Acute lymphoblastic leukemia/lymphoma

Current Concepts in Hematopathology
Harvard Medical School
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Boston Children's Hospital
Until every child is well

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Acute lymphoblastic leukemia

- Most common childhood malignancy
  - 25% of all pediatric cancer diagnoses
  - ~3000 cases annually
  - Approximately 85% B-ALL and 15% T-ALL
  - While overall survival has improved, ALL is still one of the leading causes of cancer deaths in children
- Less common in adults
  - Slightly less than 3000 cases annually
  - <1% of all adult cancer diagnoses

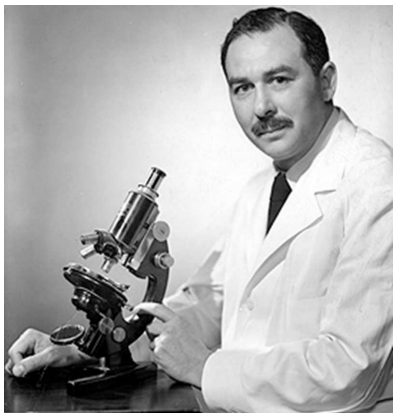
History

A success story of modern oncology

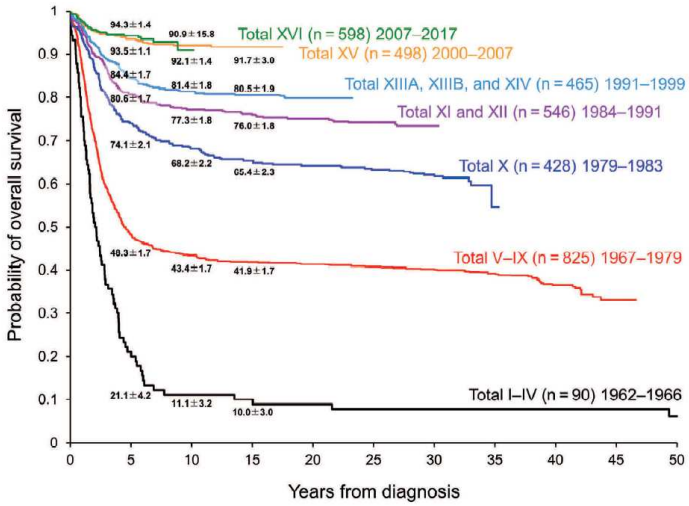
- 1950s: fatal
- Today
  - ~90% survival for children
  - ~40% survival for adults (age dependent)

Progress through both:

- advances in treatment
- improved understanding of B-ALL biology



Outcome improvement in pediatric lymphoblastic leukemia



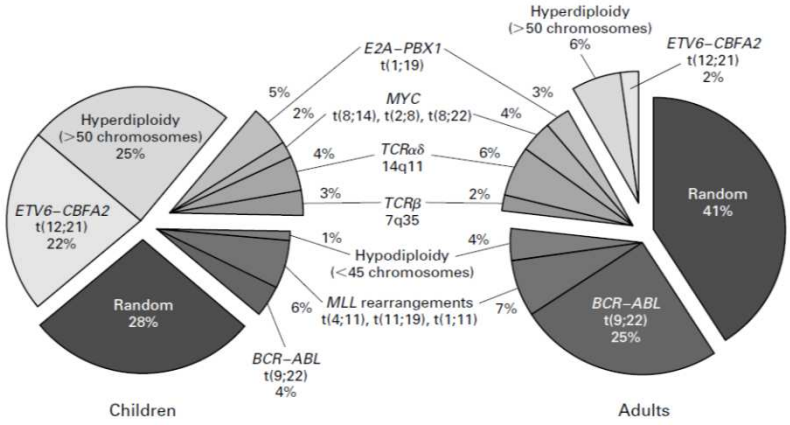
Inaba and Mullighan, Haematologica, 2020

Classification of acute leukemias is increasingly complex

- French-American-British classification of 1976
  - Morphology
  - Cytochemistry
- WHO classifications of 2001 and 2008
  - Morphology
  - Clinical features
  - Immunophenotype
  - Genetics
- 2016 revision of WHO classification: new provisional subtypes
- Current state: many new subtypes based on new genetic knowledge

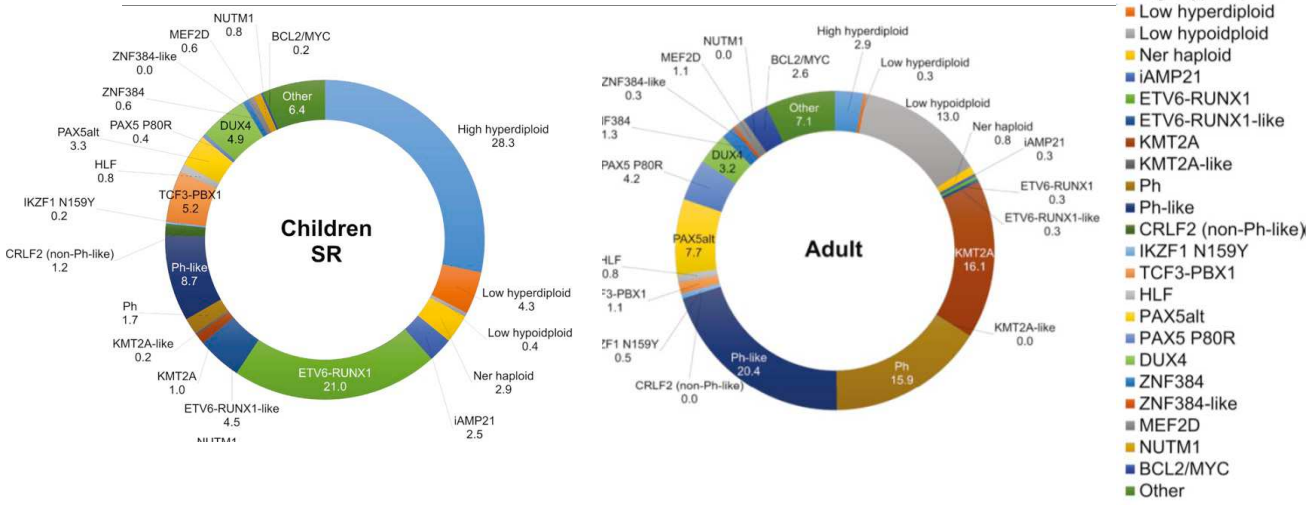
B-ALL

Genetic sub-types 1998



Pui and Evans, NEJM 1998

B-ALL genetic sub-types today



Kimura and Mullighan, BP&RCH, 2020

2016 WHO classification of ALL

13 subtypes of lymphoblastic leukemia, including

- 2 new provisional subtypes of B-ALL
  - B-ALL, BCR-ABL1-like
  - B-ALL with iAMP21
- 1 new provisional subtype of T-ALL
  - Early T-cell precursor lymphoblastic leukemia
- New provisional entity of NK cell lymphoblastic leukemia

- Incorporation of refined molecular understanding in existing subtypes
- 9 subtypes include specific genetic alterations

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 (NK) cell lymphoblastic leukemia/lymphoma

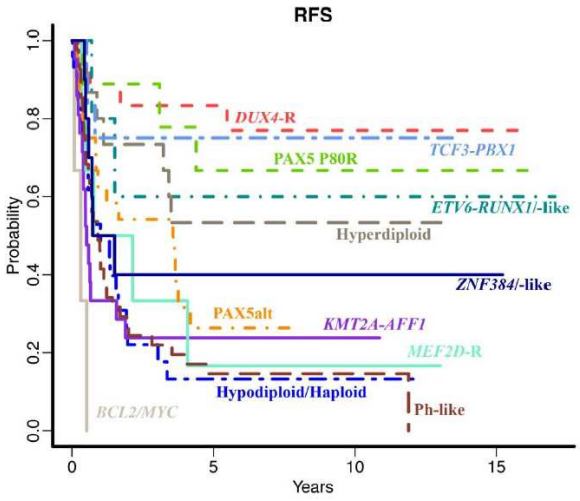
Arber et al., Blood, 2016

Why does classification matter?

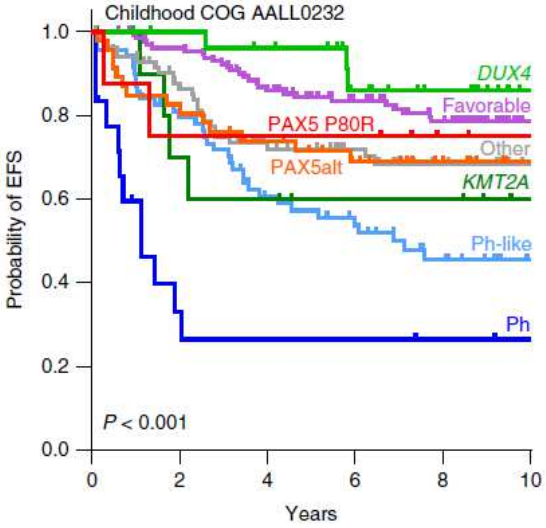
- Facilitates diagnosis
- Informs prognosis and risk stratification
- May suggest utility of targeted therapy

Outcome differences by subtype in adults and children

Adult BCR-ABL1-negative B-ALL

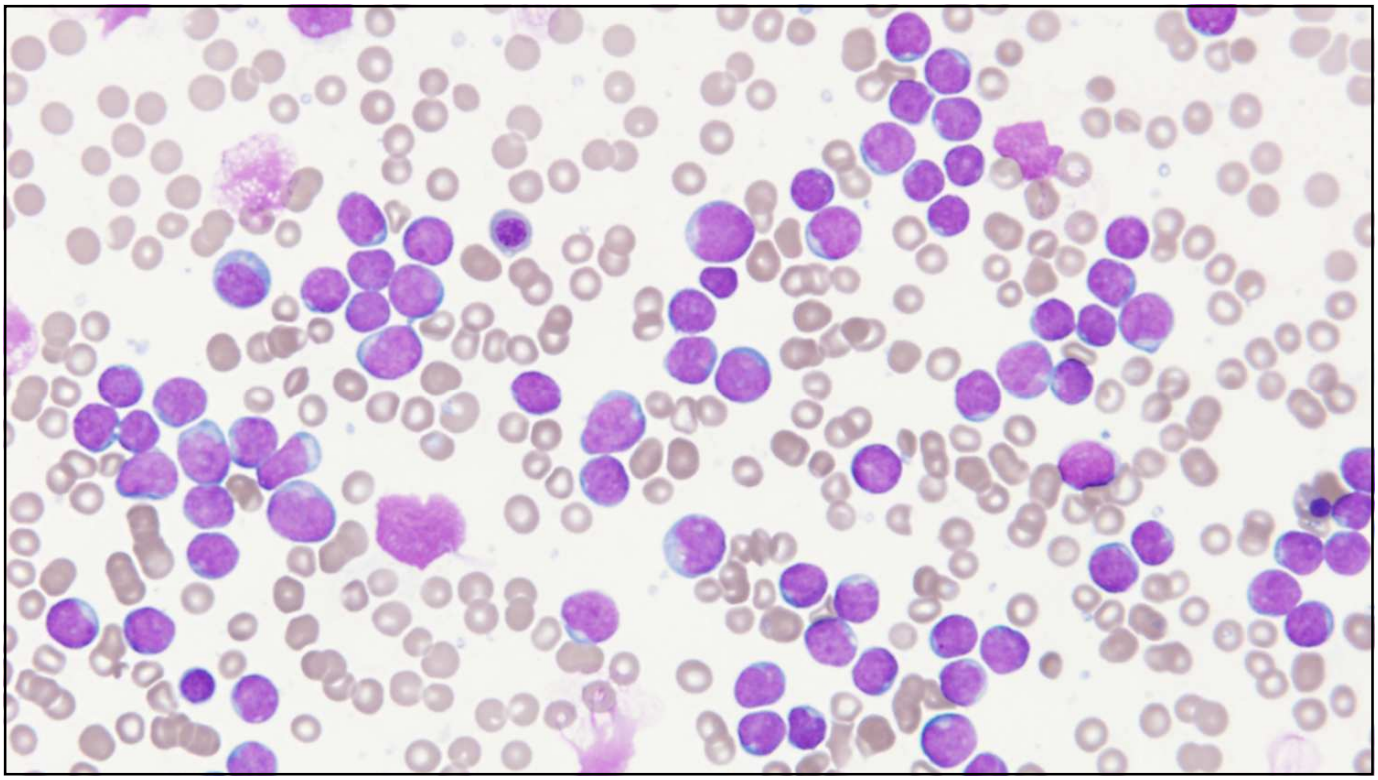


Pediatric B-ALL



Paietta E, et al. Blood 2021 Apr 25;blood.2020010144.

Gu Z, et al. Nat Genet. 2019 Feb;51(2):296-307.



Overview

- Common subtypes
  - *ETV6::RUNX1*
  - High hyperdiploid
  - *KMT2A* rearranged
  - *TCF3::PBX1*
  - *BCR::ABL1*
- Newer subtypes
  - iAMP21
  - Hypodiploidy
  - *BCR::ABL1*-like
  - *TCF3::HLF*
  - *DUX4* rearranged
  - *PAX5* alterations
  - *MEF2D* rearranged
  - *ZNF384* rearranged
  - Others

Where are the new subtypes coming from?

Studies of large cohorts with gene expression profiling

Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia

Henrik Lilljebjörn [1], Rasmus Henningsson [2], Axel Hyrenius-Wittsten [1], Linda Olsson [1], Christina Orsmark-Pietras [1], Sofia von Palffy [1], Maria Askmyr [1], Marianne Rissler [1], Martin Schrappe [3], Gunnar Cario [3], Anders Castor [4], Cornelis J H Pronk [4], Mikael Behrendtz [5], Felix Mitelman [1], Bertil Johansson [1 6], Kajsa Paulsson [1], Anna K Andersson [1], Magnus Fontes [2], Thoas Fioretos [1 6]

Nature Communications, 2016

195 cases, 11 subtypes

Transcriptional landscape of B cell precursor acute lymphoblastic leukemia based on an international study of 1,223 cases

Jian-Feng Li[a,1], Yu-Ting Dai[a,1], Henrik Lilljebjörn[b,1], Shu-Hong Shen[c], Bo-Wen Cui[a], Ling Bai[a], Yuan-Fang Liu[a], Mao-Xiang Qian[d], Yasuo Kubota[e], Hitoshi Kiyoi[f], Itaru Matsumura[g], Yasushi Miyazaki[h], Linda Olsson[b], Ah Moy Tan[i], Hany Ariffin[j], Jing Chen[c], Junko Takita[k], Takahiko Yasuda[l], Hiroyuki Mano[m], Bertil Johansson[b,n], Jun J. Yang[d,o], Allen Eng-Juh Yeoh[p], Fumihiko Hayakawa[q], Zhu Chen[a,r,s,2], Ching-Hon Pui[o,2], Thoas Fioretos[b,n,2], Sai-Juan Chen[a,r,s,2], and Jin-Yan Huang[a,s,2]

PNAS, 2018

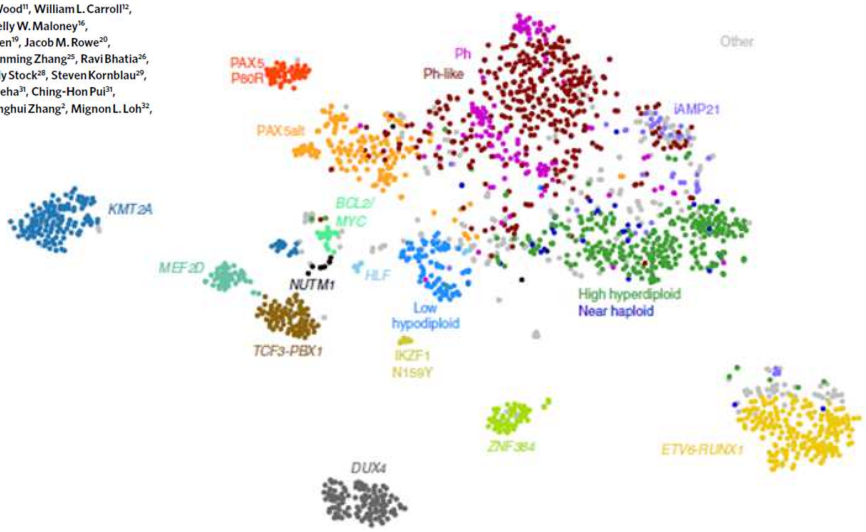
1223 cases; 14 subtypes

PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia

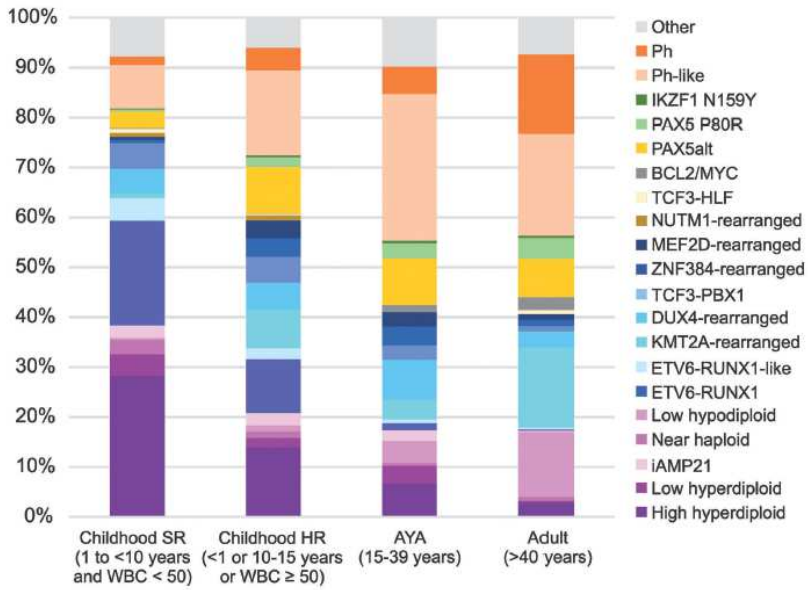
Zhaohui Gu[1,34], Michelle L. Churchman[1,34], Kathryn G. Roberts[1,34], Ian Moore[1], Xin Zhou[2], Joy Nakitandwe[1], Kohei Hagiwara[2], Stephane Pelletier[3], Sebastien Gingras[4], Hartmut Berns[5], Debbie Payne-Turner[1], Ashley Hill[1], Ilaria Iacobucci[1], Lei Shi[6], Stanley Pounds[4], Cheng Cheng[6], Deqing Pei[6], Chunxu Qu[1], Scott Newman[2], Meenakshi Devidas[7], Yunfeng Dai[7], Shalini C. Reshmi[8], Julie Gastier-Foster[8], Elizabeth A. Raetz[9], Michael J. Borowitz[10], Brent L. Wood[11], William L. Carroll[12], Patrick A. Zweidler-McKay[13], Karen R. Rabin[14], Leonard A. Mattano[15], Kelly W. Maloney[16], Alessandro Rambaldi[17], Orietta Spinelli[17], Jerald P. Radich[18], Mark D. Minden[19], Jacob M. Rowe[20], Selina Luger[21], Mark R. Litzow[22], Martin S. Tallman[23], Janis Racevskis[24], Yanming Zhang[25], Ravi Bhatia[26], Jessica Kohlschmidt[27], Krzysztof Mrózek[27], Clara D. Bloomfield[27], Wendy Stock[28], Steven Kornblau[29], Hagop M. Kantarjian[29], Marina Konopleva[29], Williams E. Evans[30], Sima Jeha[31], Ching-Hon Pui[31], Jun Yang[30], Elisabeth Paietta[24], James R. Downing[1], Mary V. Relling[30], Jinghui Zhang[2], Mignon L. Loh[32], Stephen P. Hunger[33] and Charles G. Mullighan[1*]

Nature Genetics, 2019

1988 cases; 23 subtypes



Distribution of B-ALL subtypes differs by age



Inaba and Mullighan, Haematologica, 2020

B-ALL with *ETV6::RUNX1*

Previously known as B-ALL with *TEL-AML*

t(12;21)(p13.2;q22.1), but often cryptic by karyotype (need FISH or molecular to detect routinely)

25% pediatric B-ALL, rare in adults

Thought to be acquired *in utero*

Favorable prognosis

Deletion of other ETV6 allele is common

B-ALL with high hyperdiploidy

Definitions may vary slightly, but usually 51-65 chromosomes

25-30% pediatric B-ALL, rare in adults

Favorable prognosis

Co-occurring Ras pathway mutations common

B-ALL with *KMT2A* rearrangement

KMT2A previously known as *MLL*

Karyotype includes translocation at 11q23, though some *KMT2A* rearrangements may be cryptic

Common in infant B-ALL (70-80%), less common in older children, then becomes somewhat more common with age into adulthood

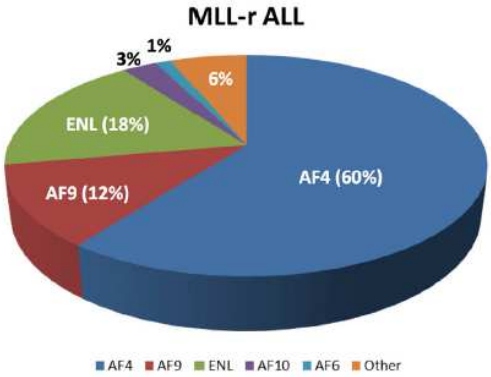
- Rearrangement may be acquired *in utero*

Frequently high white blood cell count at presentation (>100x10^9/L)

Frequently CD10-negative

Poor prognosis

Encouraging preclinical responses to menin inhibitors, currently in clinical trials



Common fusion partners in *KMT2A*r B-ALL
(current preferred name in red)

AF4=AFF1=MLLT2 (4q21.3-q22.1)
- most common partner across age groups

AF9=MLLT3 (9p21.3)
ENL=MLLT1 (19p13.3)
AF10=MLLT10 (10p12.31)
AF6=AFDN=MLLT4 (6q27)

Winters and Bernt, Frontiers in Pediatrics, 2017

B-ALL with *BCR::ABL1*

Also known as Philadelphia chromosome-positive B-ALL, or Ph+ B-ALL

t(9;22)(q34;q11.2)

40-50% of B-ALL in adults; less common in children

Historically poor prognosis, now somewhat improved with use of tyrosine kinase inhibitors

Deletions in IKZF1 are common and associated with higher risk disease

Distinguish from CML in B-lymphoid blast crisis if possible

Hypodiploid B-ALL

Well-known high risk subtype of B-ALL, can be divided into two groups:

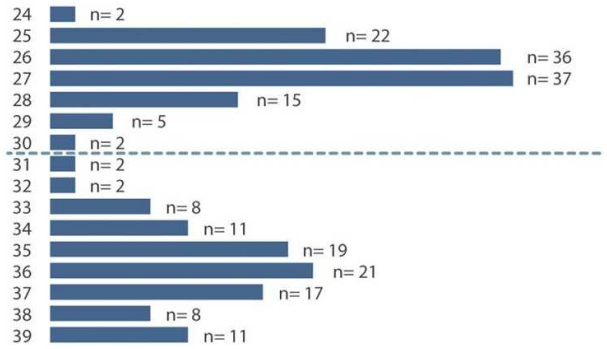
Low hypodiploid: ~32-39 chromosomes

- Mutations in TP53 in ~90%
  - Half are germline, consistent with Li Fraumeni syndrome
- Also mutations in IKZF2 and RB1

Near haploid: ~24-31 chromosomes

- Mutations targeting receptor tyrosine kinases, Ras pathway, and IKZF3

Modal number of chromosomes in hypodiploid B-ALL



Safavi and Paulsson, Blood 2017

B-ALL with *TCF3::PBX1 vs* B-ALL with *TCF3::HLF*

B-ALL WITH *TCF3::PBX1*

~8% pediatric B-ALL

Break-apart FISH for *TCF3*: positive

Karyotype: t(1;19)(q23;p13.3)

Good prognosis

B-ALL WITH *TCF3::HLF*

<1% pediatric B-ALL, rare adult cases

Break-apart FISH for TCF3: positive

Karyotype: t(17;19)(q22;p13.3)

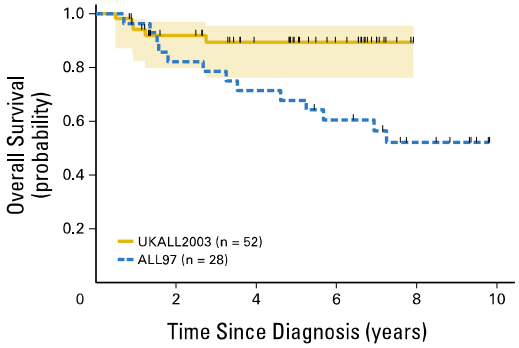
Very poor prognosis

Patients present with hypercalcemia and coagulopathy

BCL2 inhibitor venetoclax has shown promise in preclinical models

B-ALL with intrachromosomal amplification of chromosome 21(B-ALL with iAMP21)

- Approximately 2% of pediatric B-ALL
  - Rare in adults
- Patients tend to be older than other children with ALL, with low presenting white blood cells counts
- Multiple copies of RUNX1 by cytogenetic analysis
- Usually these copies are on chromosome 21, though they may also be on a marker chromosome
- Treatment with intensified therapy significantly reduces risk of relapse



Moorman et al., JCO, 2013

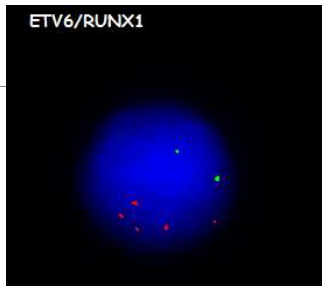
B-ALL with iAMP21: detection/diagnosis

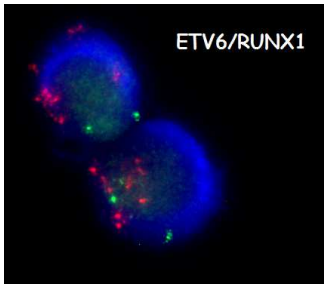
Detected with the same FISH assay used to detect ETV6-RUNX1

iAMP21 defined as:

- 5 or more copies of RUNX1 in one nucleus by interphase FISH, or
- 3 or more copies of RUNX1 on one chromosome by metaphase FISH
- Caution: additional copies of chromosome 21 are common in B-ALL, especially hyperdiploid B-ALL, usually 3-4 copies total

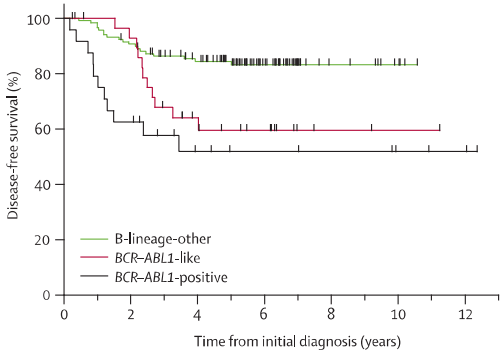
May also be suspected with karyotype findings of add(21), dup(21), der(21), or loss of chromosome 21 associated with gain of a marker chromosome





BCR-ABL1-like (Ph-like) B-ALL

- Defined by a gene expression profile similar to B-ALL with *BCR::ABL1*, but without the *BCR::ABL1* rearrangement
  - Originally described in 2009
- Approximately 15% childhood B-ALL overall, with increasing incidence by age
  - From 10% (standard risk children) to ~20% (adolescents) to ~25% (young adults)
- Approximately 20% of adult B-ALL
- Overall inferior survival with standard therapy



Den Boer et al., Lancet Oncology 2009

BCR-ABL1-like B-ALL: biology

Activation of kinase signaling pathways via many different alterations

CRLF2 rearrangements leading to CRLF2 overexpression
- ~50% of BCR-ABL1-like
- Cytokine receptor-like factor 2 located in pseudo-autosomal region of the X and Y chromosomes
- Rearrangement with IGH (chromosome 14) or P2RY8 (Xp22/Yp11)
- Many of these cases also have activating alterations in the JAK/STAT pathway, particularly JAK2 point mutations

ABL1-class rearrangements
- ~15-20% BCR-ABL1-like
- Rearrangements of ABL1, ABL2, CSF1R, PDGFRB (“ABL1-class”)
- Diverse partners with common result of kinase signaling activation

Activating rearrangements of JAK2 or EPOR
- ~10-15% BCR-ABL1-like
- Diverse partners with common result of signaling pathway activation

Table 4 | Kinase rearrangements and therapeutic targets in Ph-like ALL[49]*

Kinase	Tyrosine kinase inhibitor	Number of gene partners	Number of patients	Fusion partner genes
ABL1	Dasatinib	6	14	*ETV6, NUP214, RCSD1, RANBP2, SNX2, ZMIZ1*
ABL2	Dasatinib	3	7	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Dasatinib	1	4	*SSBP2*
PDGFRB	Dasatinib	4	11	*EBF1, SSBP2, TNIP1, ZEB2*
CRLF2	JAK2 inhibitor	2	30	*IGH, P2RY8*
JAK2	JAK2 inhibitor	10	19	*ATF7IP, BCR, EBF1, ETV6, PAX5, PPFIBP1, SSBP2, STRN3, TERF2, TPR*
EPOR	JAK2 inhibitor	2	9	*IGH, IGK*
DGKH	Unknown	1	1	*ZFAND3*
IL2RB	JAK1/JAK3 inhibitor	1	1	*MYH9*
NTRK3	Crizotinib	1	1	*ETV6*
PTK2B	FAK inhibitor	2	1	*KDM6A, STAG2*
TSLP	JAK2 inhibitor	1	1	*IQGAP2*
TYK2	TYK2 inhibitor	1	1	*MYB*

Roberts et al., Nat Rev Clin Onc, 2015

BCR-ABL1-like B-ALL: detection/diagnosis

Diversity of underlying genetic alterations makes detection complex!

Expression analysis
- Can identify category as a whole, but not specific alteration
- Low density arrays can be used as screening tool

Targeted fusion analysis
- Multiplex FISH
- Multiplex RT-PCR
- Targeted RNA sequencing

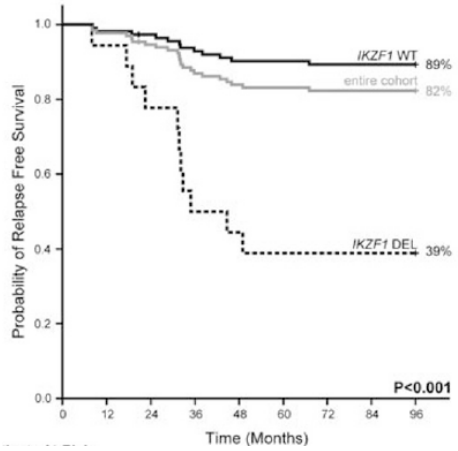
Comprehensive analysis
- Whole transcriptome sequencing
- Whole genome sequencing

IKZF1 deletions

- Zinc finger transcription factor important in B cell development
- Approximately 15% pediatric and 30% adult B-ALL
- IKZF1 deletions may occur in multiple subtypes
  - Frequency is particularly high in BCR-ABL1-positive (~70%) and BCR-ABL1-like (~40%) B-ALL
- Higher incidence of induction failure and relapse
  - Independent prognostic feature
  - DUX4-rearrangement is exception

Variety of different breakpoints and different deletion sizes complicates detection

- Commonly used methods include multiplex ligation-dependent probe amplification (MLPA), and copy number arrays, and next-generation sequencing with copy number analysis



Kuiper et al., Leukemia 2010

B-ALL with *DUX4* rearrangement

5-10% B-ALL, described in 2016

Seen across age groups, most commonly adolescent and young adult (AYA)

IGH::DUX4 translocations lead to expression of truncated *DUX4* isoform, which in turn leads to the expression of an aberrant *ERG* isoform (ERGalt), which is transforming

Cytogenetically cryptic and difficult to detect due to repetitive nature of *DUX4* in genome

- *ERG* deletions recurrent, but often subclonal and not present in all cases, so not ideal for diagnosis
- Whole transcriptome RNAseq can identify rearrangement and unique expression profile
- Flow cytometry may be useful: 75% of cases expressed CD2 and 98% expressed CD371 in one study (Schinnerl, D et al, Haematologica, 2019)

Typically favorable prognosis, even in the presence of IKZF1 deletion (~40% of cases)

B-ALL with *ZNF384* rearrangement

~5% of B-ALL

Most common in children, adolescents and young adults

ZNF384 (12p13.31) is a zinc-finger transcription factor, which is the C-terminal gene with a range of different fusion partners, most commonly *EP300*, *TCF3*, and *TAF15*

- Detection by FISH or RNA sequencing

Immunophenotype shows weak expression of CD10, with frequent co-expression of myeloid antigens such as CD13 or CD33

- Also a common rearrangement in MPAL, with co-expression of MPO; probably all a phenotypic spectrum of the same disease
- Common FLT3 overexpression, with case reports of responses to FLT3 inhibition
- Immunophenotype may shift, including loss of CD19, over course of disease (Oberley et al, 2018))

Prognosis may be dependent on partner gene (Hirabayashi et al, 2021)

B-ALL with *MEF2D* rearrangement

5-10% B-ALL

Most common in adolescents and young adults

MEF2D (1q22) is a transcription factor regulated by class II histone deacetylases and is the N-terminal gene with multiple different fusion partners

Immunophenotype shows weak to negative expression of CD10, with high expression of CD38 and cytoplasmic μ

Intermediate to unfavorable prognosis

May be sensitive to HDAC inhibition

PAX5-driven B-ALL: *PAX5*-altered and *PAX5* P80R

PAX5-ALTERED

~10% B-ALL, typically found in children

PAX5 fusions with various partners and PAX5 intragenic amplifications
- *ZCCHC7::PAX5* not included

Intermediate prognosis

PAX5 P80R

~4% B-ALL, typically found in adults

Specific point mutation leading to P80R amino acid change, with inactivation of other allele by deletion, mutation, or LOH

Intermediate to favorable prognosis

PAX5 is a transcription factor essential for normal B cell development.
PAX5 deletions and mutations may be seen in multiple subtypes.

Other subtypes of B-ALL

NUTM1-rearranged

IKZF1 N159Y

BCL2/MYC-rearranged

KMT2A-rearranged-like

ZNF384-rearranged-like

ZEB2 H1038R and *IGH::CEBPE*

Others…

T-ALL

The only WHO subtype of T-ALL is a provisional entity: early T precursor T-ALL

- Defined by immunophenotype
  - positive for CD3 (usually cytoplasmic) and CD7, negative for CD8 and CD1a, co-expression of myeloid/stem cell markers, and expression of CD5 on less than 75% of blasts
- Mutational pattern – not diagnostic
  - Less frequent alterations of *NOTCH1* and *CDKN2A*
  - More frequent alterations in signaling, transcriptional, and epigenetic pathways

Common genetic findings in T-ALL

- Rearrangements between T cell receptor loci and various partner genes are most common
- Alterations in *NOTCH1* and/or *FBXW7*, both of which result in *NOTCH1* pathway activation
- Deletions of *CDKN2A/B*
- *JAK-STAT*, *PI3K-AKT*, *RAS-MAPK* pathway activation

Recurrent T-ALL rearrangements

Rearrangements resulting in deregulated expression of a target gene

Target gene	*n*	Rearrangement partner (number of cases)
TLX1	17	*TRB* (7), *TRA* (5), *TLX1*-upstream (4), *LINC00502–TLX1* (1)
TLX3	13	*BCL11B–TLX3* (8), *CDK6–TLX3* (2), *TRB* (1), *TLX3–CASC15* (1), *TLX3–TARBP1* (1)
TAL1	58	*STIL* (50), *TRA* (5), *DHX9–TAL1* (1), *GNPAT–TAL1* (1), *TAL1–TARP* (1)
TAL2	6	*TRB* (6)
LMO1	3	*TRB* (2), *TRA* (1)
LMO2	13	*TRA* (6), *TRB* (5), *CSTF3–LMO2* (1), *FOXJ3–LMO2* (1)
LYL1	1	*TRB* (1)
NKX2-1	9	*TRA* (6), *NKX2-1–BCL11B* (1), *CDK6–NKX2-1* (1), *NKX2-1–DIO2* (1)
HOXA	7	*TRB* (4), *HOXA* insertion (1), *LINC01260–HOXA* (1), *POLR2E–HOXA* (1)
MYB	11	*TRB* (2), *SLC12A9–MYB* (1), *MYB–PLAGL1* (1), *MYB–BDP1* (1), *MYB–CHMP1A* (1) *AHI1–MYB* (5)

Rearrangements resulting in chimeric fusions

Gene	*n*	Partner gene
MLLT10	15	*PICALM* (9), *DDX3X* (2), *KMT2A* (1), *FAM171A1* (1), *NAP1L1* (1), *CAPS2* (1)
KMT2A	12	*MLLT1* (7), *ELL* (1), *MLLT10* (1), *AFDN* (1), *MLLT6* (1), *CT45A3* (1)
ABL1	7	*NUP214* (4), *SLC9A3R1* (1), *ETV6* (1), *MBNL1* (1)
NUP98	5	*RAP1GDS1* (2), *CCDC28A* (1), *LNP1* (1), *PSIP1* (1)
TFG	3	*ADGRG7* (3)
JAK2	2	*PCM1* (1), *CD99* (1)
ETV6	2	*ABL1* (1), *CTNNB1* (1)
ZC3HAV1	2	*ABL2* (1), *AKAP11* (1)
LMAN2	2	*NSD1* (1), *PAPOLA* (1)

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Diagnostic work-up for new ALL

Morphology
- Aspirate smear and core biopsy

Flow immunophenotyping

Karyotype/FISH: Most diagnostically/therapeutically significant molecular subtypes
- Karyotype: Hyperdiploid, hypodiploid
- FISH
- Consider extended FISH, RT-PCR, and/or RNA sequencing

Minimal residual disease
- Characterization of leukemia by flow cytometry or genetic analysis sufficient to enable MRD studies

In conclusion…

Genetic characterization is an increasingly important part of B-ALL pathology

- Diagnosis
- Prognosis/risk stratification
- Therapy (intensified/de-intensified therapy, targetable sequence alterations and fusions)

Increasingly complex risk stratification is being used to improve outcome

- Requires increasingly complex molecular sub-classification

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