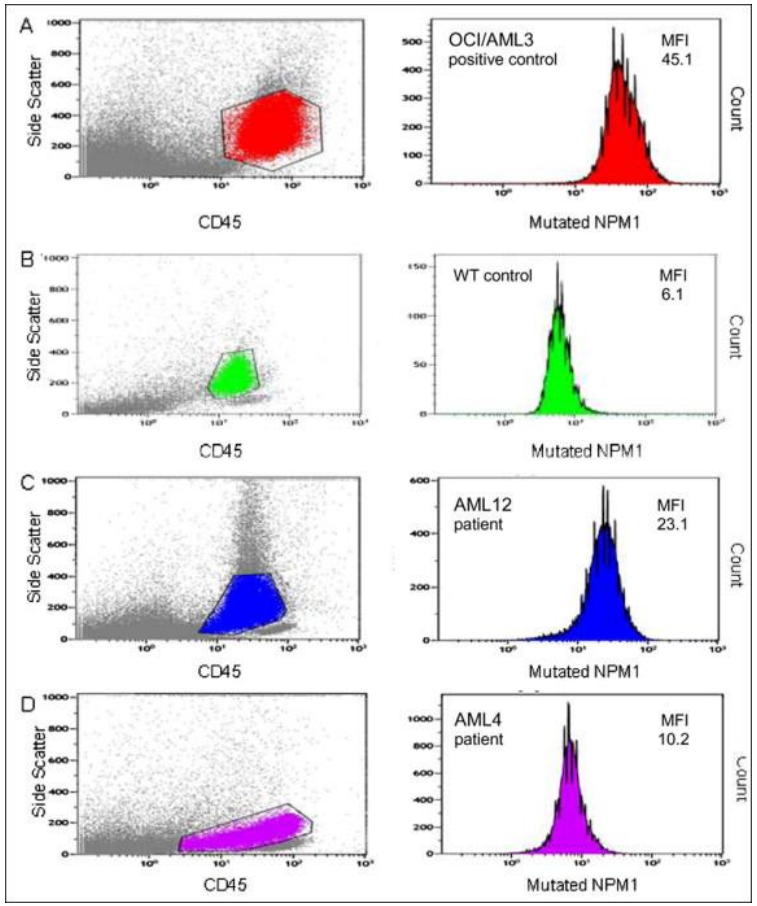
- **t(11;17)(q23;q11) PLZF, RARalfa AML-M3 benzeri**
  $CD45^{+}/CD34^{-}/HLA\text{-}DR^{-}/CD19^{-}/CD2^{+}/CD13^{+}/CD33^{+}$

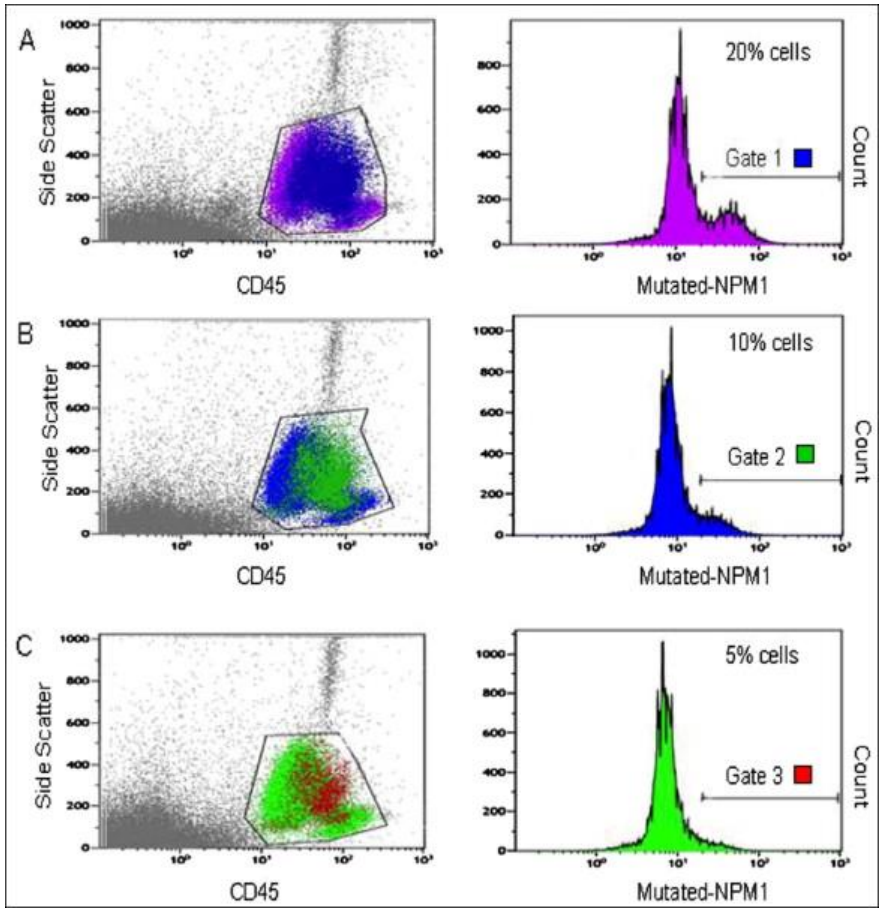
- **inv(16)(p13;q22) MYH11, CBFalfa AML-M4Eo (bazı M2)**
  $CD45^{+}/CD34^{+}/HLA\text{-}DR^{+}/CD19^{-}/CD2^{+}/CD13^{+}/CD33^{+}/CD56^{+}$

CD135 (FLT3)



NPM1 MUTASYONLARININ AKAN HÜCRE ÖLÇER İLE SAPTANMASI





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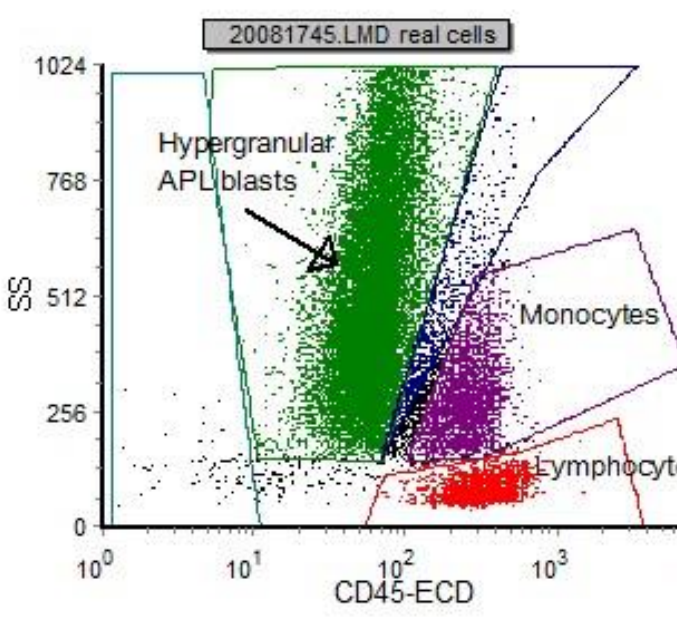
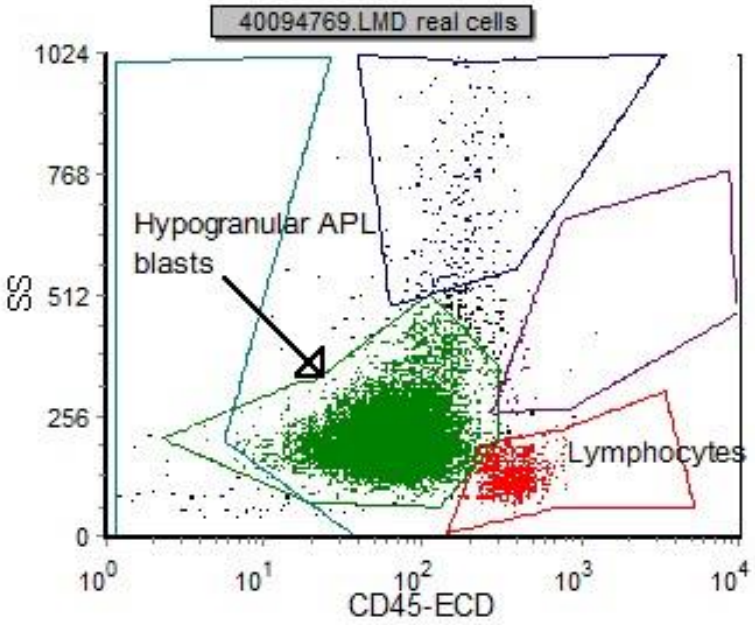
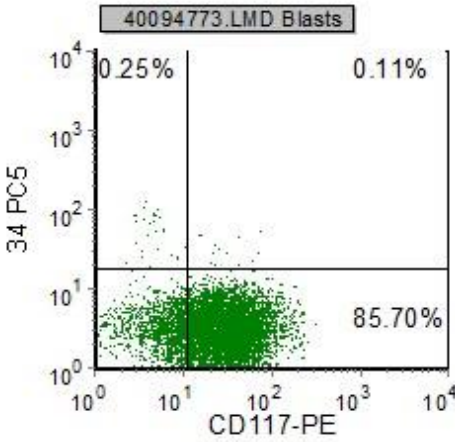
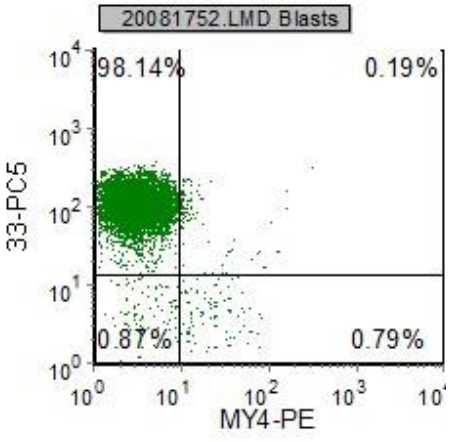
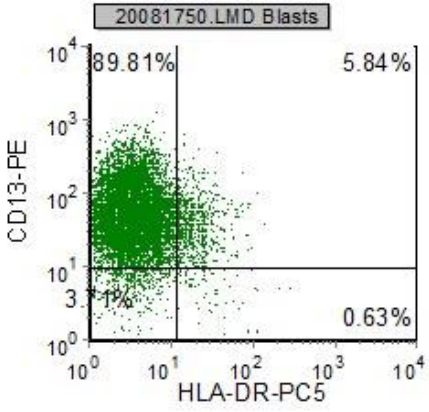
AML t(15;17)(q22;q12)

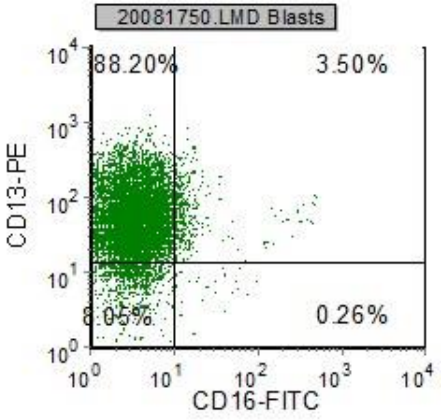












CD123 (IL-3Ralfa)

- AML olgularında $CD34^{+}CD38^{-}$ hücrelerin >%90 oranında pozitif, sağlıklı kişilerde <%1
- Ayırıcı tanı açısından yararlı

RUNX1

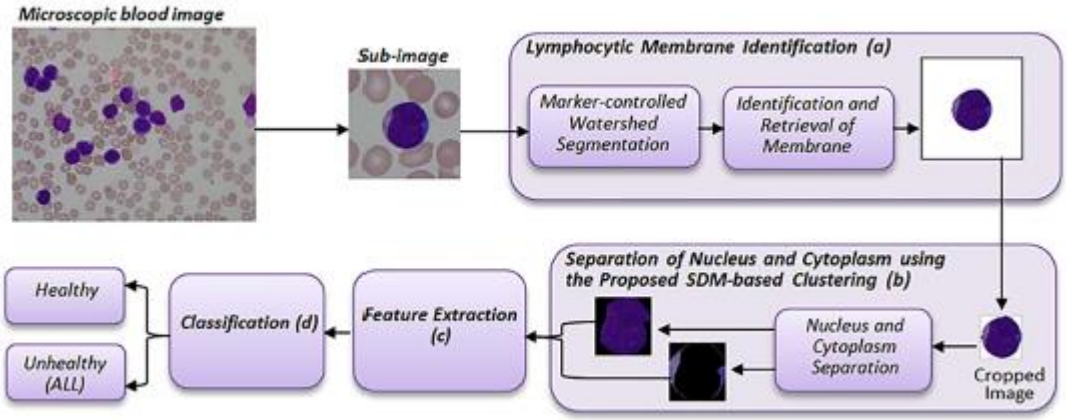
(runt-related transcription factor)

- Hematopoezde etkin transkripsiyon faktörü
- de novo AML olgularında pozitif
- Sitogenetik sonuçları normal hastalarda pozitif

WHO AML SINIFLAMASI İLE İLGİLİ ZORLUKLAR

- Yeni nesil dizileme henüz tümü ile rutin uygulamalara uygun değil
- Genetik testlerde doğruluk oranı henüz düşük düzeyde
- Yeni sınıflama ile dikey çalışmalar kısıtlı düzeyde
- Morfoloji/sitoloji hala en çok karar verdirici unsur

YAPAY ZEKA ÇÖZÜM OLUR MU?



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An Intelligent Decision Support System for Leukaemia Diagnosis using Microscopic Blood Images

Siew Chin Neoh[1], Worawut Srisukkham[1], Li Zhang[1], Stephen Todryk[2], Brigit Greystoke[3], Chee Peng Lim[4], Mohammed Alamgir Hossain[5] & Nauman Aslam[1]

This research proposes an intelligent decision support system for acute lymphoblastic leukaemia diagnosis from microscopic blood images. A novel clustering algorithm with stimulating discriminant measures (SDM) of both within- and between-cluster scatter variances is proposed to produce robust segmentation of nucleus and cytoplasm of lymphocytes/lymphoblasts. Specifically, the proposed between-cluster evaluation is formulated based on the trade-off of several between-cluster measures of well-known feature extraction methods. The SDM measures are used in conjuction with Genetic Algorithm for clustering nucleus, cytoplasm, and background regions. Subsequently, a total of eighty features consisting of shape, texture, and colour information of the nucleus and cytoplasm sub-images are extracted. A number of classifiers (multi-layer perceptron, Support Vector Machine (SVM) and Dempster-Shafer ensemble) are employed for lymphocyte/lymphoblast classification. Evaluated with the ALL-IDB2 database, the proposed SDM-based clustering overcomes the shortcomings of Fuzzy C-means which focuses purely on within-cluster scatter variance. It also outperforms Linear Discriminant Analysis and Fuzzy Compactness and Separation for nucleus-cytoplasm separation

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Review Article

Intelligent Techniques Using Molecular Data Analysis in Leukaemia: An Opportunity for Personalized Medicine Support System

Haneen Banjar,[1,2] David Adelson,[3] Fred Brown,[1] and Naeem Chaudhri[4]

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- Güvenilir moleküler yöntemlerle yapılmış geniş grup çalışmaları az sayıda
- Sadece lösemi ile ilgili genetik mutasyonlara değil diğer sistemlerle ilgili mutasyonlara da bakılmalı
- Kişiye yönelik tedaviler yapılabilmesi için genetik mutasyonların doğru bilinmesi önemli

SONUÇ OLARAK

- **WHO Sınıflaması teorik olarak diğer sınıflamaların ötesinde, klinik ve biyolojik özelliklere göre bir sınıflandırma**
- **Henüz klinik bulgularla desteklenmiş değil**
- **Genetik testlerin doğruluğu henüz düşük oranda**
- **Klinik özellikler ve immunobiyolojik özellikler için ayrı bir sınıflandırma daha yararlı olabilir.**
- **Akan hücre ölçer ile yapılan immünfenotipleme çabuk sonuç alınması nedeni ile tanıya önemli bir destek, ancak özellikle blast sayısı düşük oranda ise tek başına karar verdirici değil.**
- **Morfoloji ilk tanıda önemini koruyor.**


TEŞEKKÜRLER