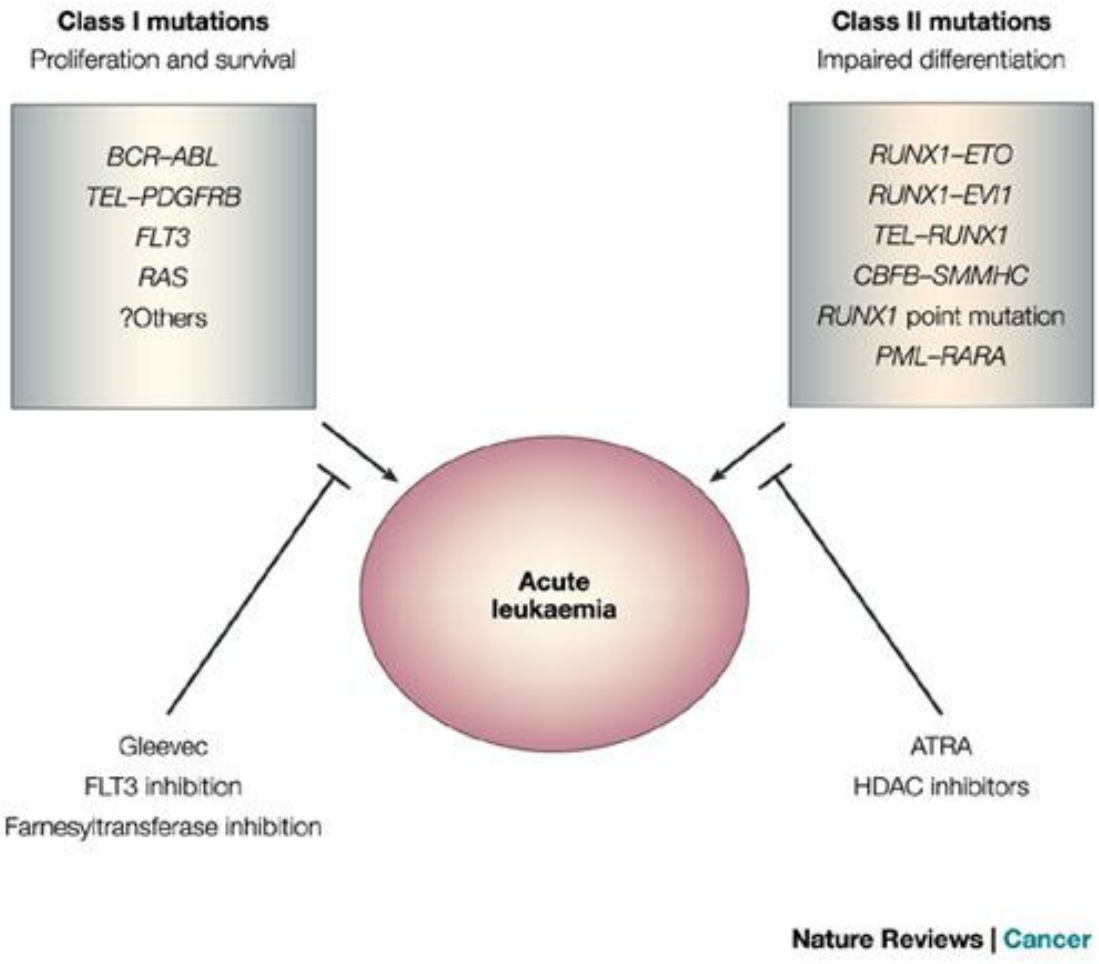
Acute leukemia and myelodysplastic syndromes

Peter Vandenberghe
Centrum Menselijke Erfelijkheid &
Afdeling Hematologie, UZ Leuven

1. Acute myeloid leukemia
2. Myelodysplastic syndromes
3. Acute lymphoblastic leukemia/lymphoma

Acute leukemia : two cooperating classes of mutations



Speck & Gilliland, Nat Rev Cancer. 2002 ;2:502-13

Genetics of AML ~2000

Abnormal cytogenetics

favorable

intermediate

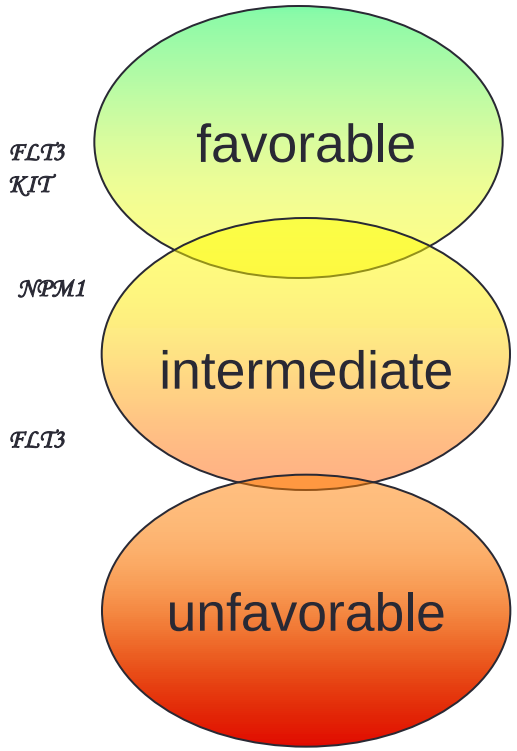
unfavorable

Normal cytogenetics

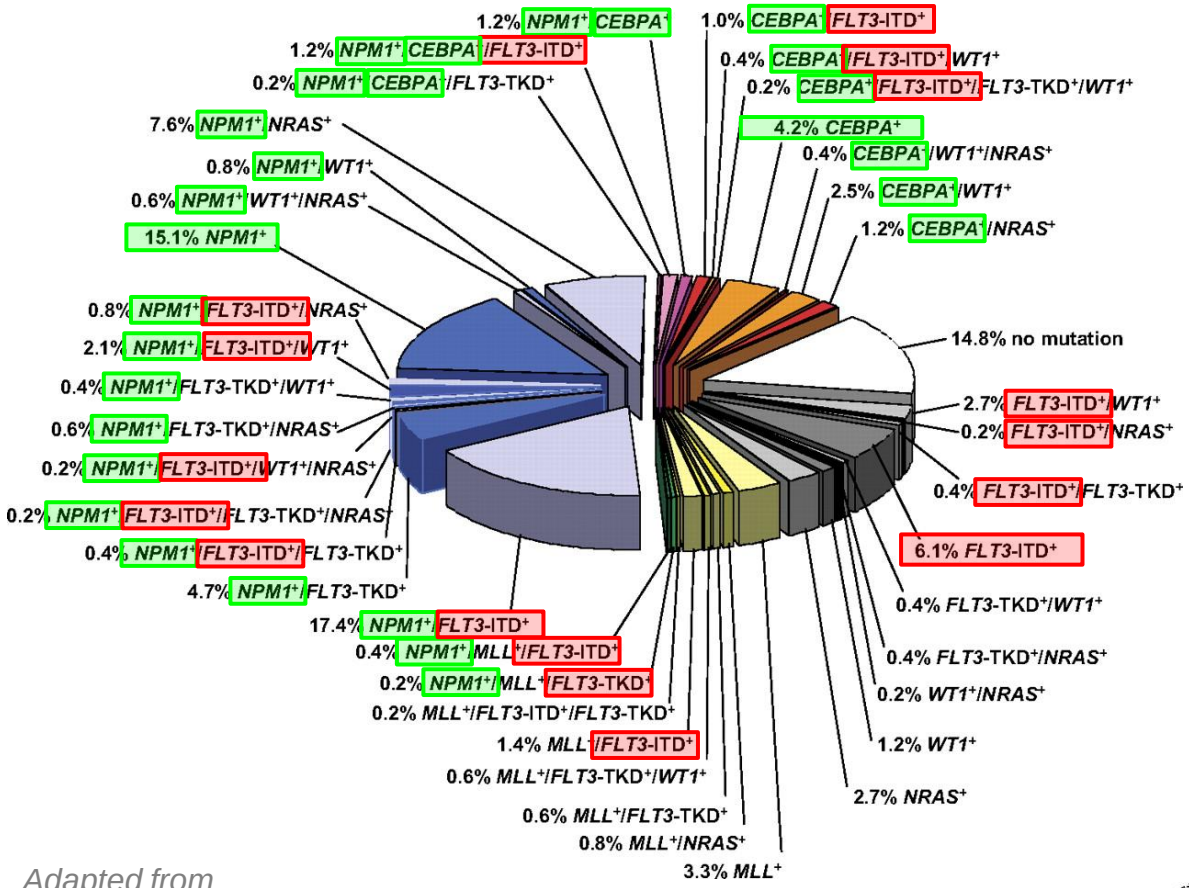
intermediate

Contemporary view on the genetic complexity of acute myeloid leukemia

Abnormal cytogenetics

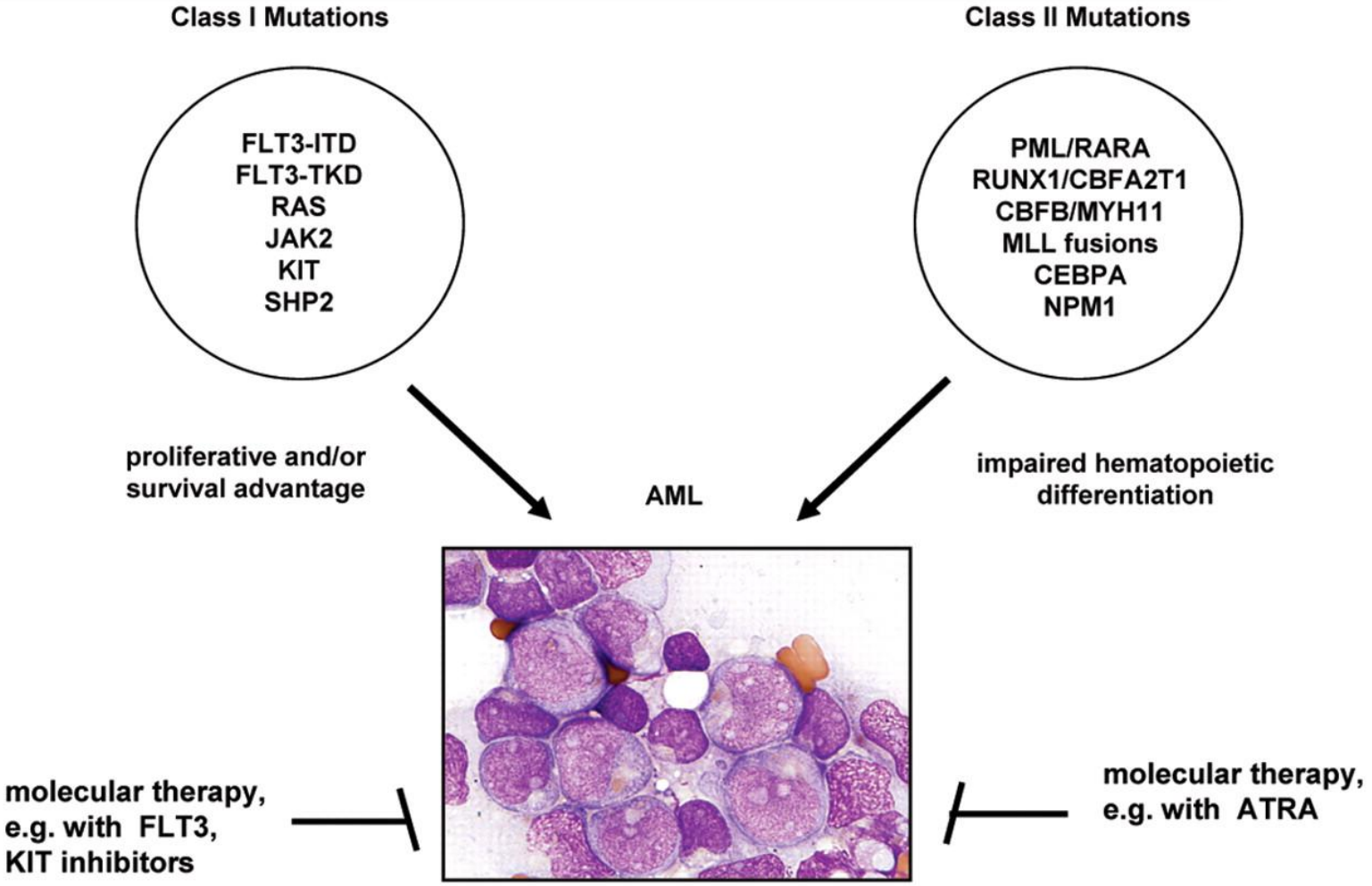


Normal cytogenetics



Adapted from
Döhner H et al. Blood 2010;115:453-474

Acute myeloid leukemia : two cooperating classes of mutations



Updated from

Speck & Gilliland, Nat Rev Cancer. 2002 ;2:502-13

SNP arrays / Next generation sequencing

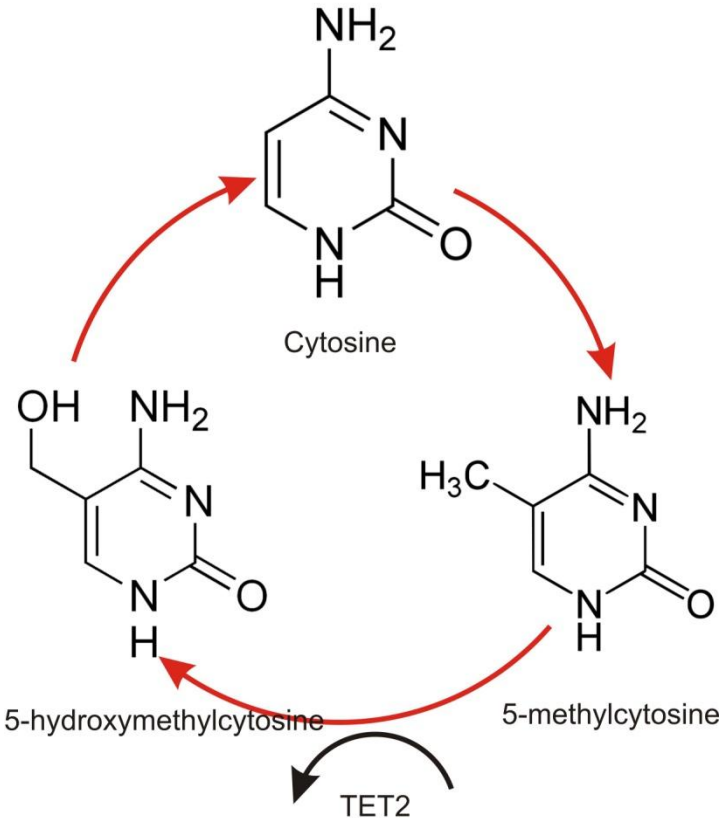
Genome-Wide Human SNP Array 6.0

- *CGH/SNP arrays*
  - Gains
  - Losses
  - LOH
  - TET2/EZH2/IKZF1
- *Next generation sequencing (NGS) / massive parallel sequencing*
  - Whole genome sequencing
  - Exome sequencing
  - Transcriptome sequening
  - Methylome
  - Histon code
  - IDH1/IDH2/DNMT3A/ ….

Recent mutations in CN AML

IDH1 (2q33)/ IDH2 (15q26) : oncometabolites and transformation

- ***incidence***
  - IDH1 / IDH2 : 15-22%
  - TET2 : 12-27%
- ***Patterns***
  - IDH1 (R132)/ IDH2 (R140)
    - IR karyotype, normal karyotype, NPM1 mut
  - IDH2 (R172)
    - IR karyotype, no other mutations
- ***Prognosis in CN- AML***
  - TET2 :
  - IDH1 R132:
  - IDH2 R140:
  - IDH2 R172:



Recent mutations in AML

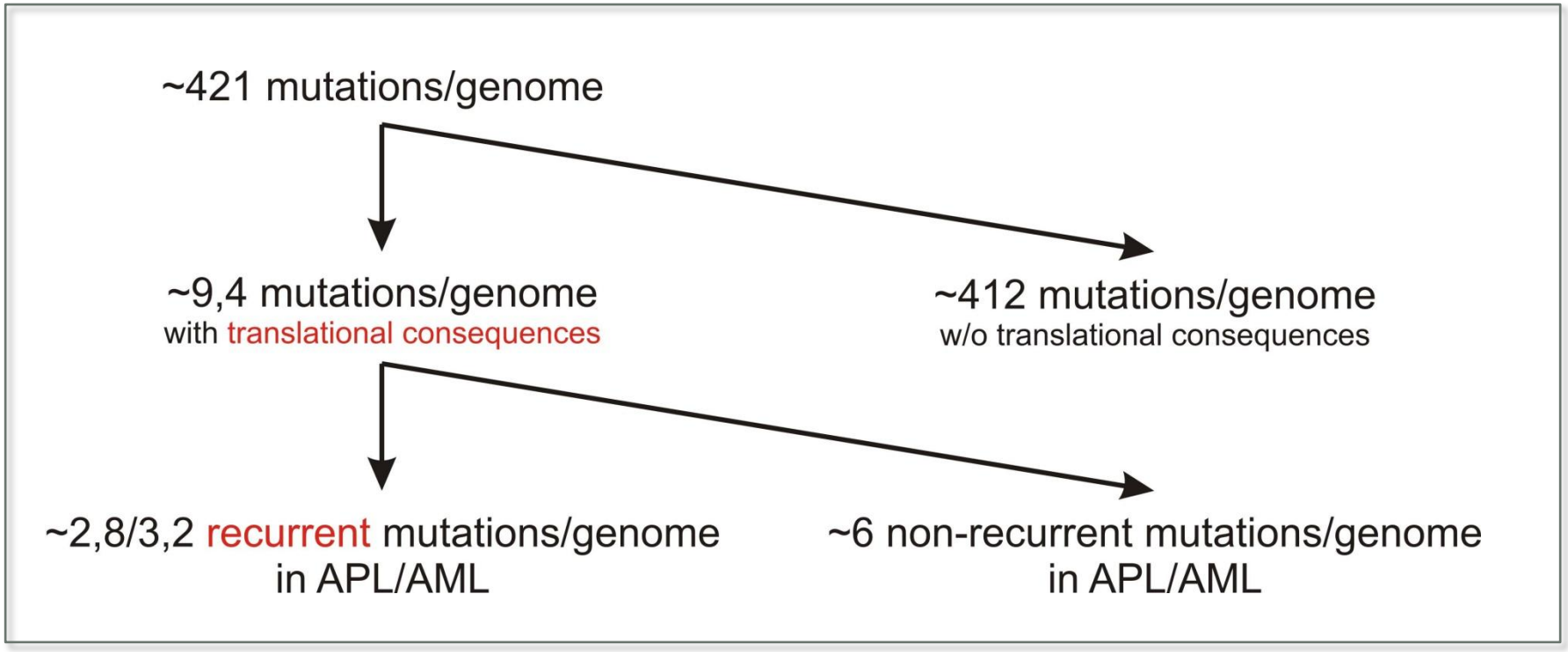
DNMT3A (2p23), a de novo DNA-methyltransferase

- *Incidence*
  - adult AML ~17-22 %, ped AML 0% (MDS 10%, T-ALL 10% #407)
  - Intermediate risk cytogenetics (never with favorable risk cytogenetics)
  - AML-M4-M5, older age, high WBC
  - Associated with Flt3-ITD, NPM1 mut, IDH1/2 mut
  - Heterozygous in myeloid, can be biallelic in lymphoid
- *Associated with worse prognosis in multivariate analysis OS 12.3 mo*
- *Unresolved:*
  - *biomarker for demethylating therapy ?*
  - *Transforming mechanism : increased SC renewal ? (quid role of FLT3/NPM1 context)*

New mutations in AML

 # 404 Complete Sequencing and Comparison of 12 Normal Karyotype M1 AML Genomes with 12 t(15;17) Positive M3-APL Genomes

- Whole genome sequencing : CN AML-M1 (n=12), APL (n=12), additional testing in 34 CN-AML M1 and 9 APL

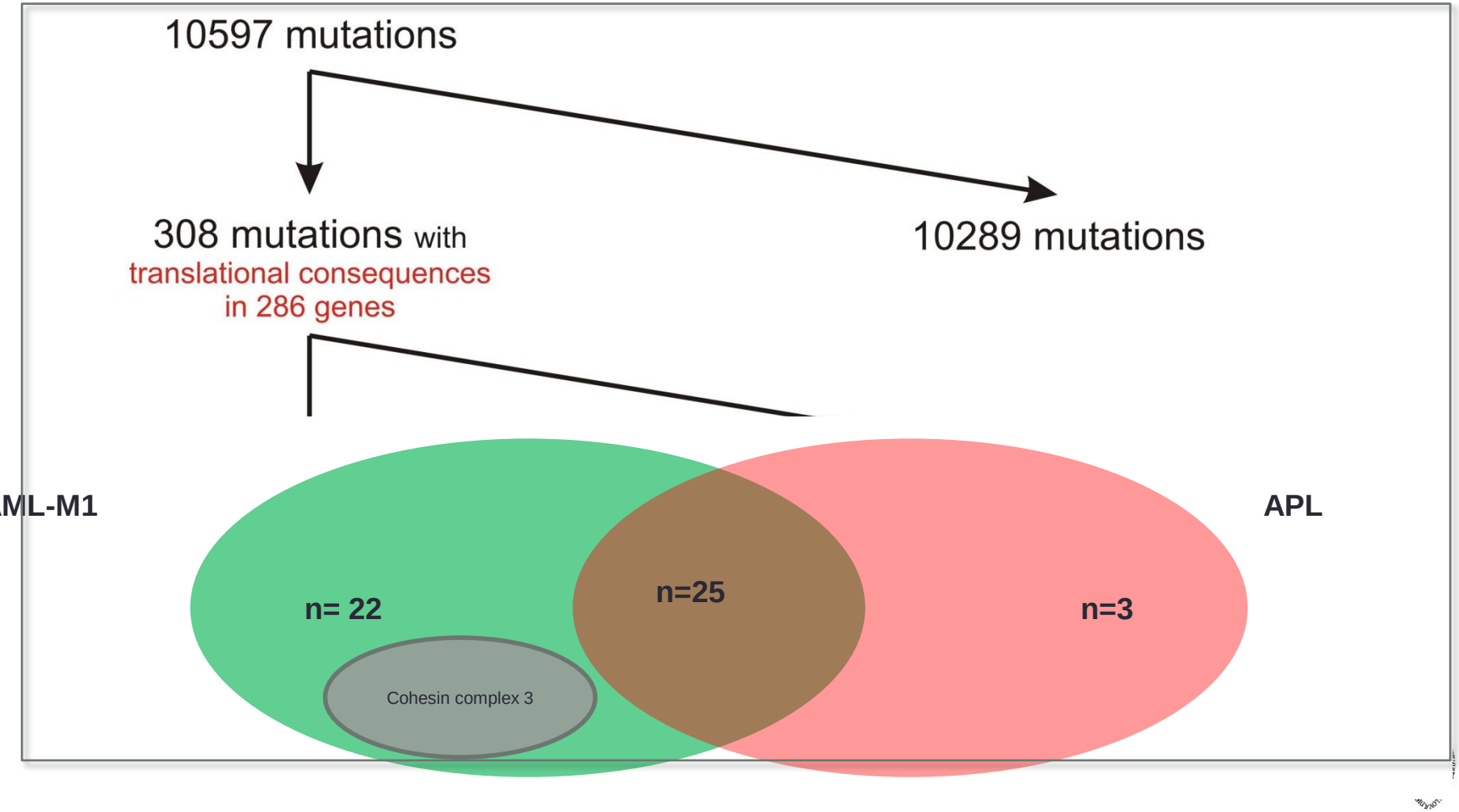


- Far less mutations compared with solid tumors; #SNV increases with age

New mutations in AML

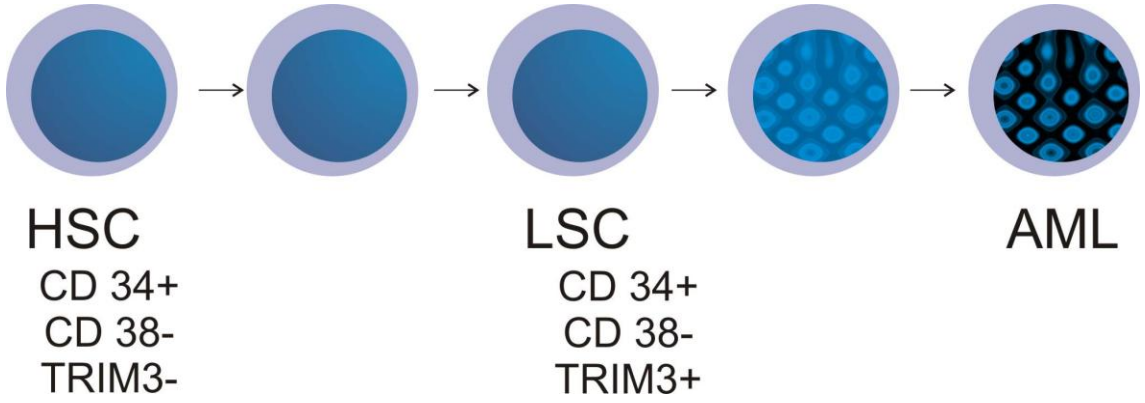
 # 404 Complete Sequencing and Comparison of 12 Normal Karyotype M1 AML Genomes with 12 t(15;17) Positive M3-APL Genomes

- Whole genome sequencing : CN AML-M1 (n=12), APL (n=12), additional testing in 34 CN-AML M1 and 9 APL



New mutations in AML

4 Clonal Evolution of Pre-Leukemic Hematopoietic Stem Cells Precedes Human Acute Myeloid Leukemia



Prospective isolation of HSC, LSC, AML
Exome sequencing of AML
Retrieval of mutations in single HSC or LSC

New mutations in AML

#4 Clonal Evolution of Pre-Leukemic Hematopoietic Stem Cells Precedes Human Acute Myeloid Leukemia

HSC
CD 34+
CD 38-
TRIM3-

LSC
CD 34+
CD 38-
TRIM3+

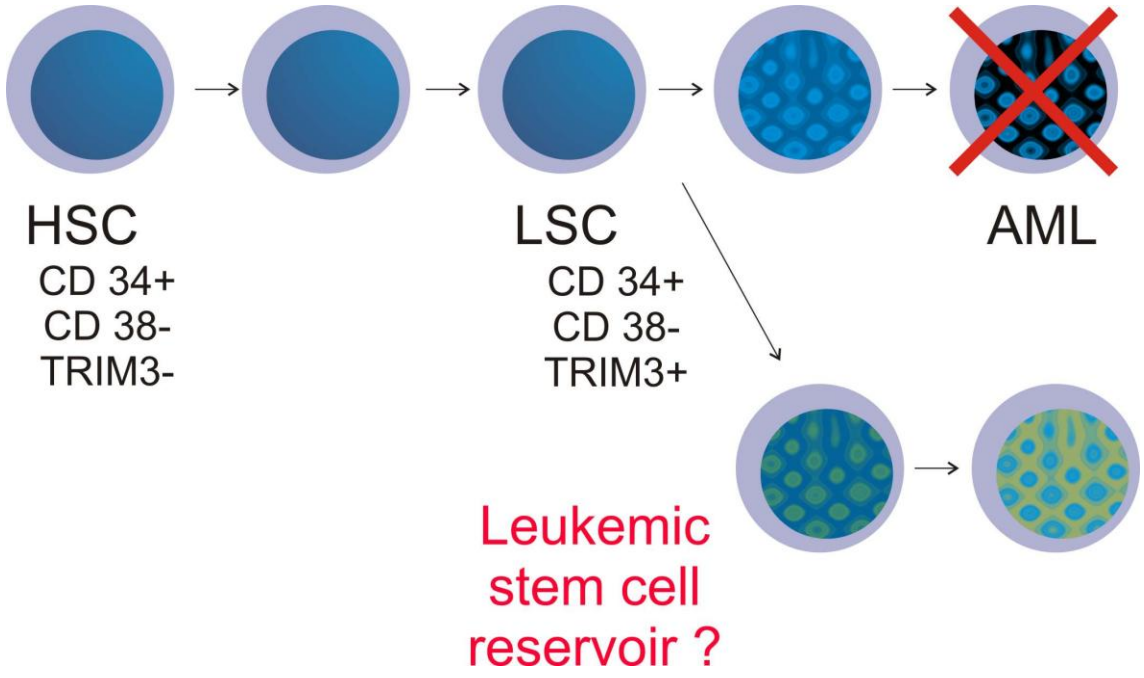
AML

Founder mutations
TET2
NPM1
SMC1A
....

Late events
FLT3 ITD
IDH1 R134
.....

New mutations in AML

#4 Clonal Evolution of Pre-Leukemic Hematopoietic Stem Cells Precedes Human Acute Myeloid Leukemia



New mutations in AML : *BECOR (Xp11.4)*

 # 71 Whole-Exome Sequencing Identifies Recurrent Mutations of BCOR in Acute Myeloid Leukemia with Normal Karyotype

- Whole exome sequencing of CN-AML w/o mutations of CEBPA, NPM1, FLT3-ITD or MLL-PTD
- BCOR (BCL6 corepressor, Xp11.4)
  - Germline mutations in oculo-facio-cardio-dental syndrome
- Nonsense, frameshift, splice site mutations
  - in 14/82 cases with CN-AML w/o mutations of CEBPA, NPM1, FLT3-ITD or MLL-PTD
  - in 11/262 cases with unselected CN-AML
  - never in good risk cytogenetics or CEBPA dm, very rarely with NPM1
  - Strongly associated with DNMT3A and RUNX1 mutations
- Associated with poor prognosis (2y OS 28% vs 66 % in CN AML)

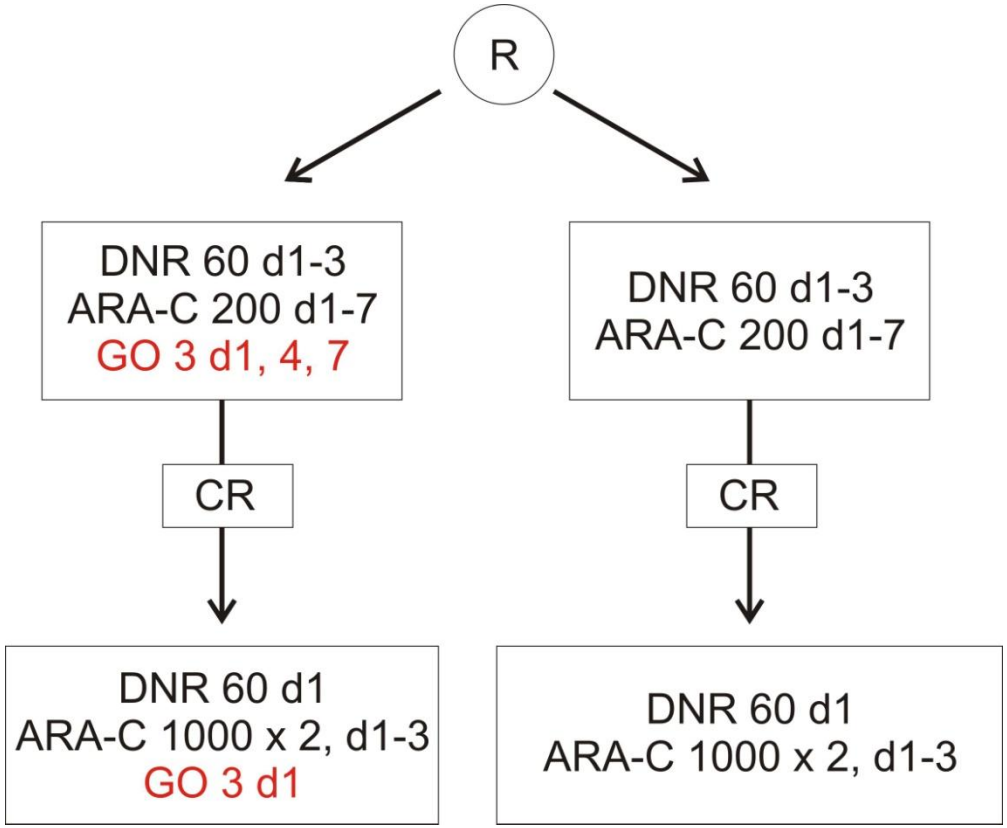
Genetics and therapy of AML

- Perspective of personalized diagnosis coming soon but perspective of personalised therapy remains more remote
  - Many new & unexpected driver mutations and pathways discovered
  - Heterogeneity of the disease, need for increased accrual in clinical trials
- Development of existing drugs vs. searching new ones ?
- Which strategies to target the LSC ?

Therapy of AML

#6 Fractionated Doses of Gemtuzumab Ozogamicin (GO) Combined to Standard Chemotherapy (CT) Improve Event-Free and Overall Survival in Newly-Diagnosed De Novo AML Patients Aged 50-70 Years Old: A Prospective Randomized Phase 3 Trial From the Acute Leukemia French Association (ALFA)

- De novo AML (excluding APL), age 50-70, n = 280



Therapy of AML

6 Fractionated Doses of Gemtuzumab Ozogamicin (GO) Combined to Standard Chemotherapy (CT) Improve Event-Free and Overall Survival in Newly-Diagnosed De Novo AML Patients Aged 50-70 Years Old: A Prospective Randomized Phase 3 Trial From the Acute Leukemia French Association (ALFA)

	DAGO	DA	p
N	137	134	
CR-CRp	81%	75%	0.31
Early death	9	5	0.41
EFS (30 mo)	41 %	20%	0.0018
Med OS	34 mo	19 mo	0.037
Med RFS	28 mo	12 mo	

- 1. Acute myeloid leukemia

2. Myelodysplastic syndromes

3. Acute lymphoblastic leukemia/lymphoma

Myelodysplastic syndromes

3 Somatic Mutation of SF3B1 (2q33), a Gene Encoding a Core Component of RNA Splicing Machinery, in Myelodysplasia with Ring Sideroblasts

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic *SF3B1* Mutation in Myelodysplasia with Ring Sideroblasts

E. Papaemmanuil, M. Cazzola, J. Boultwood, L. Malcovati, P. Vyas, D. Bowen, A. Pellagatti, J.S. Wainscoat, E. Hellstrom-Lindberg, C. Gambacorti-Passerini, A.L. Godfrey, I. Rapado, A. Cvejic, R. Rance, C. McGee, P. Ellis, L.J. Mudie, P.J. Stephens, S. McLaren, C.E. Massie, P.S. Tarpey, I. Varela, S. Nik-Zainal, H.R. Davies, A. Shlien, D. Jones, K. Raine, J. Hinton, A.P. Butler, J.W. Teague, E.J. Baxter, J. Score, A. Galli, M.G. Della Porta, E. Travaglino, M. Groves, S. Tauro, N.C. Munshi, K.C. Anderson, A. El-Naggar, A. Fischer, V. Mustonen, A.J. Warren, N.C.P. Cross, A.R. Green, P.A. Futreal, M.R. Stratton, and P.J. Campbell for the Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium

N ENGL J MED 365;15 NEJM.ORG OCTOBER 13, 2011

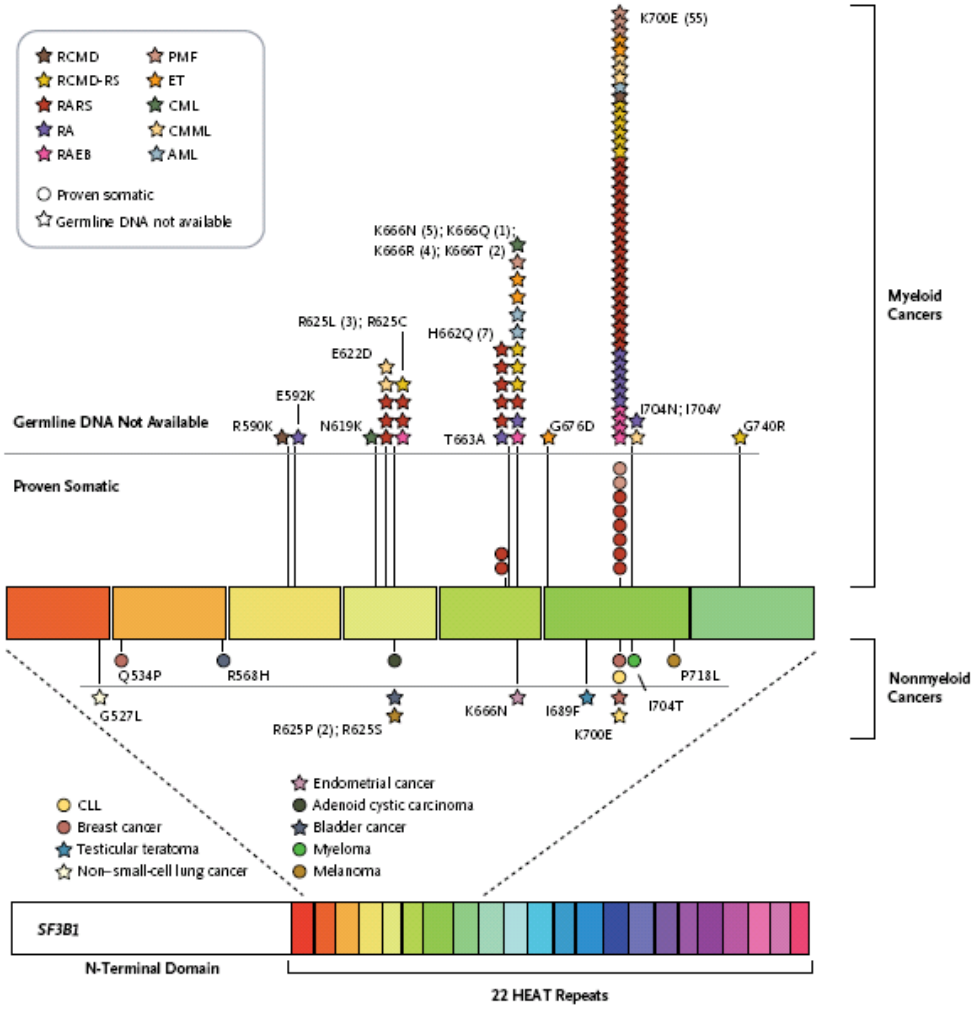
- Whole Exome Sequencing in 9 cases
- 64 point mutations

- RNA splicing factor 3B subunit1 mutation exon12-15) in 72/354 (20%) patients with MDS, and in 53/82 (65 %) patients with MDS-RS

- Associated with TET2

- Also found in other malignancies

- Associated with favorable OS and LFS



- 1. Acute myeloid leukemia
- 2. Myelodysplastic syndromes
- 3. Acute lymphoblastic leukemia/lymphoma

Acute lymphoblastic leukemia: how to optimize long term outcome in adult Ph(+) acute lymphoblastic leukemia ? (Adele Fielding, educational session)

- 25% of adult B-ALL, older population
- Superior CRs with TKI in initial remission induction therapy
  - ? How much chemo is required for an optimal long-term response ? Is chemo required at all ?
  - Which TKI ? Increased toxicity with DAS ?
- Postremission therapy : allo-HCT is key for long term outcome in adults (OS 50-70 % @ 3y in several studies (UKALL12/GMALL/JALSG))
  - How much myeloablation is required for optimal long term response ? Myeloablative versus RIC, with RIC gaining more widespread use
- TKI after alloHCT ?: insufficient evidence for general recommendation: case by case, qBCR-ABL1 monitoring

Acute lymphoblastic leukemia: how to improve long term outcome in other subsets of poor risk ALL ?

- #69 Whole Genome Sequence Analysis of 22 MLL Rearranged Infant Acute Lymphoblastic Leukemias Reveals Remarkably Few Somatic Mutations: A Report From the St Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project
  - MLL rearrangements can be very complex (chromotrypsis), leading to additional in frame fusions
  - In addition to MLL rearrangement, very few mutations (on average 4.8 (0-11) lesions/ case) (RAS pathway, B-cell differentiation
  - More mutations in non-infant MLL –R ALL; many more at relapse
- #70 Ras Signalling Pathway and Novel Target Genes Related to Down Syndrome Contribute to the Development of B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) in iAMP21 patients (n=1 +44) (exome sequencing)
- # 67 Novel Chromosomal Rearrangements and Sequence Mutations in High-Risk Ph-Like Acute Lymphoblastic Leukemia (n=12 + 94) (15% of childhood/adolescent B-ALL) with IKZF1 deletions/mutations
  - Lesions impairing normal B-cell development (PAX5, EBP, IKZF1, ….)
  - Constitutive growth signals
    - 40 % IGH-CRLF2 +/- JAK 2 mutations
    - EBF-PDGFRA
    - STRN3-JAK2
    - NUP214-ABL1
    - BCR-JAK2
    - IGH-EPOR
    - IL7R mutations + loss of SH2B3 (link)

……inibs ?

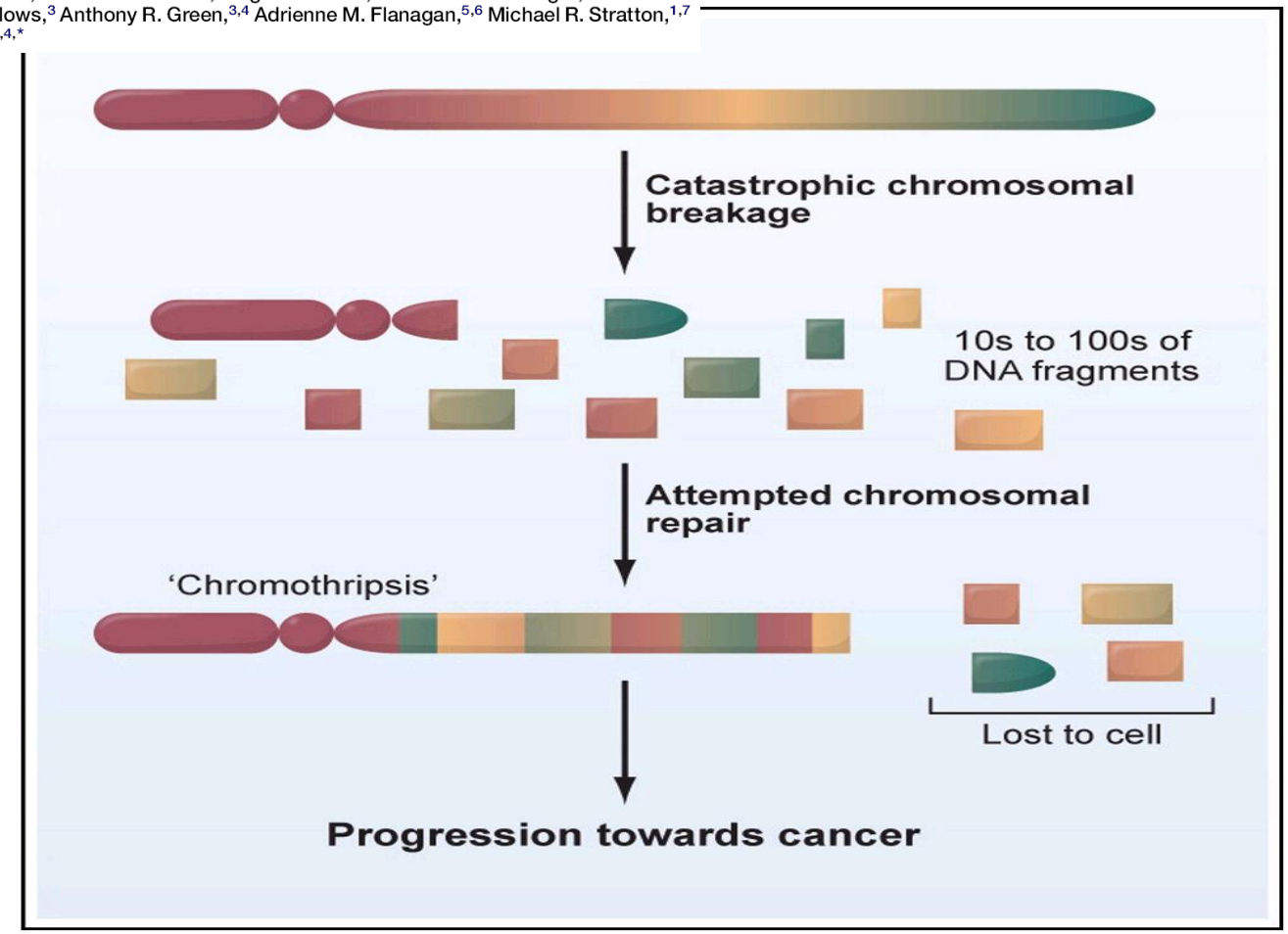
- # 68 Discovery of Novel Recurrent Mutations in Childhood Early T-Cell Precursor Acute Lymphoblastic Leukemia (n=12 +53) by Whole Genome Sequencing
  - Complex inter- en intrachromosomal reaargmnts /cytokine receptor and RAS/B-T developmental genes/ EZH2 and PRC2
  - similarities with AML
- # 403 The Genomic Landscape of TEL-AML1+ (ETV6-RUNX1) Acute Lymphoblastic Leukaemia

Acute lymphoblastic leukemia: common emerging themes

- Very few lesions / case compared with AML
  - Infant MLL R >> non-infant/adolescent ALL> adult ALL
- Structural rearrangements can be extremely complex at molecular level : “chromotrypsis”

Massive Genomic Rearrangement Acquired in a Single Catastrophic Event during Cancer Development

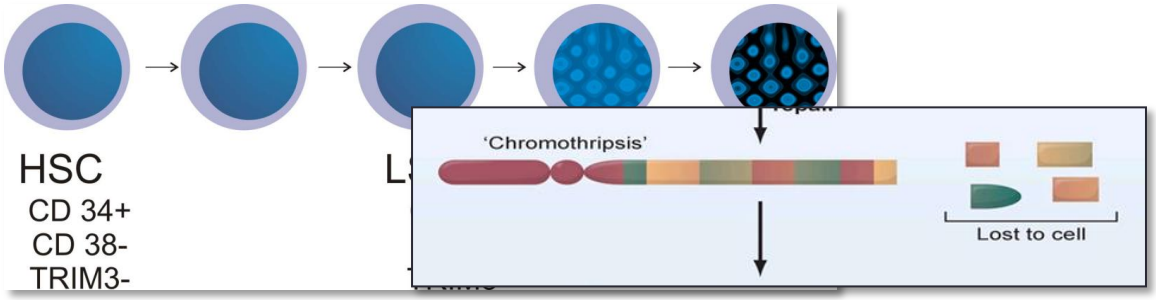
Philip J. Stephens,[1] Chris D. Greenman,[1] Beiyuan Fu,[1] Fengtang Yang,[1] Graham R. Bignell,[1] Laura J. Mudie,[1] Erin D. Pleasance,[1] King Wai Lau,[1] David Beare,[1] Lucy A. Stebbings,[1] Stuart McLaren,[1] Meng-Lay Lin,[1] David J. McBride,[1] Ignacio Varela,[1] Serena Nik-Zainal,[1] Catherine Leroy,[1] Mingming Jia,[1] Andrew Menzies,[1] Adam P. Butler,[1] Jon W. Teague,[1] Michael A. Quail,[1] John Burton,[1] Harold Swerdlow,[1] Nigel P. Carter,[1] Laura A. Morsberger,[2] Christine Iacobuzio-Donahue,[2] George A. Follows,[3] Anthony R. Green,[3,4] Adrienne M. Flanagan,[5,6] Michael R. Stratton,[1,7] P. Andrew Futreal,[1] and Peter J. Campbell[1,3,4,*]

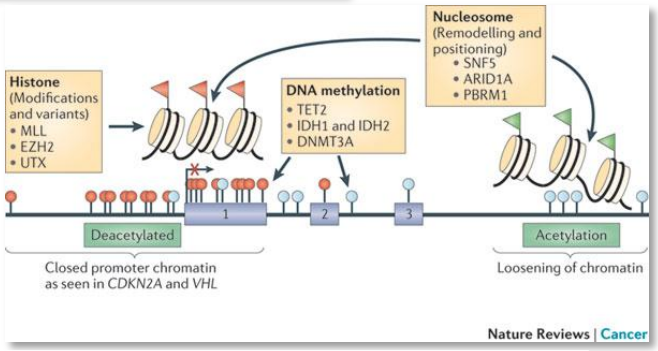


Acute lymphoblastic leukemia: common emerging themes

- Very few lesions / case compared with AML
  - Infant MLL R >> non-infant/adolescent ALL> adult ALL
- Structural rearrangements can be extremely complex at molecular level : “chromotrypsis”
- Subclonal variation common at diagnosis, minor diagnostic subclone can be origin of relapse
- Remarkable genetic heterogeneity among each of the subsets analysed, but common themes can (sometimes) be identified
  - BCR-ABL1-like ALL and potential targets for TKI
  - ETP ALL resembling HSC rather than normal ETP : case for “myeloid” induction therapy ?

Acute leukemia : 2012





Class I „events“

RAS pathway
IL7R
SH2B2
JAK1-3
novel fusions
.....

Class II „events“
('developmental')

ETV6
PAX5
EBP
RUNX1
GATA1-3
Ep300
.....