Molecular Hematopathology III Leukemias II

May 17, 2005

Acute Lymphoblastic Leukemia

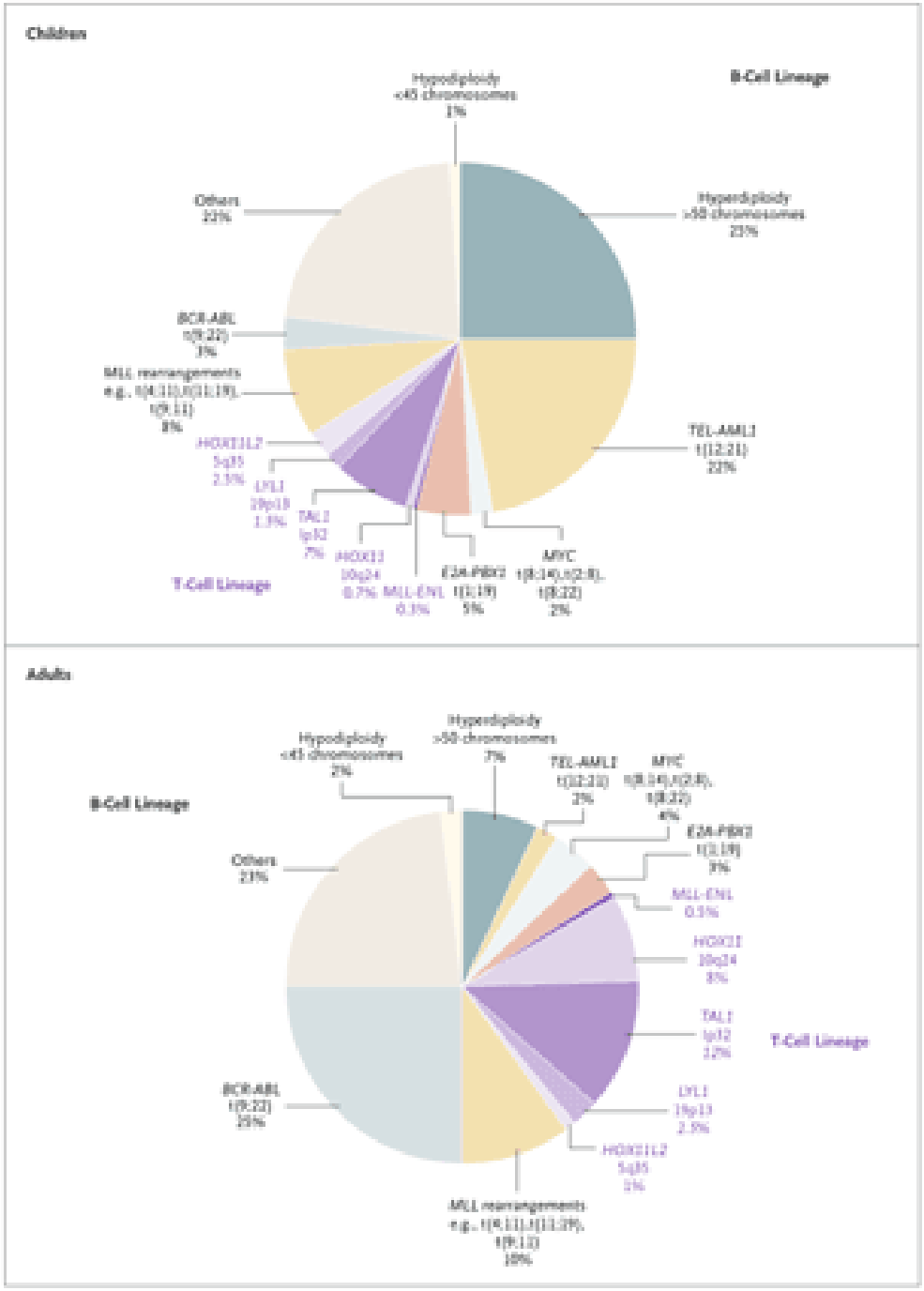
Many translocations and molecular events described

Seen in both pediatric and adult ALL, similar

Some effect prognosis and/or treatment

General Mechanisms of ALL Pathogenesis

- aberrant expression of proteins (oncogenes)
- translocations creating fusion gene with kinase fxn
- translocations creating fusion gene with altered TF fxn
- hyperdiploidy



Translocations in Acute Lymphoblastic Leukemia

Acute Lymphoblastic Leukemia

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Alterations result in aberrant regulation:

- unlimited self-renewal
- uncontrolled proliferation
- blocked differentiation
- avoid apoptosis

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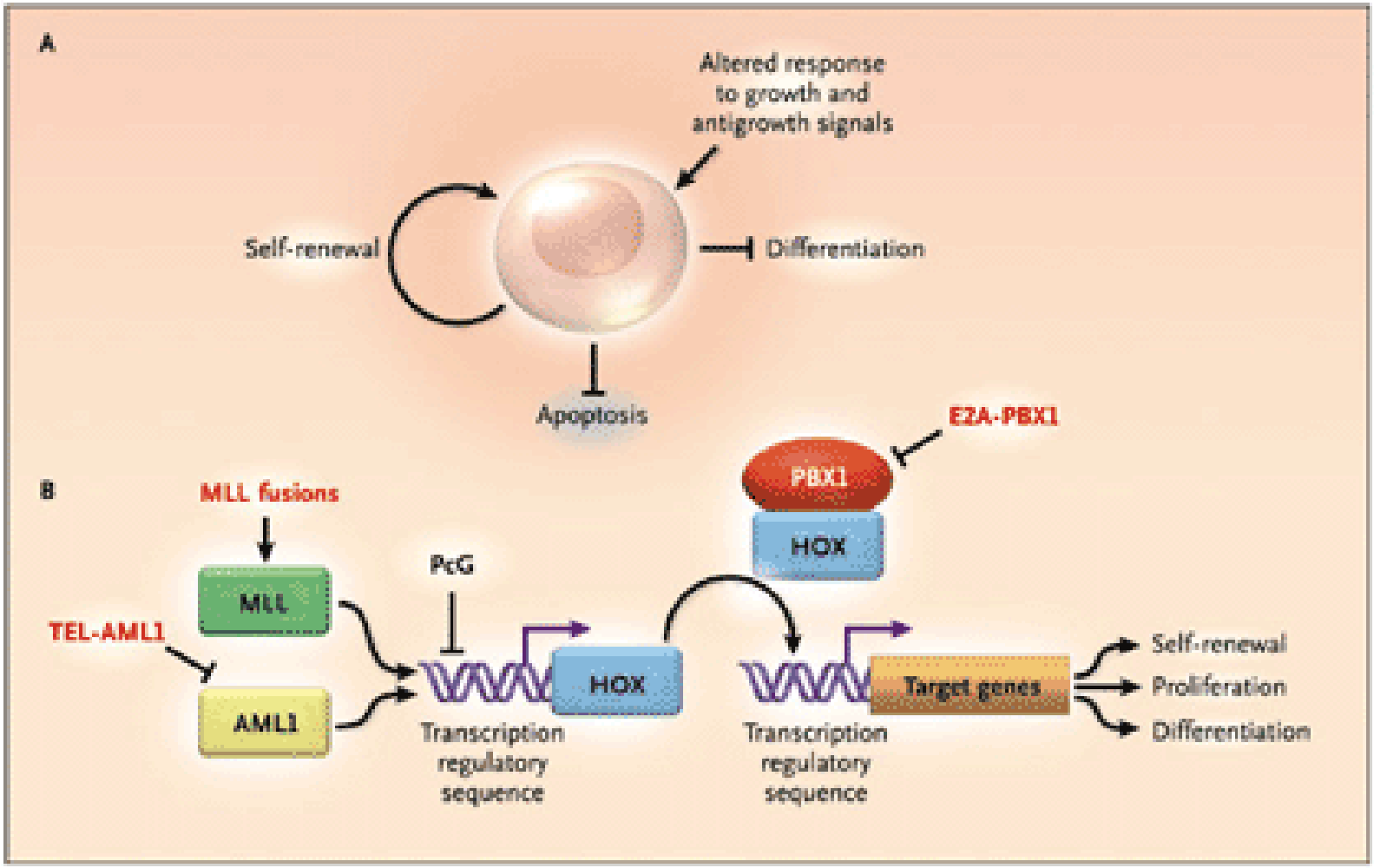

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Acute Lymphoblastic Leukemia

Philadelphia chromosome

- **t(9;22)(q34;q11)**
- most in ALL are e1a2 translocation; $p190^{Bcr\text{-}Abl}$
- 40-60% of adult ALL, 3% of pedi ALL cases
- poor outcome

Hyperdiploidy > 50 chromosomes

- 20-30% of pedi, 7-10% of adult; often pre-B pheno
- blasts are hypersensitive to chemother, esp methotrexate
- good Px, esp as #chromo ↑, esp #4, 6, 10, 17

TEL/AML1 Translocation

t(12;21)(q13;q22)

The most common translocation in pedi ALL

25% of pedi B-ALL, 1-3% of adult B-ALL

TEL (translocation ets leukemia, aka *ETV6*) gene on 12q13 translocated to *AML1* gene on 21q22

ets = family of TFs involved in development, cellular diff, prolif, apoptosis, remodeling; similar to E26, an avian retrovirus

TEL protein normally helps regulate h'poesis and progenitor homing to BM; inhibits megakaryo/promotes erythro develop

TEL/AML1 Translocation

TEL/AML1 fusion protein is a dominant negative inhibitor of normal AML1; consists of 5' end of TEL and most of AML1

Results in repression, not activation, of HOX genes, due to HDAC recruitment

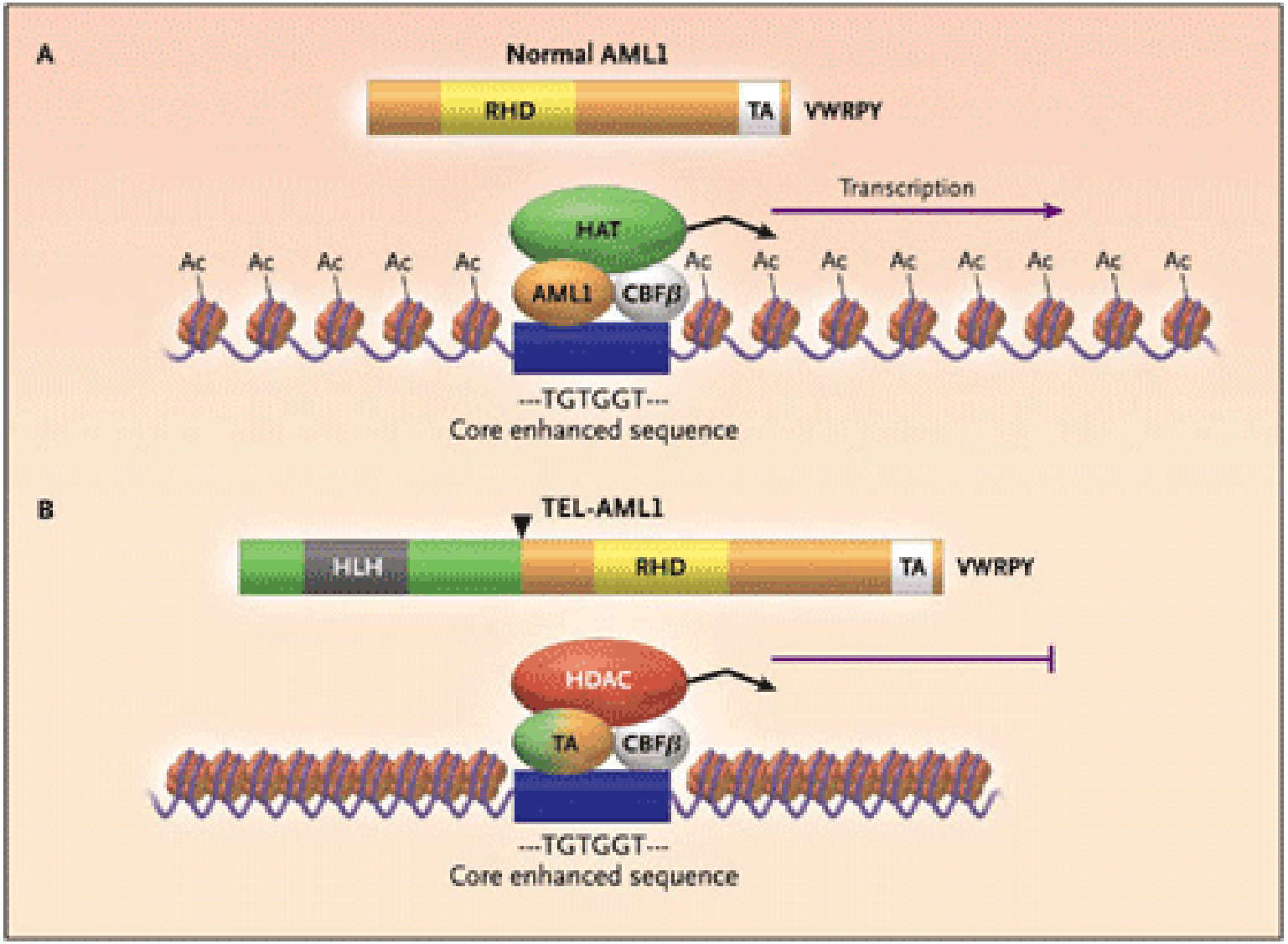
Alters self-renewal capacity and differentiation of h'poeitic stem cells

Clinical trials for HDAC inhibitors

B-ALL cases with this translocation have favorable Px, if use intense chemo that includes asparaginase

Detection- FISH, RT-PCR

Transcriptional Repression By TEL/AML1



Homeobox Genes

Homeobox genes encode transcription factors (homeoproteins) involved in embryo/morphogenesis

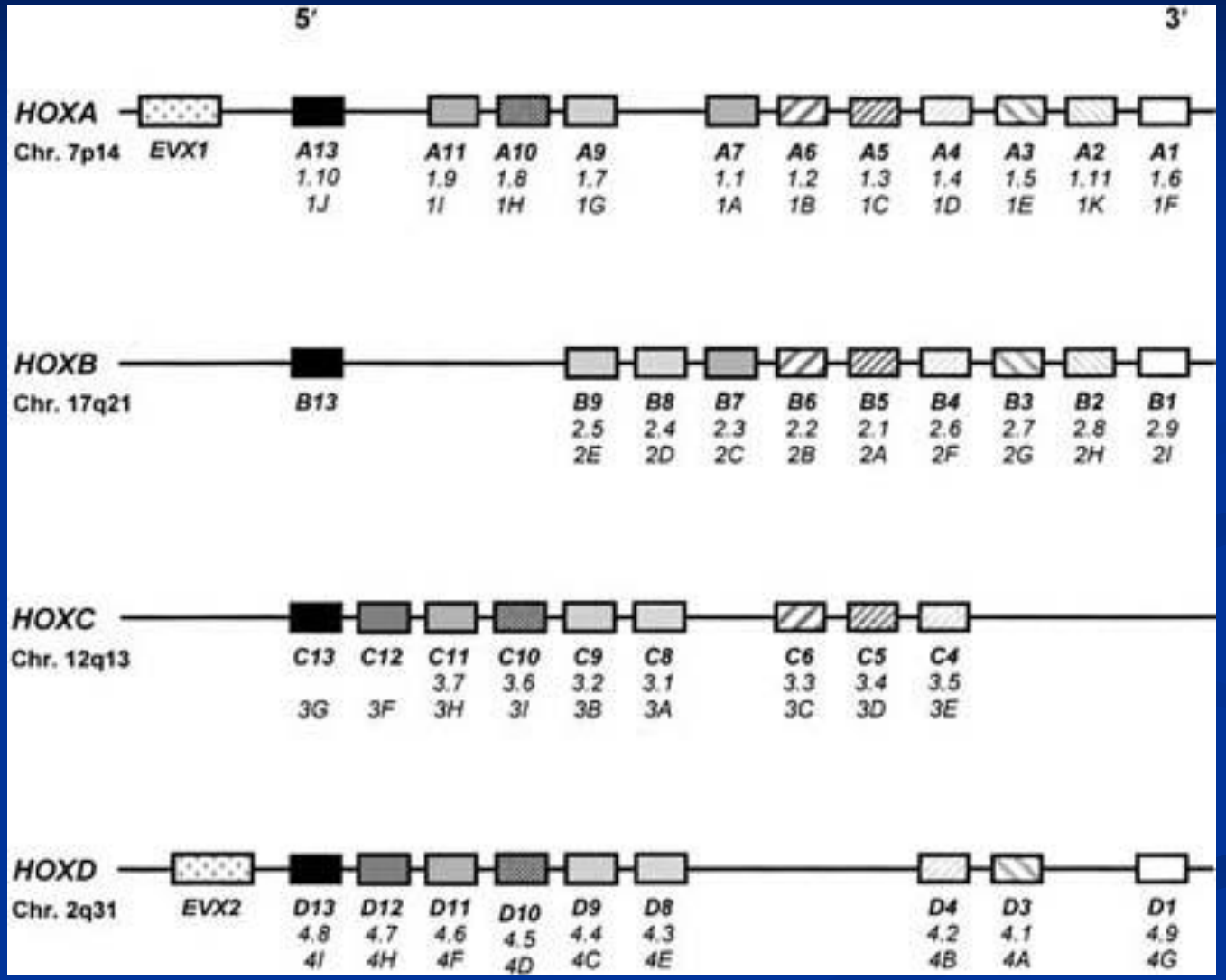
Humans have ~200 homeobox genes across genome

HOX genes – 39 genes in 4 clusters (HOXA – HOXD)

Homeobox genes are expressed in 5'→ 3' order during development

Usually only expressed in undifferentiated and/or proliferative cells

Human Homeobox Genes



Homeobox Genes

Homeodomain – a 60 aa domain within the homeoprotein (encoded by homeobox genes)

Homeodomains recognize/bind specific DNA sequences within genes all over the genome that are associated with development

Homeoproteins thus act as transcription regulators (up-regulators and down-regulators) in embryogenesis/development, cell cycle regulation, proliferation

Mixed Lineage Leukemia Gene Alterations

MLL gene is on chromosome 11q23

TF that helps maintain HOX family expression; *Drosoph trithorax*

MLL translocations create chimeric proteins, consisting of the N terminal of MLL and the C teminal of 1 of 40 different proteins

MLL fusion proteins acquire a gain of function (increased transcription activity), effects the downstream HOX gene, esp *HOXA7* and *HOXA9*, so cells have greater self-renewal and more growth of stem and progenitor cells

Present in 80% of infant ALL, usually pro-B pheno; also in many therapy-induced (esp topo II inhibitors) ALLs of adults; poor Px

MLL Translocations in ALL

t(4;11)(q21;q23)

- most frequent of the *MLL* translocations
- *MLL* on 11q23 translocates with *AF4* on 4q21; creates the fusion protein MLL/AF4
- responds to high dose cytarabine, good prognosis

t(11;19)(q23;p13.3)

- *MLL* and *ENL* translocation

t(9;11)(p21;q23)

- *MLL* and *AF9* translocation

Other Homeobox Gene Translocations

t(1;19)(q23;p13)

- 25% of pre-B-ALL, mainly pedi; 5% of adult B-ALL
- *PBX1* homeobox gene binding cofactor on 1q23
- *E2A* transcription factor on 19p13 (l'poeisis, B-cell dev)
- E2A-PBX1 is a chimeric protein, a TF that disrupts *HOX* genes and E2A targets, disrupting cell differentiation
- Poor prognosis

t(17;19)(q22;p13)

- pro-B-ALL
- *E2A* on 19p fuses with *HLF* (hepatic leukemia factor), a TF on 17q
- fusion protein suppresses apoptosis

Cooperative Mutations in ALL

Above mutations alone are insufficient for leukemagenesis

FLT-3

- receptor tyrosine kinase needed for h'poeitic stem cell devel

- overexpressed in all ALL cases with *MLL* translocations or hyperdiploidy of > 50 chromosomes

- mutations in or overexpression of *FLT-3* results in constant FLT-3 protein expression

Cooperative Mutations in ALL

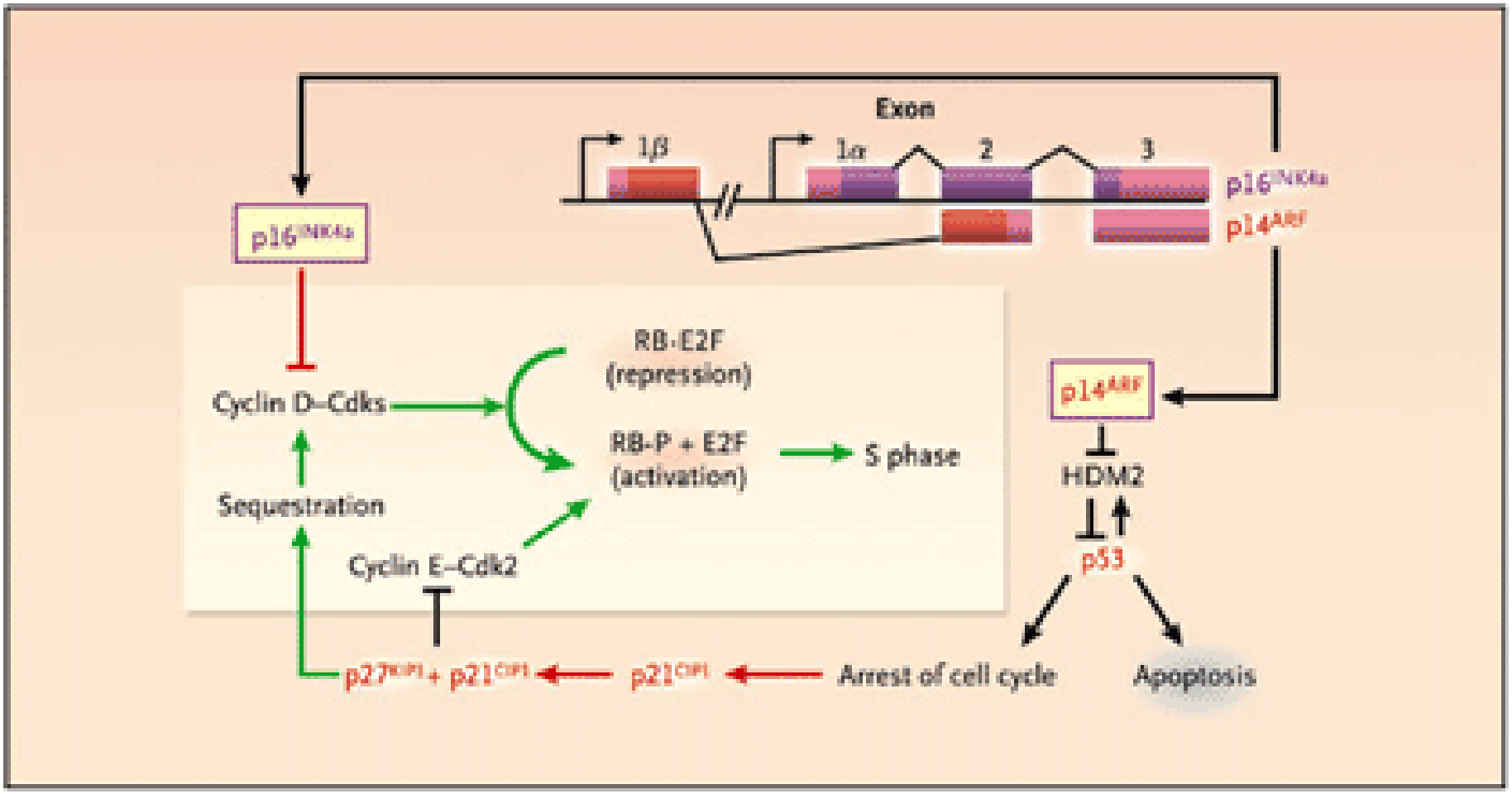
$p16^{INK4a}$ and $p15^{INK4b}$

- proteins that prevent entry into S phase by inhibiting cdk4 and cyclin D; both on 9q
- mutations seen in nearly all pediatric T-ALL cases and in 20% of pre-B-ALL

$p14^{ARF}$

- inhibits inhibition of p53
- $p14^{ARF}$ inhibits MDM2 (which normally degrades p53)
- $p14^{ARF}$mutations common in ALL
- MDM2 overexpression also common in ALL

$p16^{INK4a}$, $p15^{INK4b}$, $p14^{ARF}$ and p53 and RB Proteins in Cell Cycle Control



T-ALL Translocations

- 30% have translocations involving T-cell receptor
- Most often involves TCRα, TCRβ, or TCRγ
- In most cases the TCR enhancer or promoter translocated next to an oncogene

Table I. Genetic abnormalities in T ALL.

Gene	Location	Rearrangement
HOX11	10q24	t(10;14)(q24;q11)
		t(7;10)(q35;q24)
TAL1	1p33	t(1;14)(p33;q11)
		TALd
TAL2	9q32	t(7;9)(q34;q32)
LYL1	19p13	t(7;19)(q34;p13)
LMO1	11p15	t(11;14)(p15;q11)
LMO2	11p13	t(11;14)(p13;q11)
		t(7;11)(q35;p13)
MYC	8q24	t(8;14)(q24;q11)
LCK	1p34	t(1;7)(p34;q34)
TAN1	9q34.3	t(7;9)(q34;q34.3)
IGH	14q32.3	inv(14)(q11q32)
TCL1	14q32.1	inv(14)(q11q32)
		t(14;14)(q11;q32)

T-ALL Translocations

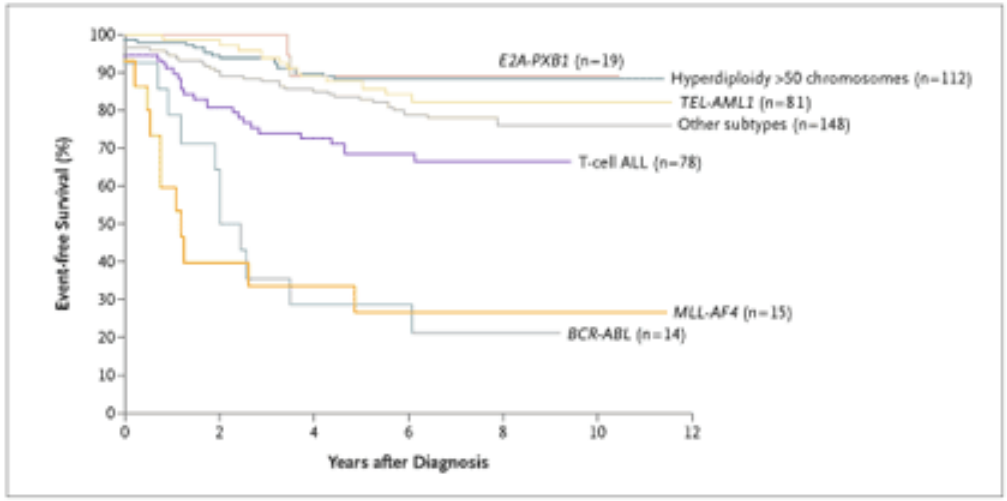
t(10;14)(q24;q11) and **t(7;10)(q35;q24)**

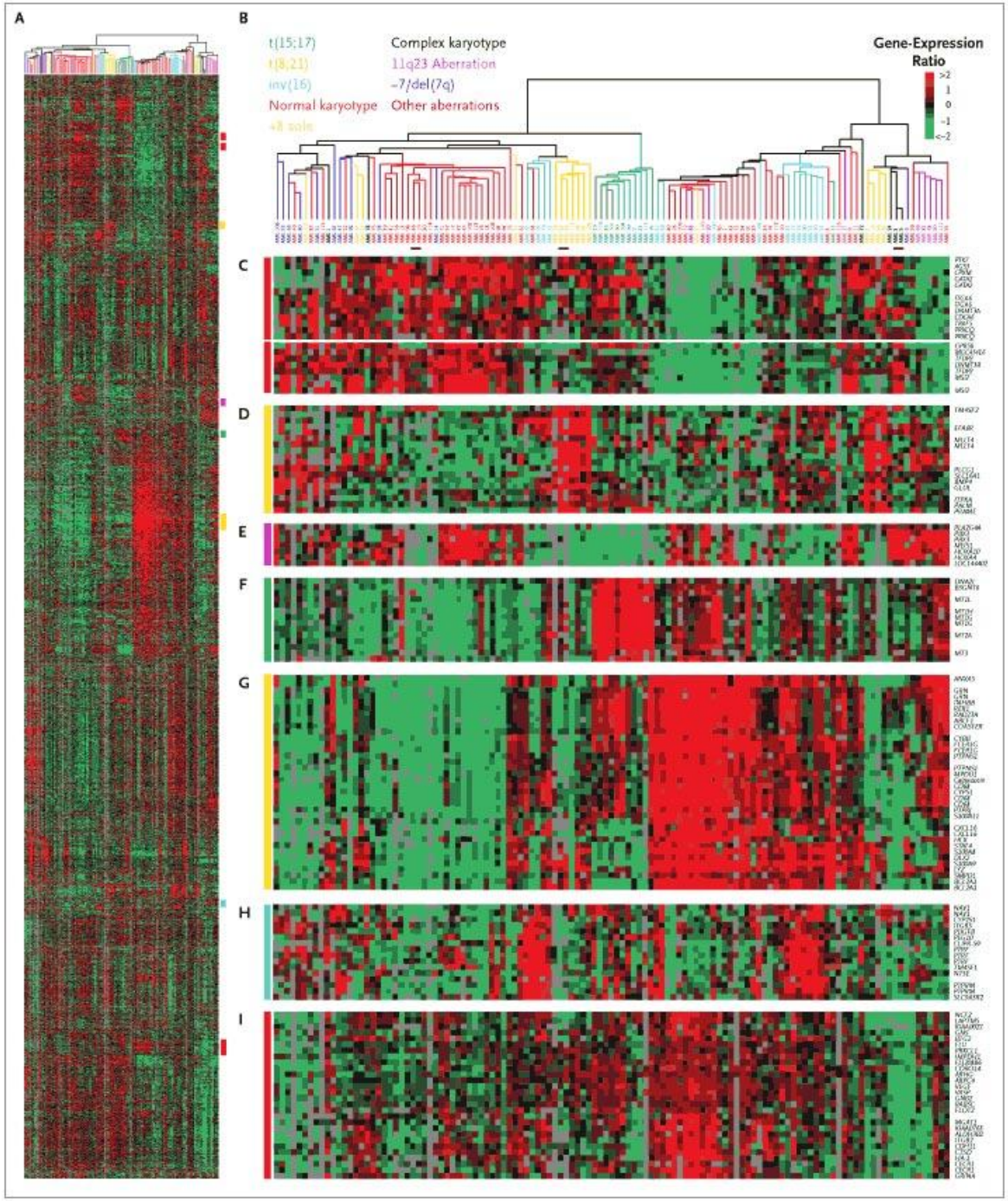
- *HOX11* (aka *TCL*, a homeobox gene) on 10q24 translocated to *TCR*α on 14q11 or *TCR*β on 7q35
- *HOX11* overexpressed since transloc near TCR promoter
- 5% of childhood T-ALL
- favorable outcomes

T-ALL Translocations

t(1;14)(p33;q11) and ***TALd***

- *TAL1* (aka *SCL*) is a TF that modulates gene expression in hematopoeisis
- *TAL1* on 1p13 translocated to *TCRα* on 14q11
- Results in overexpression of *TAL1*
- seen in 3% of T-ALL cases
- *TAL*d is a 100kb deletion putting *TAL1* near the promoter of another gene (SIL); *TAL1* gets overexpressed
- *TAL*d seen in 20% of T-ALL cases


Event-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Years after Diagnosis
E2A-PXB1 (n=19)
Hyperdiploidy >50 chromosomes (n=112)
TEL-AML1 (n=81)
Other subtypes (n=148)
T-cell ALL (n=78)
MLL-AF4 (n=15)
BCR-ABL (n=14)


A
B
t(15;17)
t(8;21)
inv(16)
Normal karyotype
+8 solo
Complex karyotype
11q23 Aberration
−7/del(7q)
Other aberrations
Gene-Expression Ratio
>2
1
0
−1
<−2
C
D
E
F
G
H
I