

# Aneuploidy in Leukemia and Cancer

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# Cancer is a genetic disease

## Activation of oncogenes

t(8;14)(q24;q32) -> CMYC overexpression  
amplification of *MLL*

## Inactivation of tumor-suppressor genes

17p deletion + mutation of the 2nd *TP53* allele

## Formation of tumor-specific fusion genes

t(15;17)(q22;q12) -> *PML-RARA*

uncontrolled proliferation

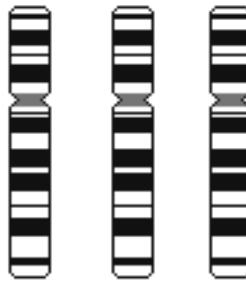
blocked differentiation

apoptosis resistance

Cancer

# Definition

- Aneuploidy
  - loss and/or gain of whole chromosomes



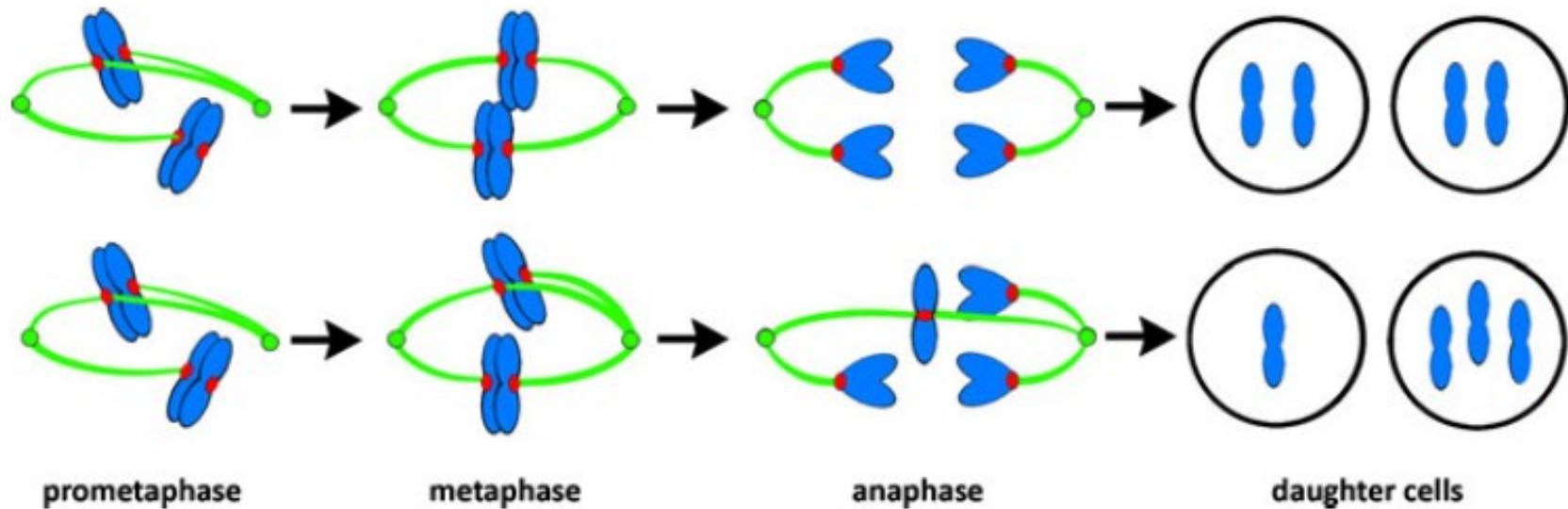
Trisomy 8



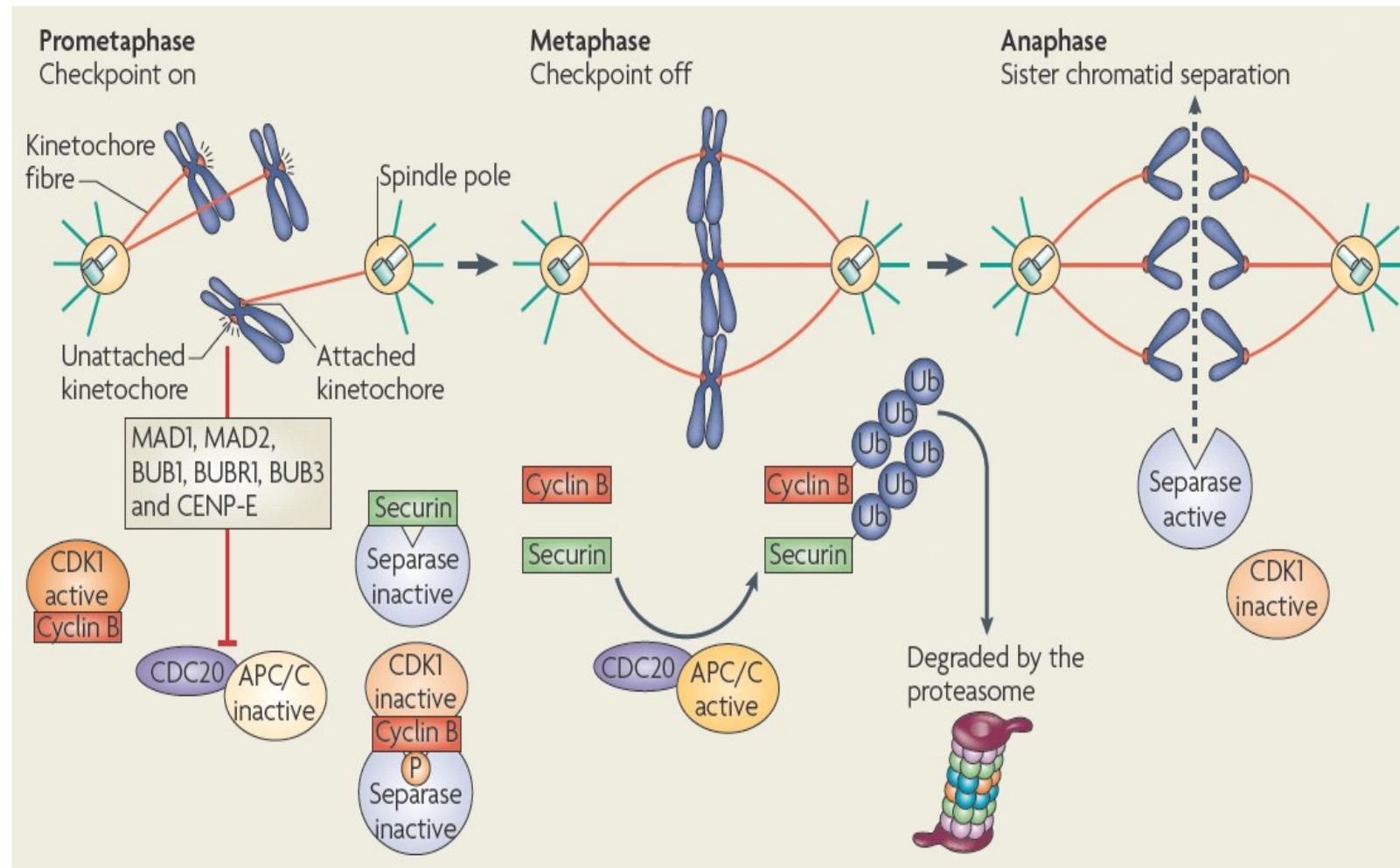
Monosomy 7

- Aneuploidy is found in most solid tumors and half of all leukemias and lymphomas (<http://cgap.nci.nih.gov/Chromosomes/Mitelman>)

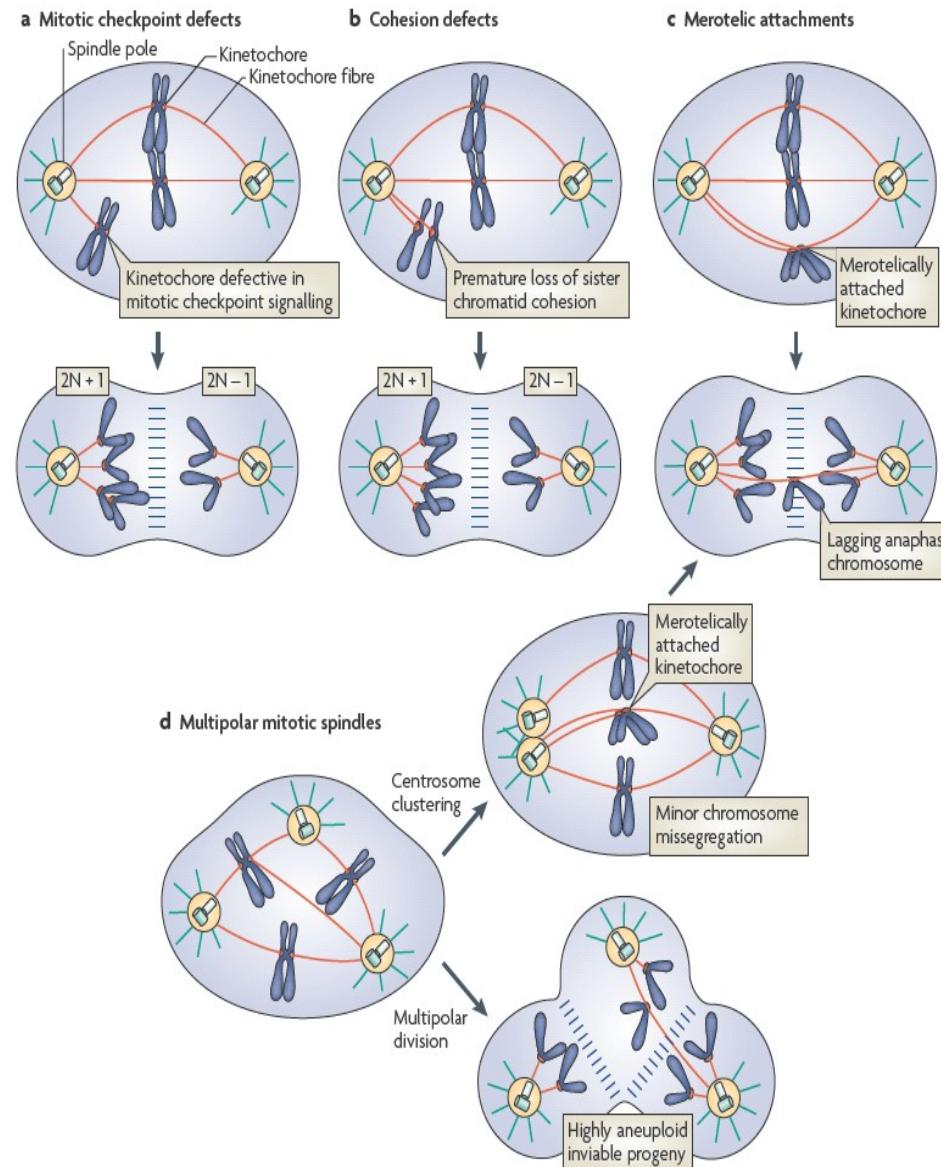
# How does aneuploidy occur?



# Many „players“ protect against aneuploidy



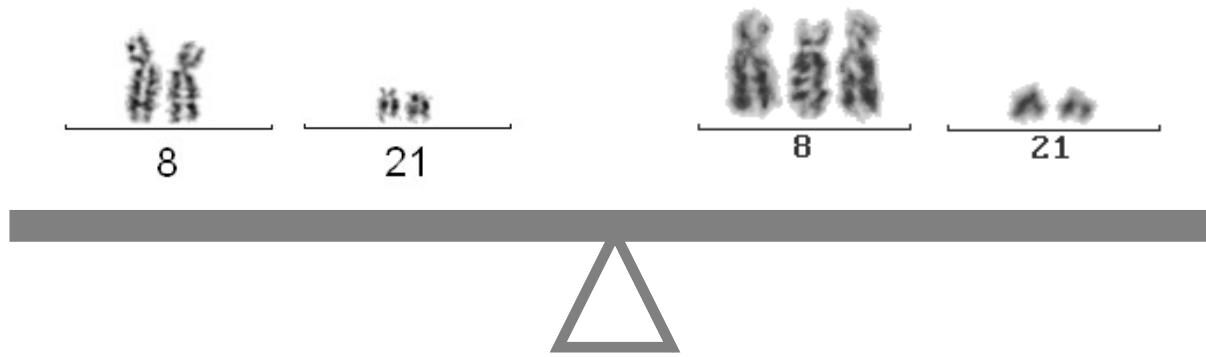
# Pathways to the generation of aneuploidy



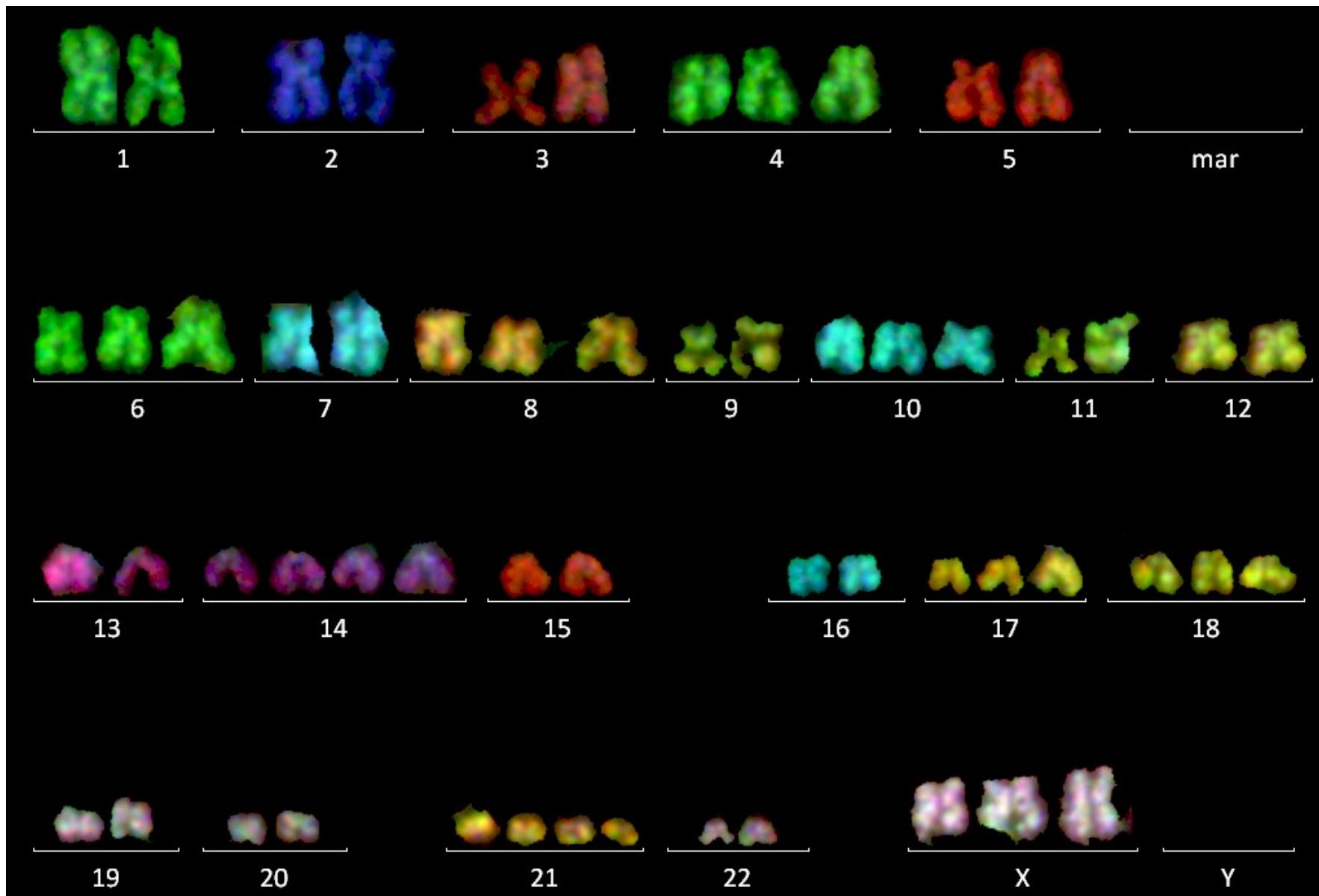
# Gain of chromosomal material

46,XX

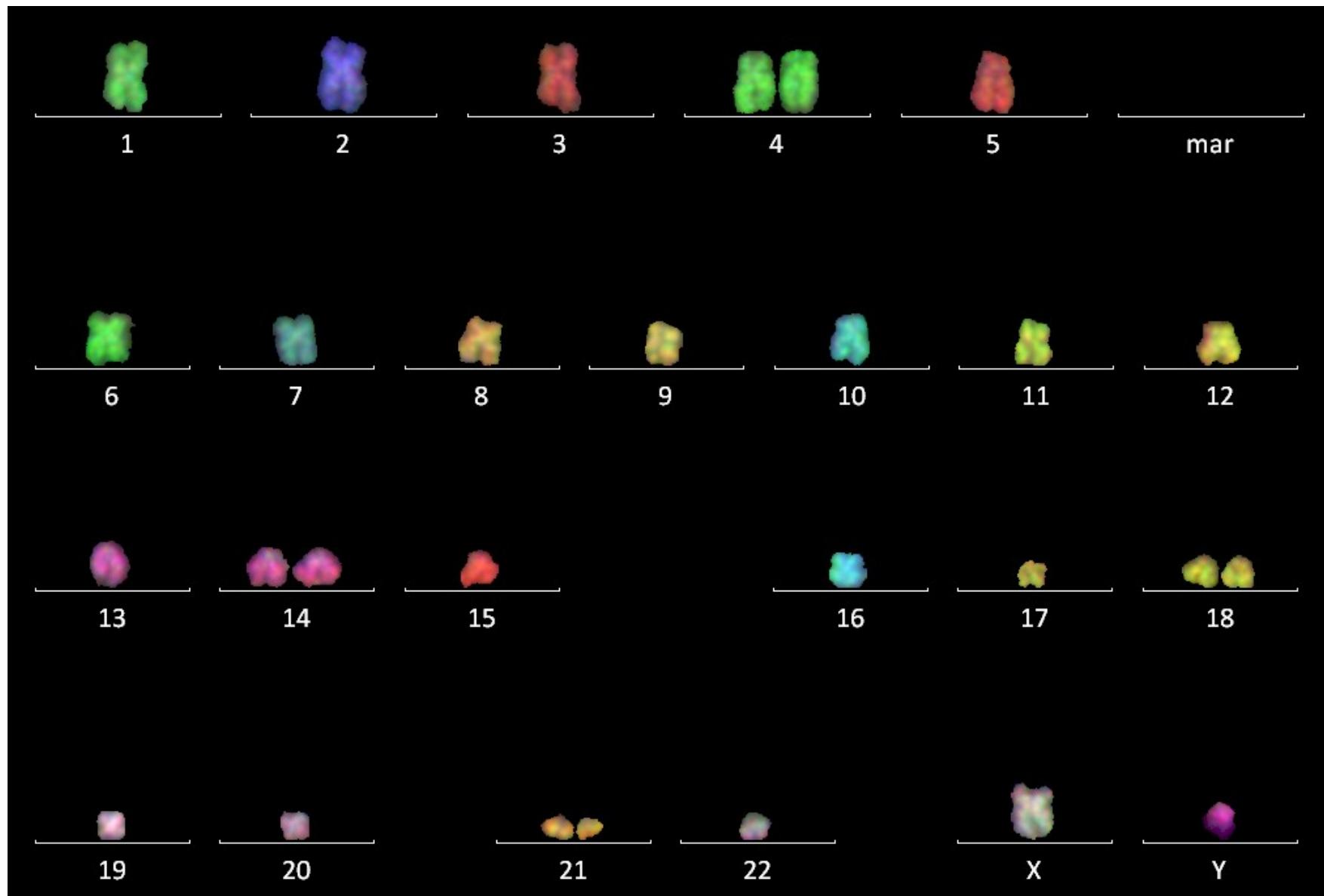
47,XX,+8



## ALL with high hyperdiploidy

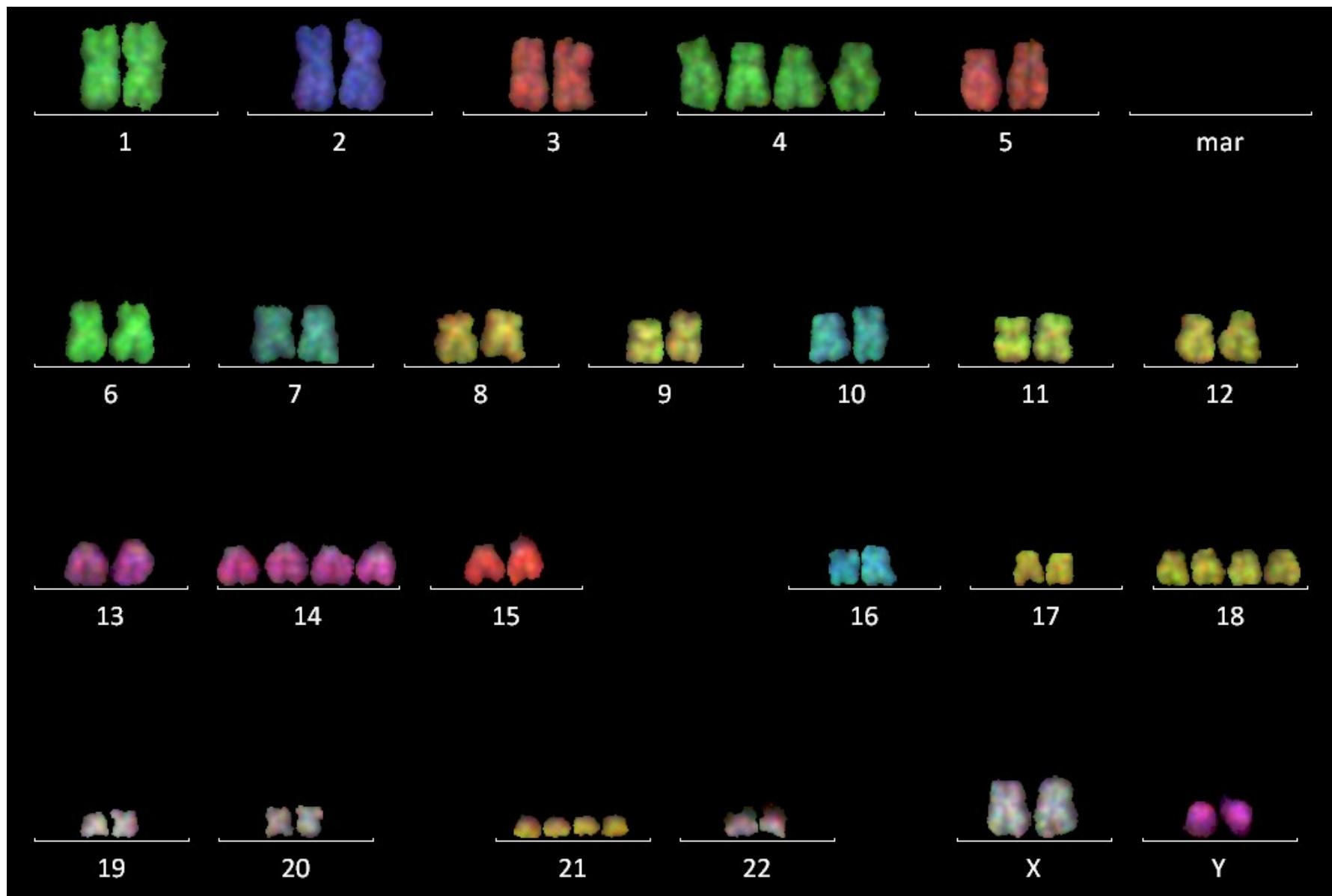


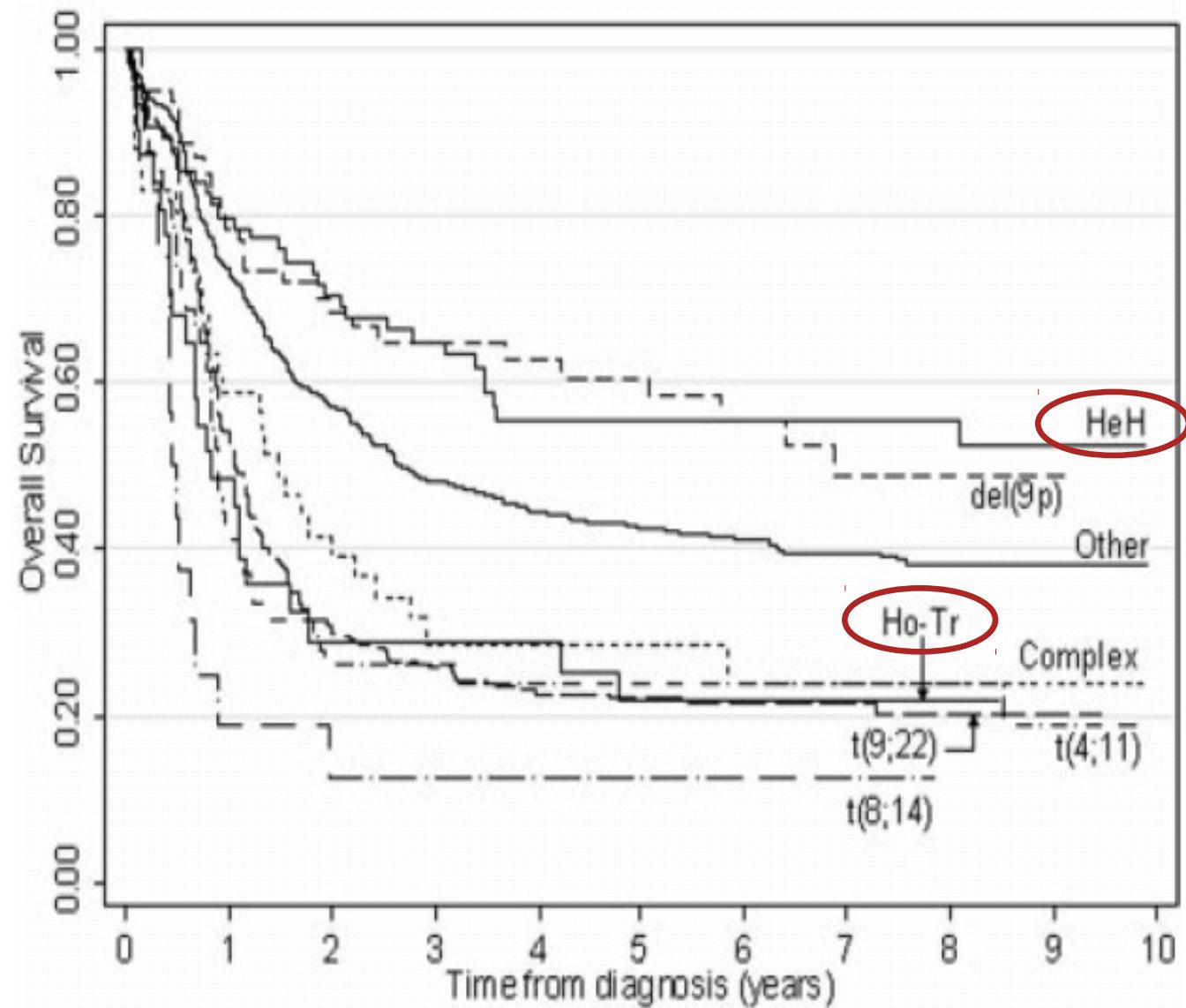
## ALL with low hypodiploidy



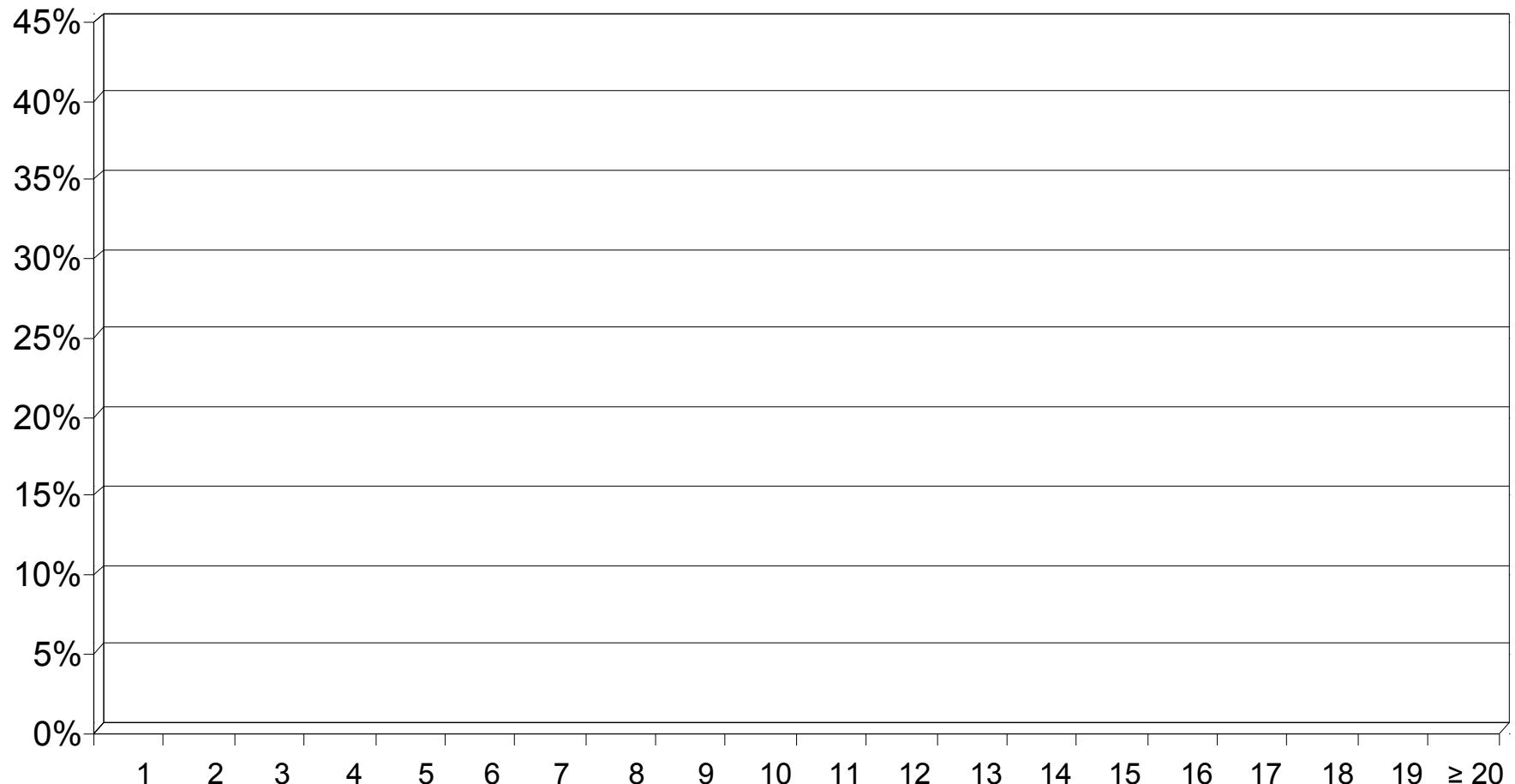


# ALL with near triploidy

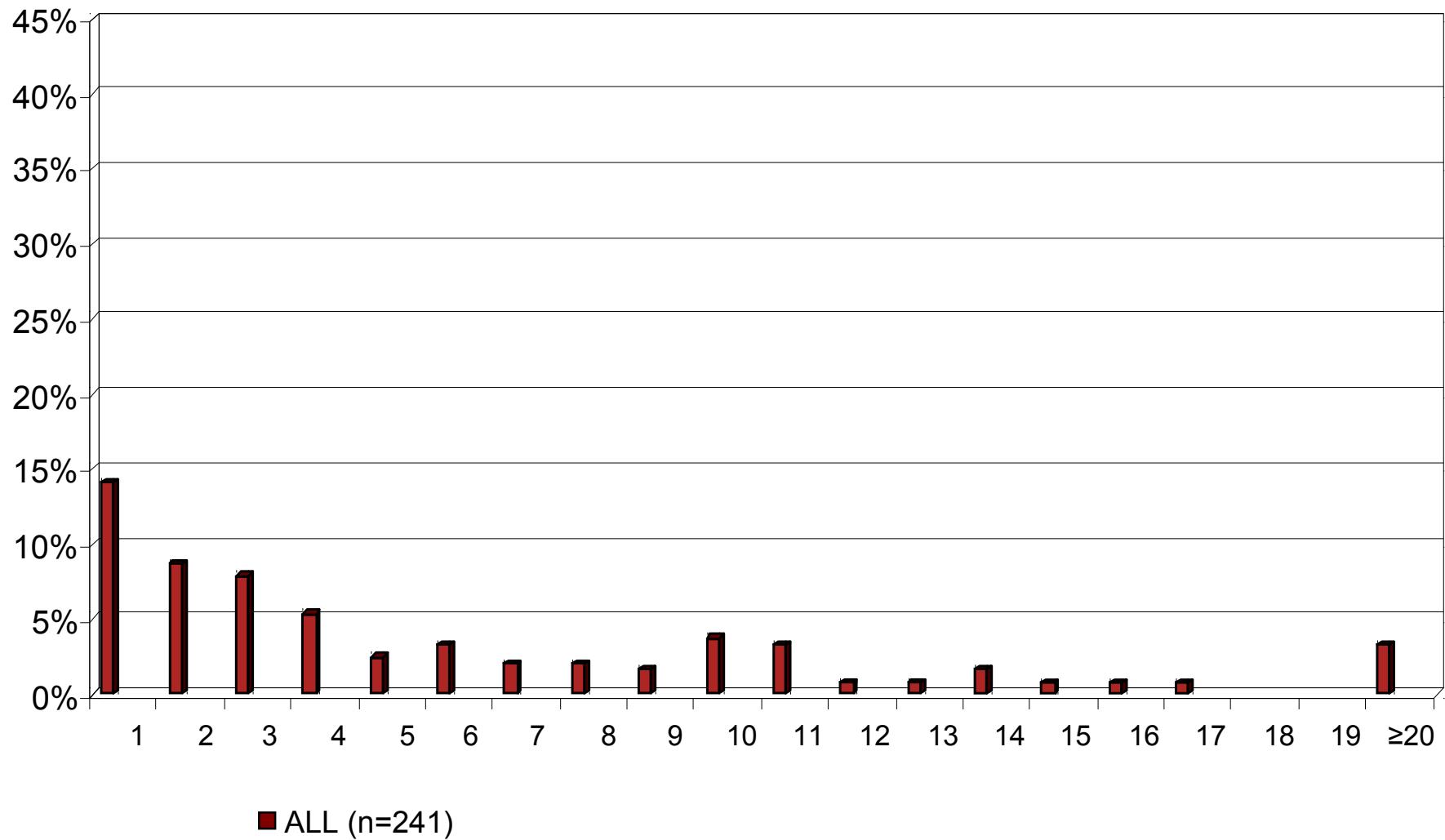




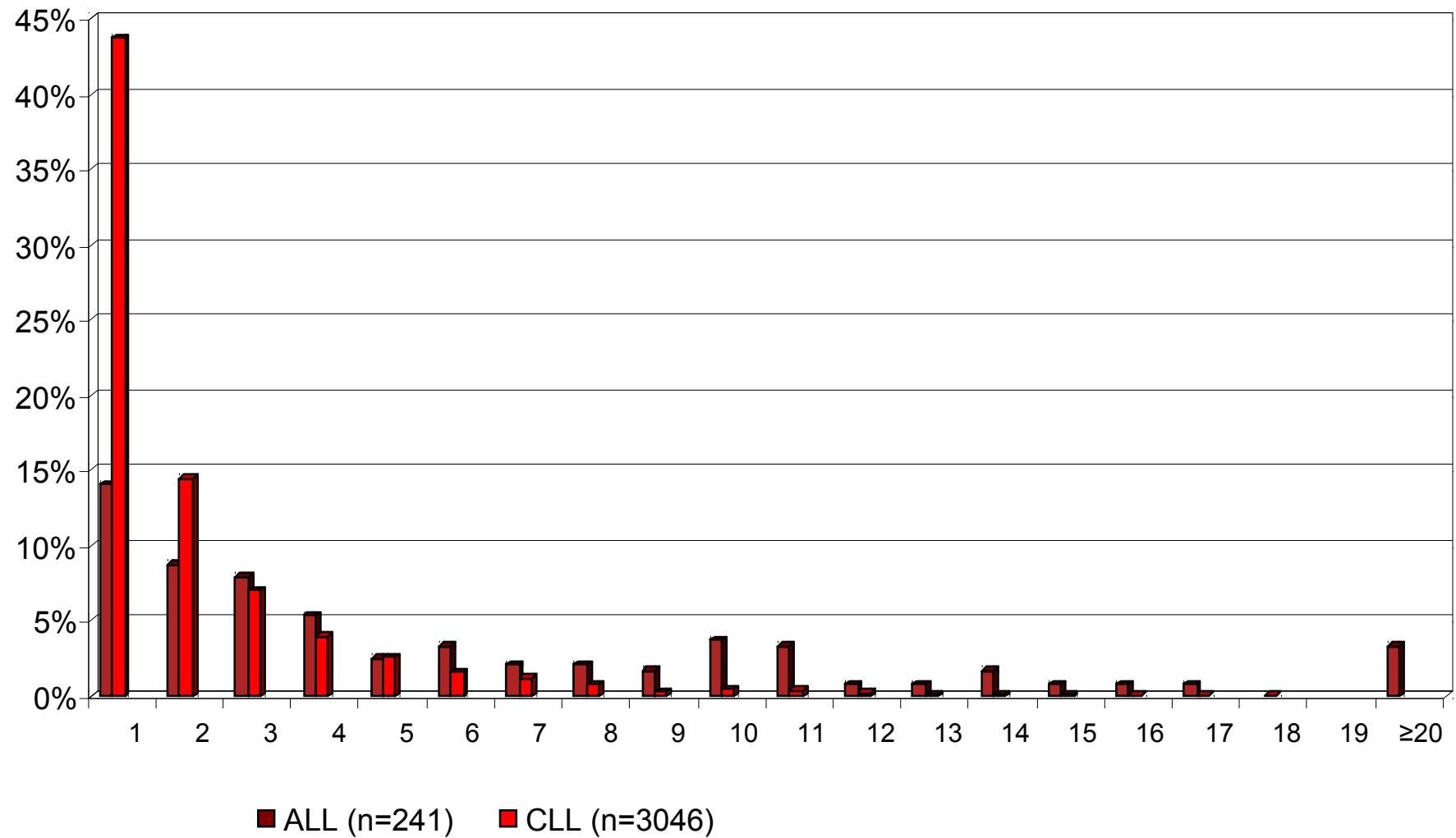
# Number of unbalanced aberrations



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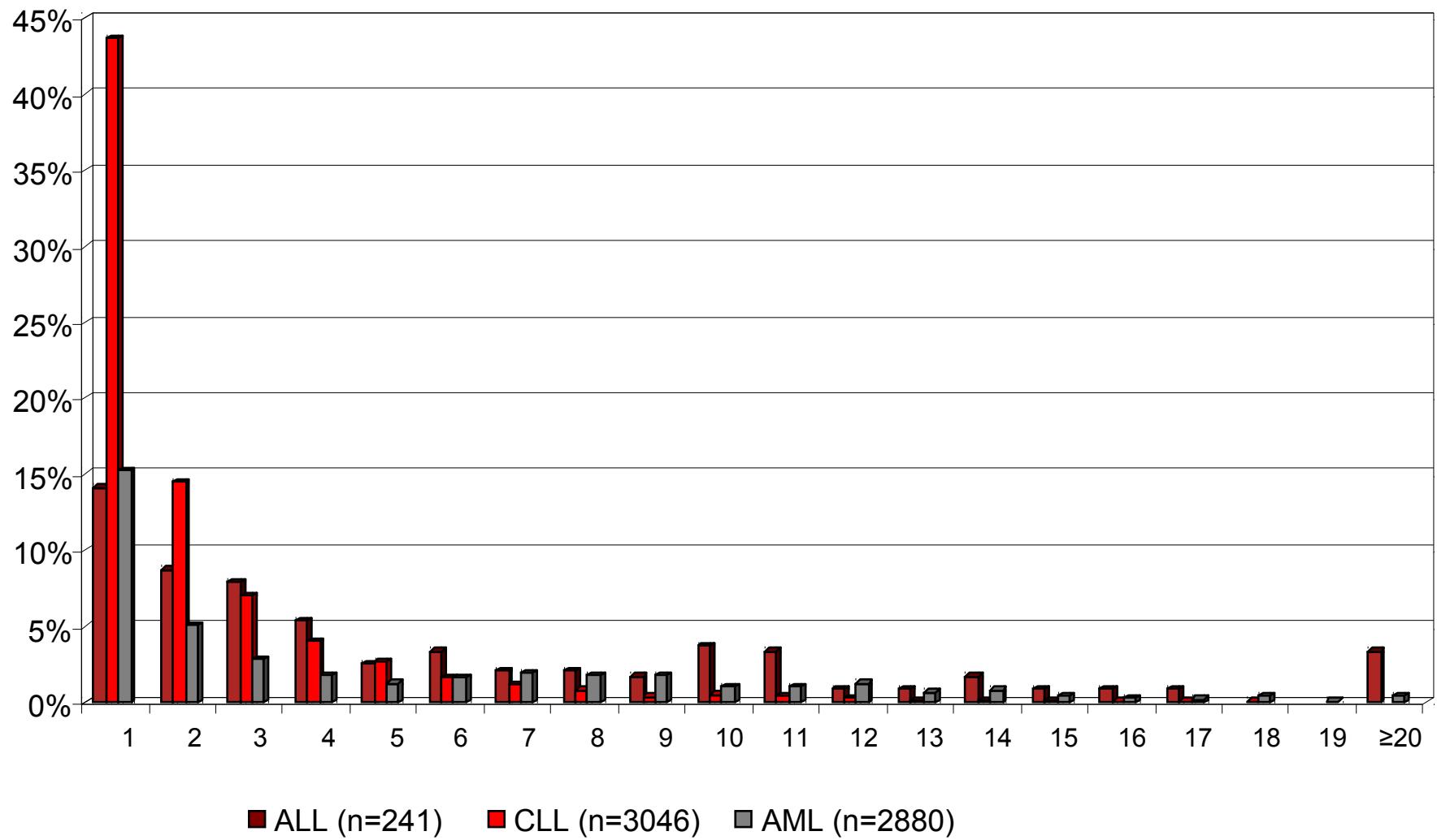


## Number of unbalanced aberrations

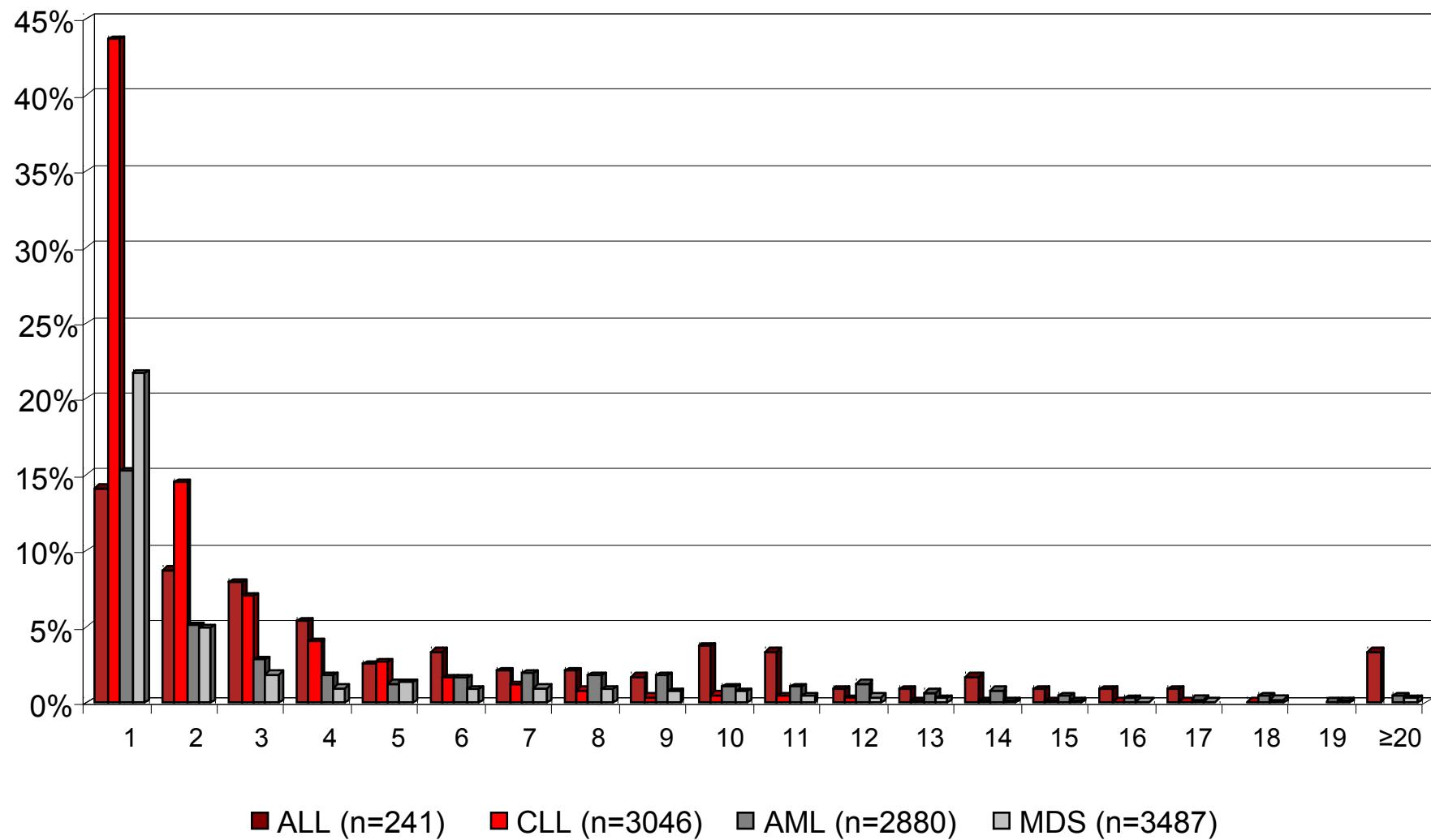


■ ALL (n=241)    ■ CLL (n=3046)

## Number of unbalanced aberrations

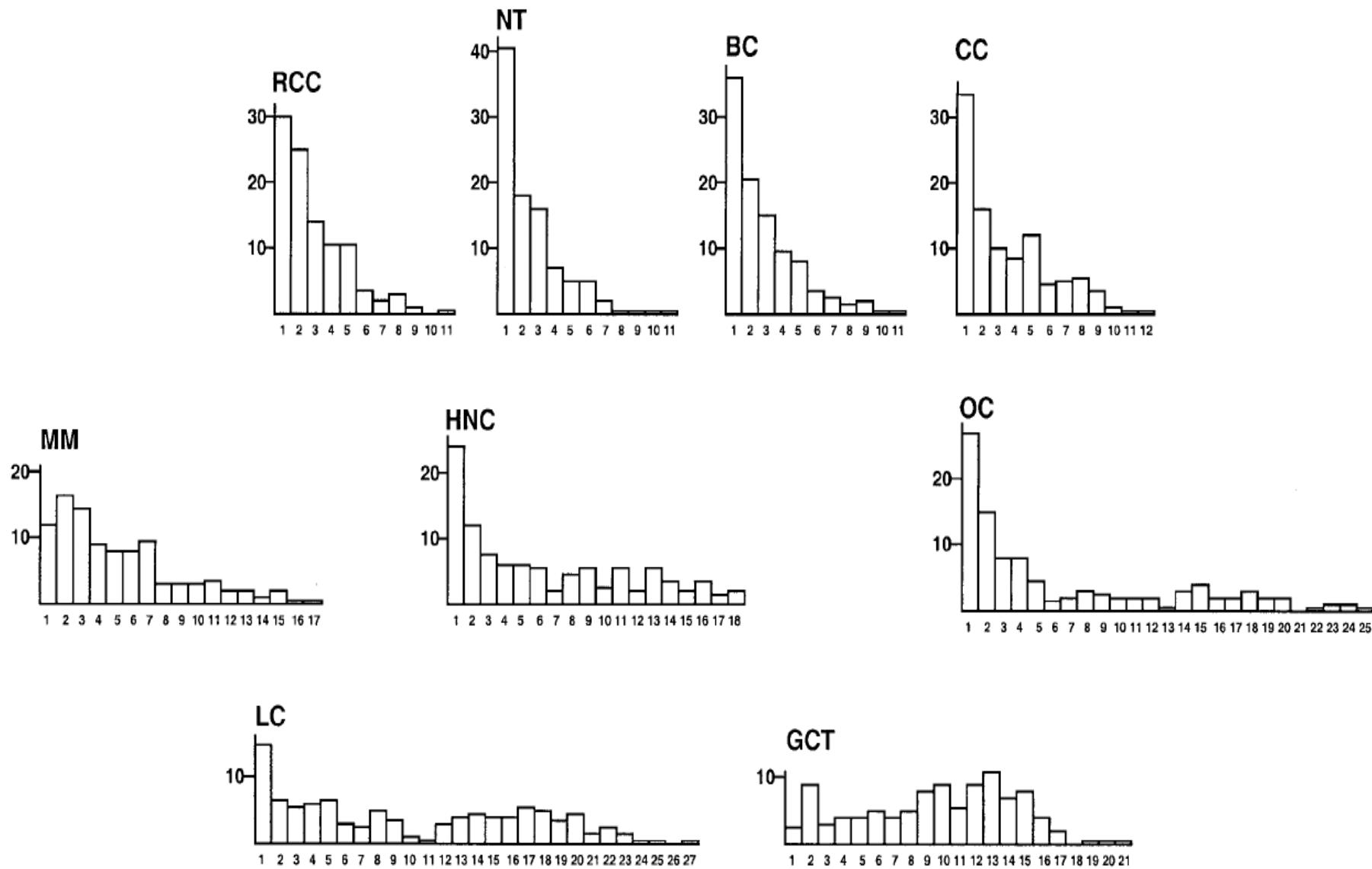


## Number of unbalanced aberrations

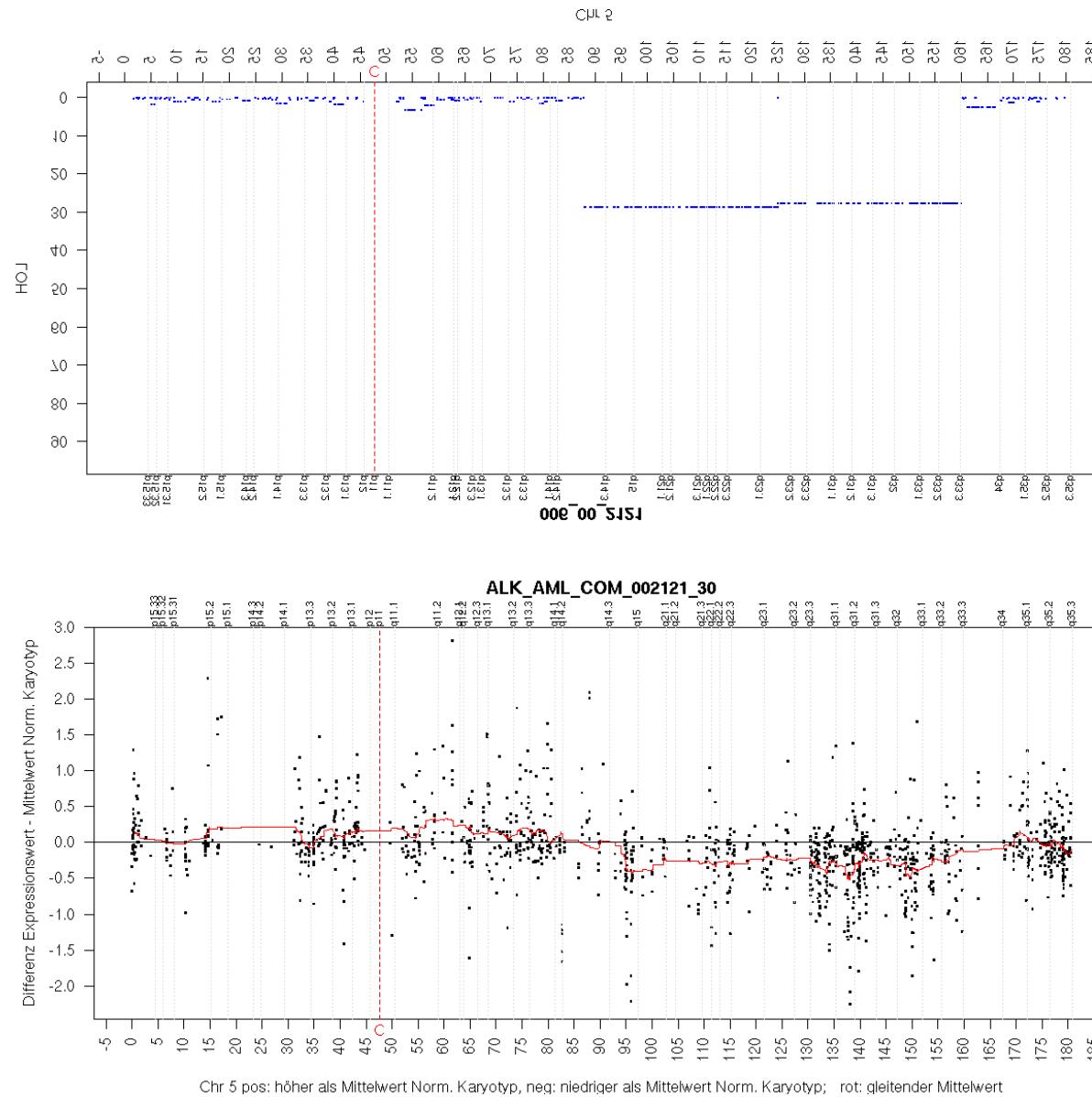


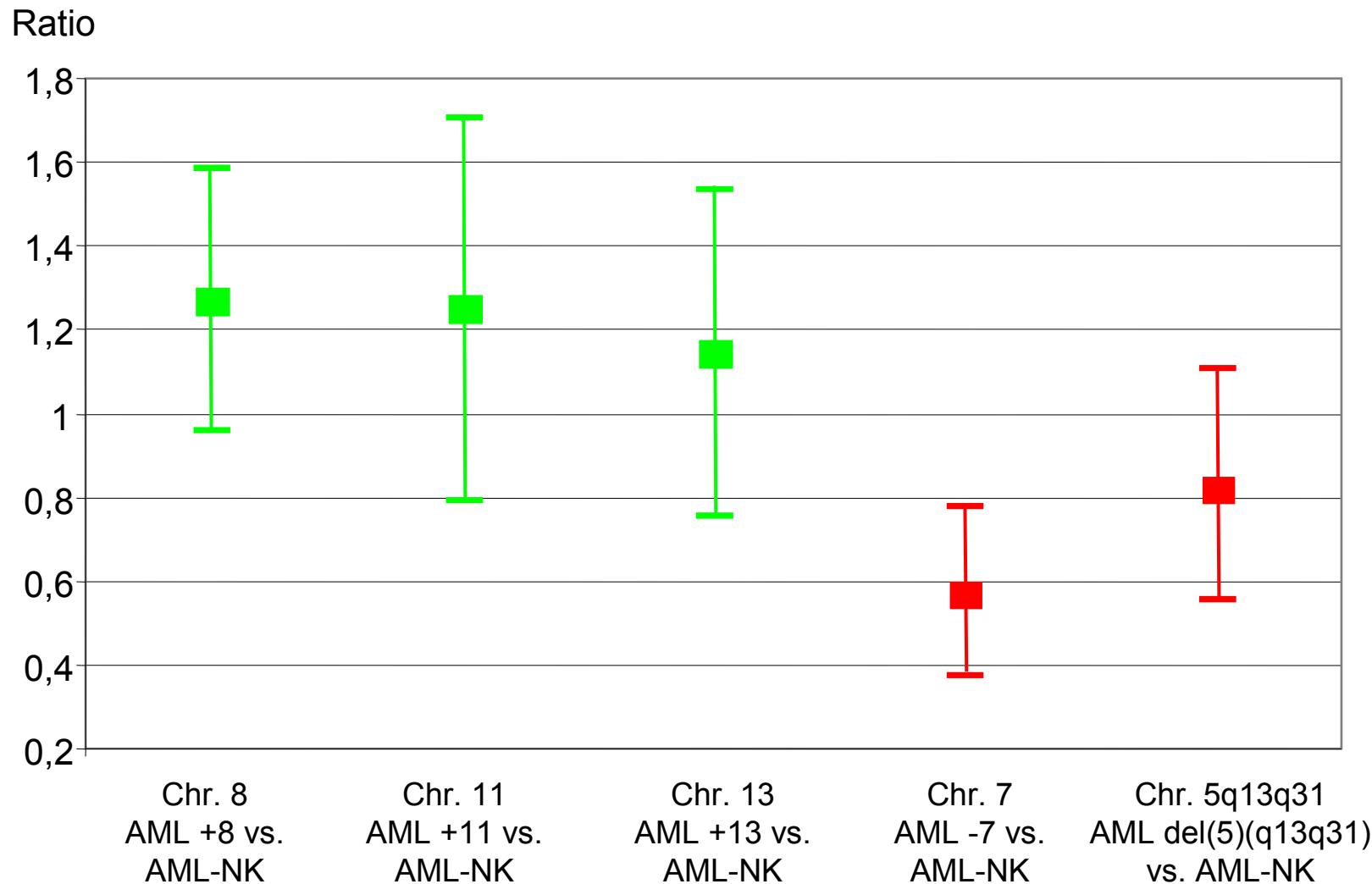
■ ALL (n=241)   ■ CLL (n=3046)   ■ AML (n=2880)   ■ MDS (n=3487)

# Number of imbalances per tumor



# LOH on chromosome 5 and corresponding gene expression in a case with 5q deletion

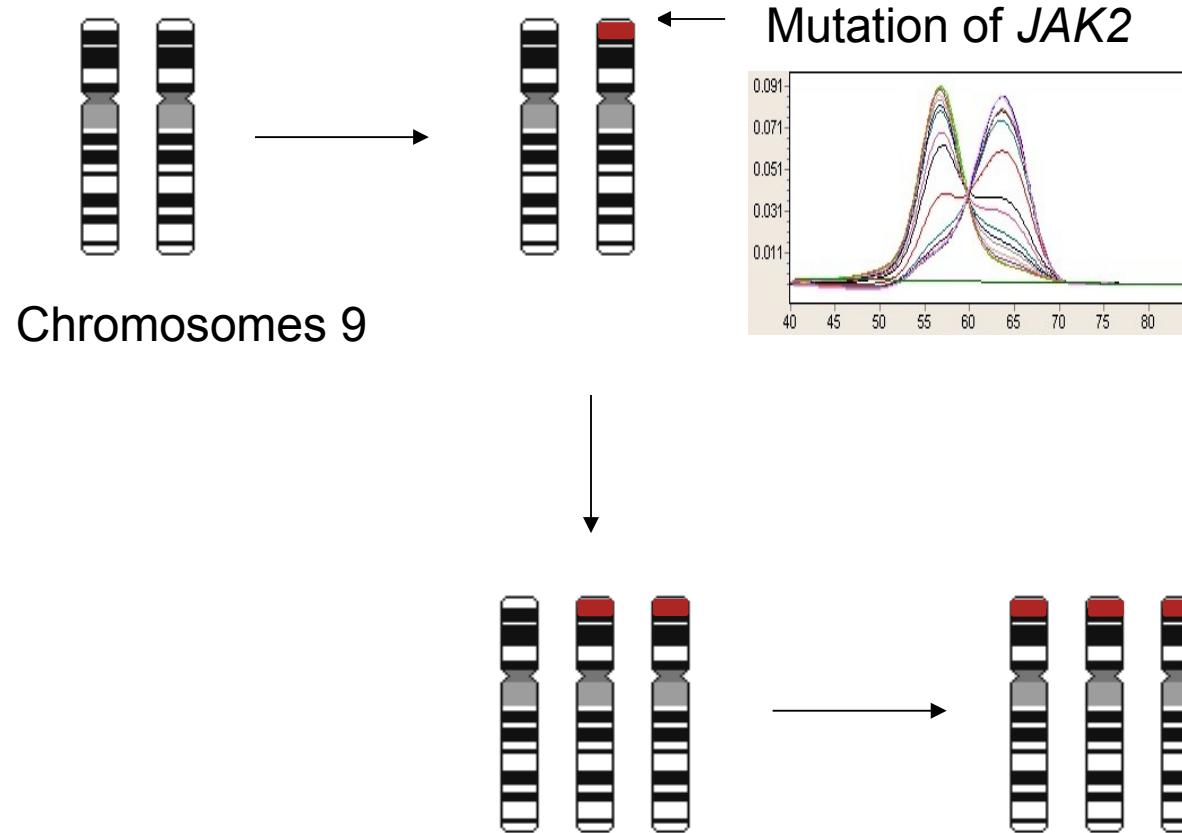






MLL

# Effect of aneuploidy in combination with molecular mutations

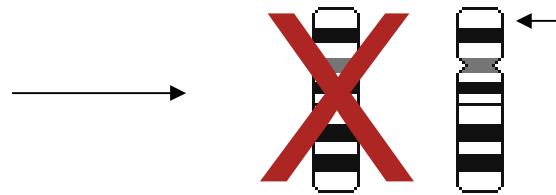




MLL

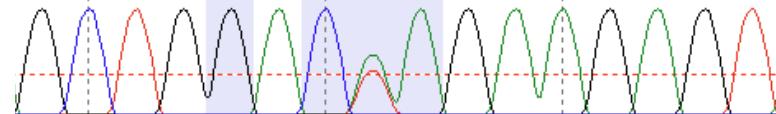
# Effect of aneuploidy in combination with molecular mutations

Chromosomes 17



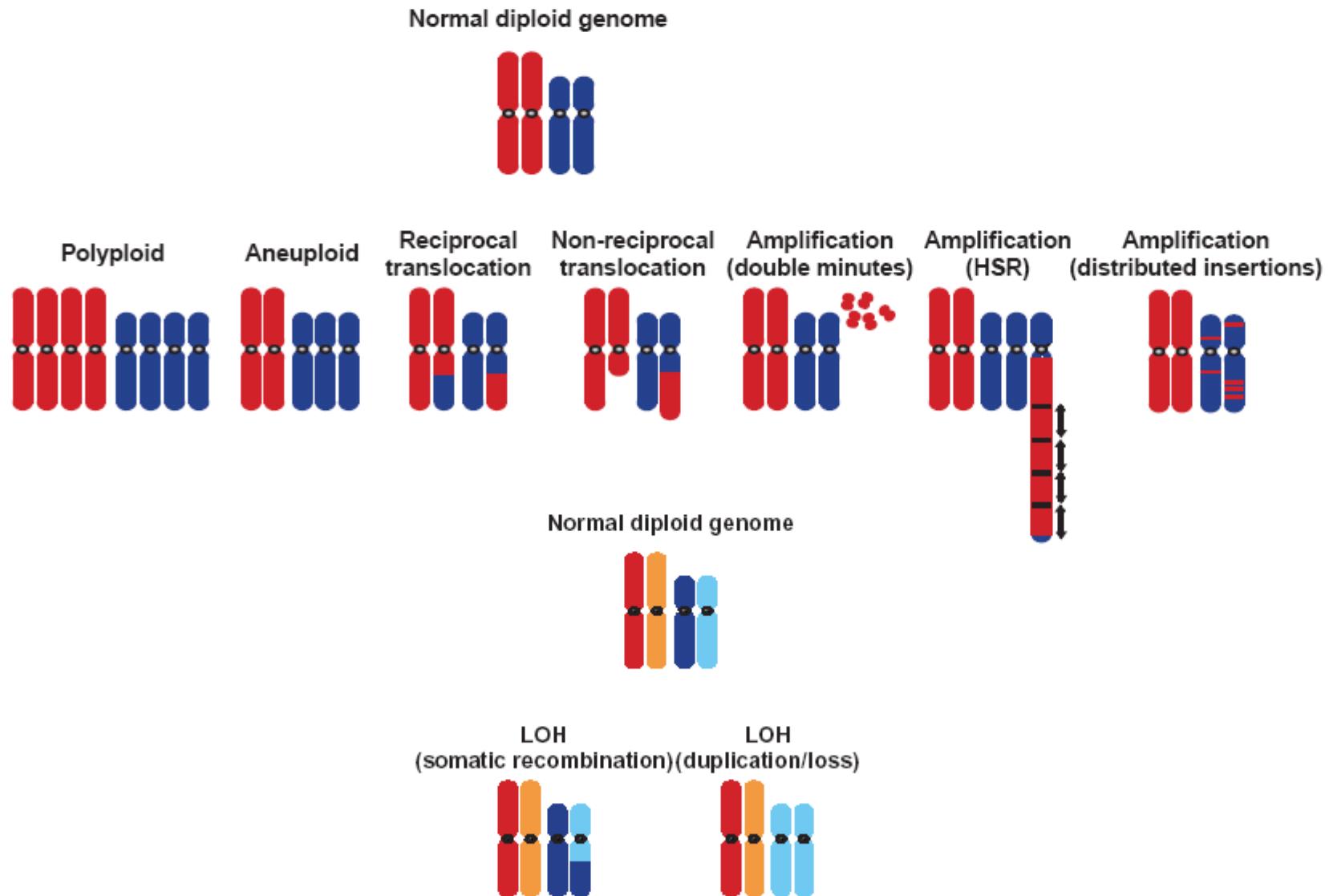
Mutation of *TP53*

A	C	T	G	G	A	Q	C	A	A	G	A	A	E	E	G	A	G	Y
A	G				L/Q					E			E	E		E		Y
G	C	T	G	G	A	C	W	A	G	A	A	G	A	G	A	G	T	
A	G			L/Q				E				E	E		E		Y	
G	C	T	G	G	A	C	W	A	G	A	A	G	A	G	A	G	T	



Complete loss of *TP53* function

# Different types of chromosome aberrations



# Chromosome aberrations

## Aneuploidy/numerical aberrations

Gains of whole chromosomes:  
Trisomy  
Tetrasomy

Loss of whole chromosomes:  
Monosomy



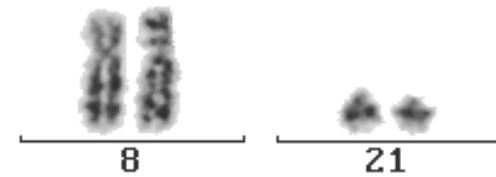
## Structural aberrations

Balanced aberrations:  
translocation  
inversion  
insertion

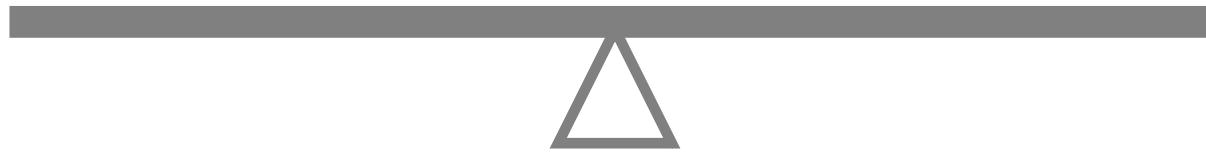
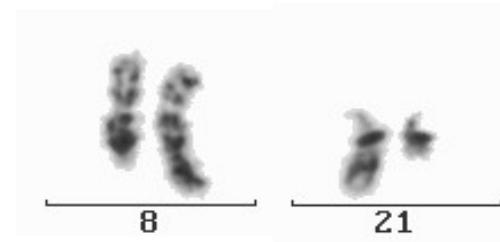
Unbalanced aberrations:  
deletion, duplication,  
ring chromosome,  
translocation

# Balanced translocation

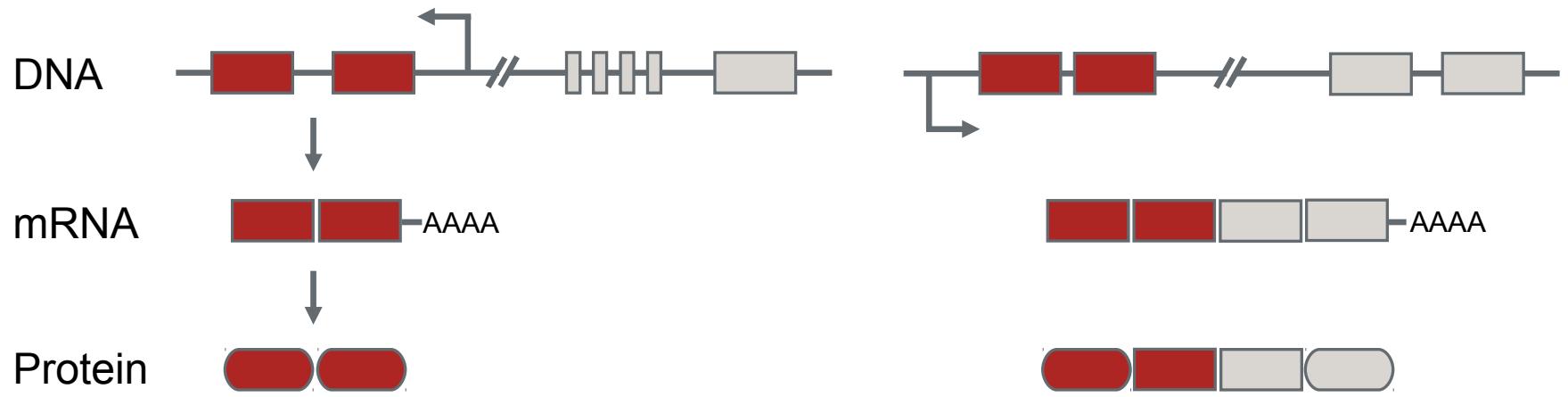
46,XX



46,XX,t(8;21)(q22;q22)



# Balanced rearrangements



Overexpression of a  
normal protein

t(8;14)(q24;q32) -> CMYC

inv(3)(q21q26) -> EVI1

Expression of a  
chimeric protein

t(15;17)(q22;q12) -> PML-RARA

inv(16)(p13q22) -> CBFB-MYH11

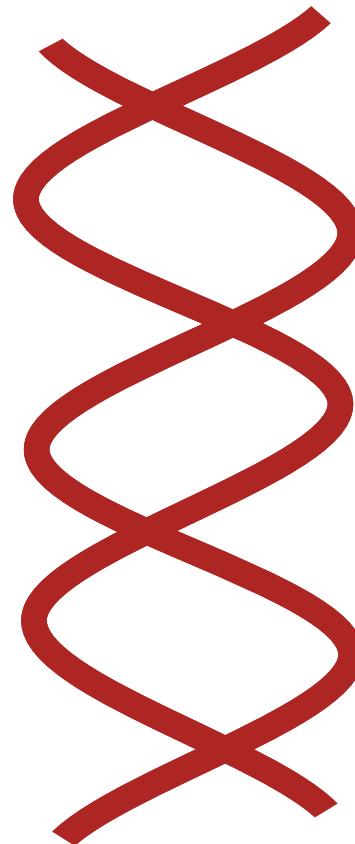
# Molecular aberrations

base exchanges:  
*JAK2, FLT3-TKD*

insertions:  
*FLT3-ITD, NPM1*

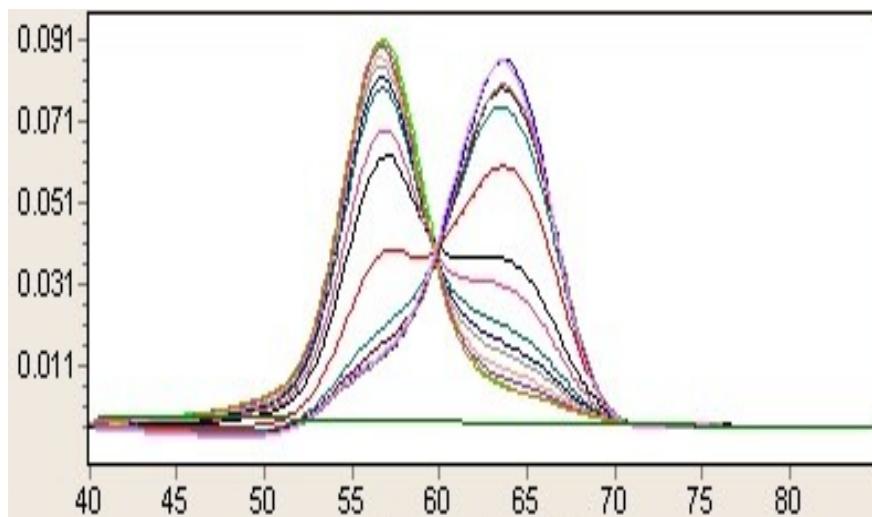
deletions:  
*IKZF1*

duplications:  
*MLL-PTD*

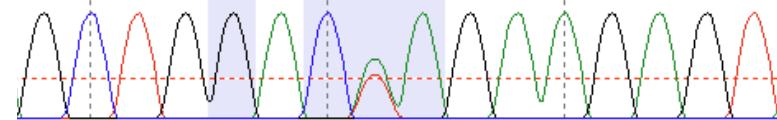


# Molecular aberrations

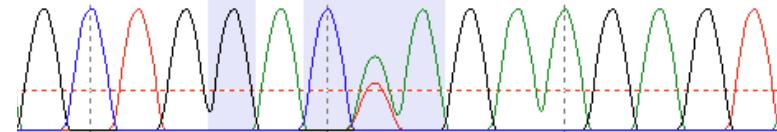
base exchanges: *JAK2*, *NRAS*, *FLT3-TKD*



A	G	C	T	G	G	A	Q	A	A	G	A	A	E	E	G	A	G	Y
A							L/Q			E			E		E			
G		C	T	G	G	A	C	W	A	G	A	A	G	A	G	T		
A							L/Q			E			E		E			
G	C	T	G	G	A	C	W	A	G	A	A	G	A	G	T			

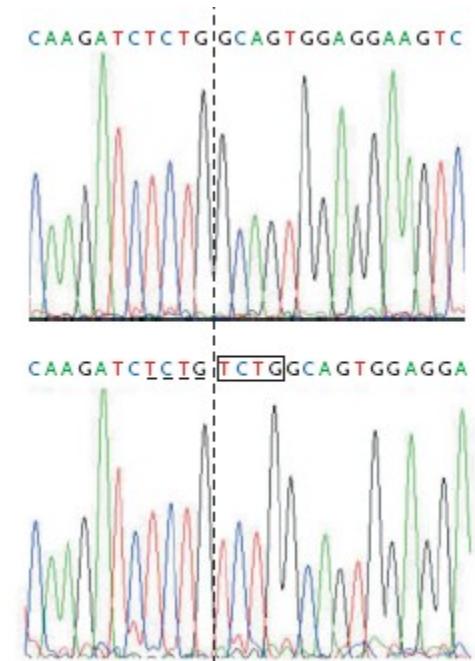
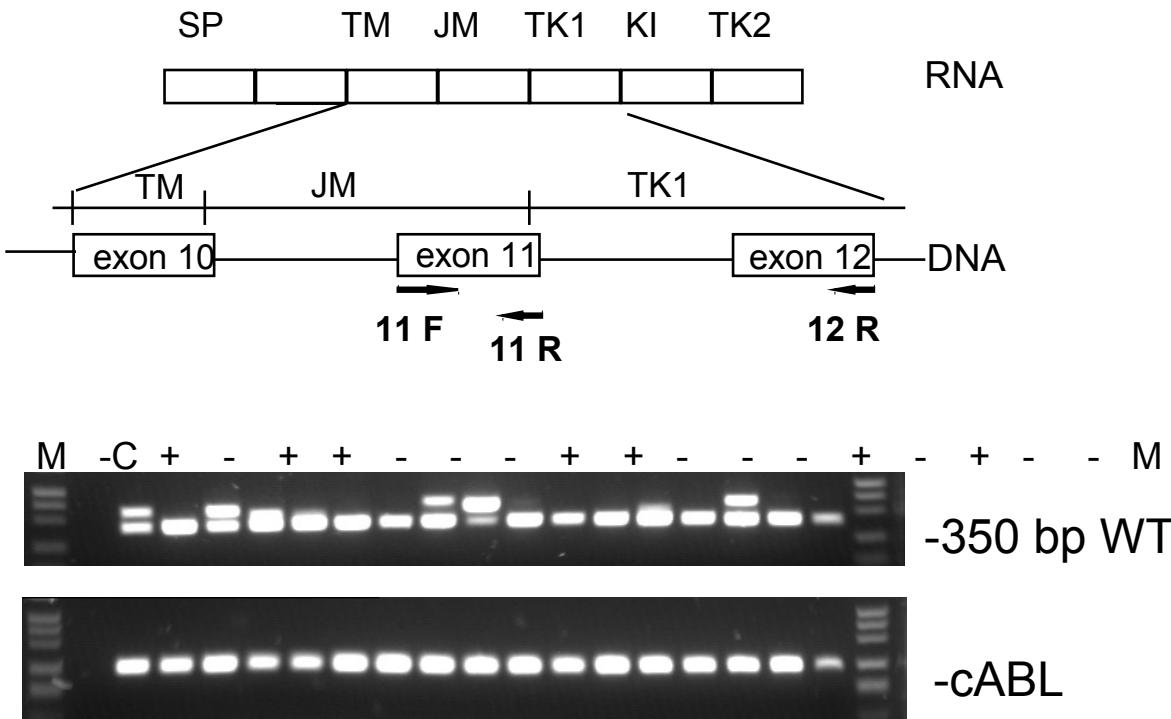


A	G	C	T	G	G	G	A	L/Q	W	A	G	A	A	E	E	G	A	Y
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# Molecular aberrations

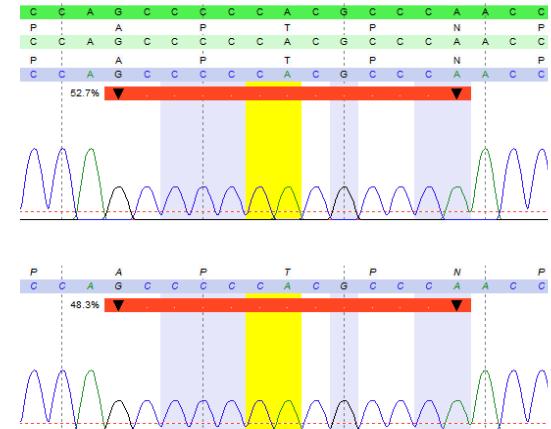
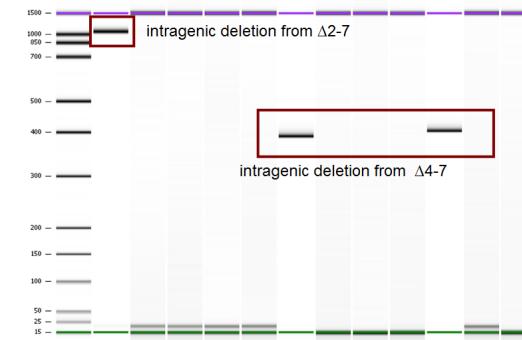
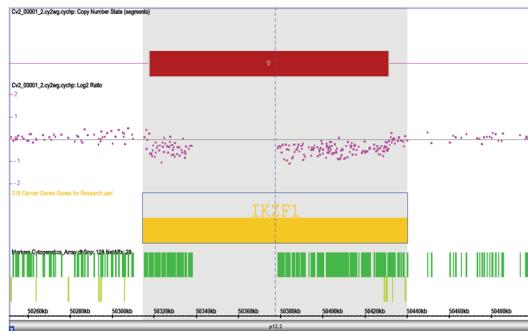
insertions: *FLT3-ITD*, *NPM1*



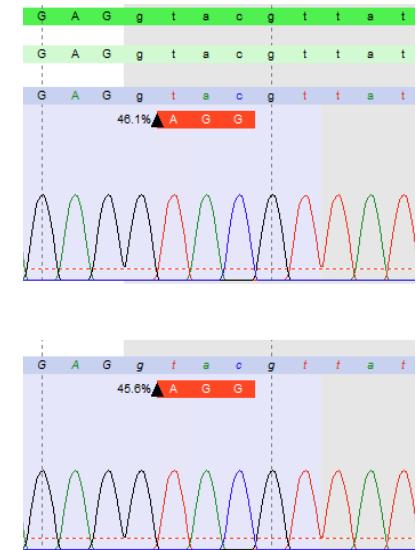
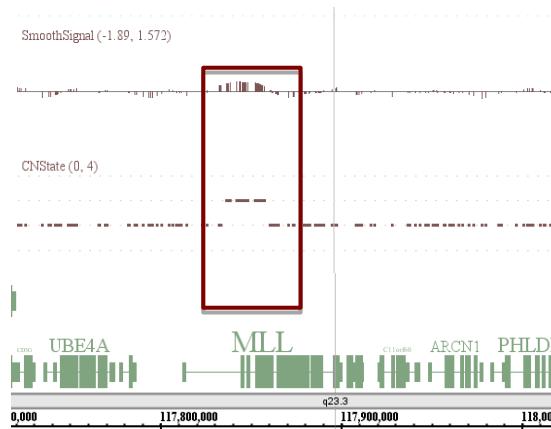
GATCTCTG...GCAGT...GGAGGAAGTCTCTTAAGAAAATAG	-DLWWRKSL
GATCTCTG <b>TCTGG</b> CAGT...GGAGGAAGTCTCTTAAGAAAATAG	-DLCLAVEEV <b>SLRK</b>
GATCTCTG <b>CATGG</b> CAGT...GGAGGAAGTCTCTTAAGAAAATAG	-DLCMAVEEV <b>SLRK</b>
GATCTCTG <b>CGTGG</b> CAGT...GGAGGAAGTCTCTTAAGAAAATAG	-DLCVAEEV <b>SLRK</b>

# Molecular aberrations

deletions: *IKZF1*, *RUNX1*



duplications: *MLL-PTD*, *RUNX1*





## Chromosome aberrations

Balanced rearrangements:

t(9;22)(q34;q11)

t(3;21)(q26;q22)

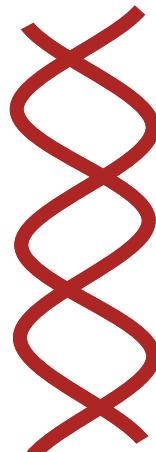
inv(3)(q21q26)

unbalanced aberrations:

+8

+der(22)t(9;22)

i(17)(q10)



## Molecular aberrations

base exchanges:

*KRAS*, *NRAS*

insertions:

*TET2*

deletions:

*IKZF1*

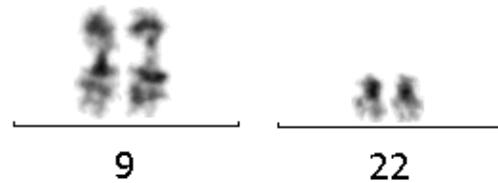
duplications:

*WT1*



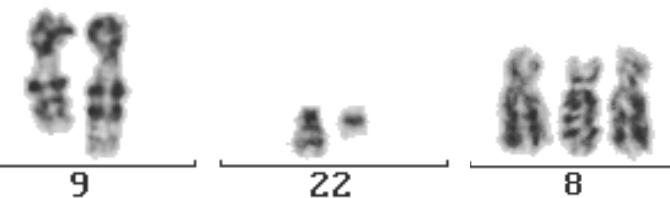
# MLL Progression to BC in CML on the cytogenetic level

46,XX



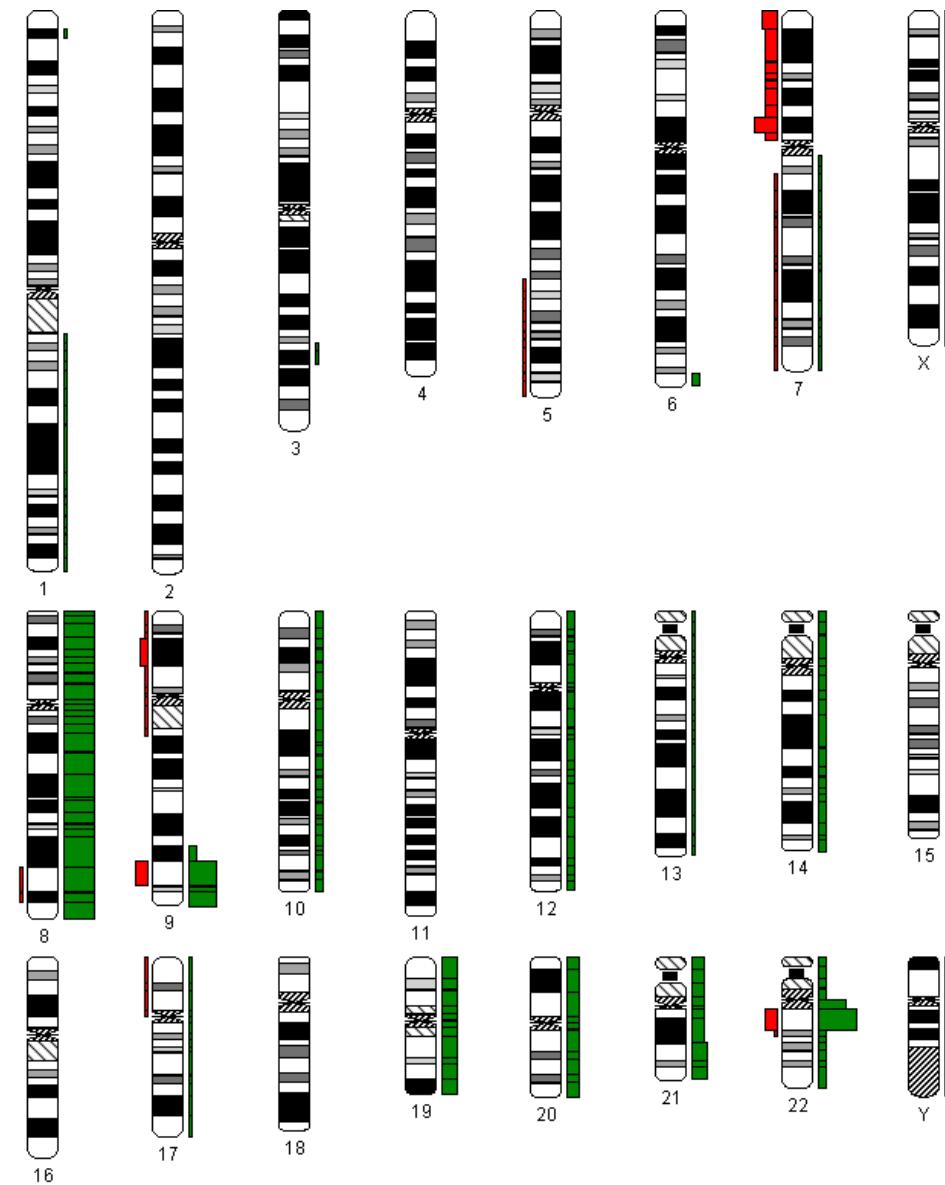
46,XX,t(9;22)(q34;q11)

47,XY,+8,t(9;22)(q34;q11)





# MLL Progression to BC in CML on the cytogenetic level

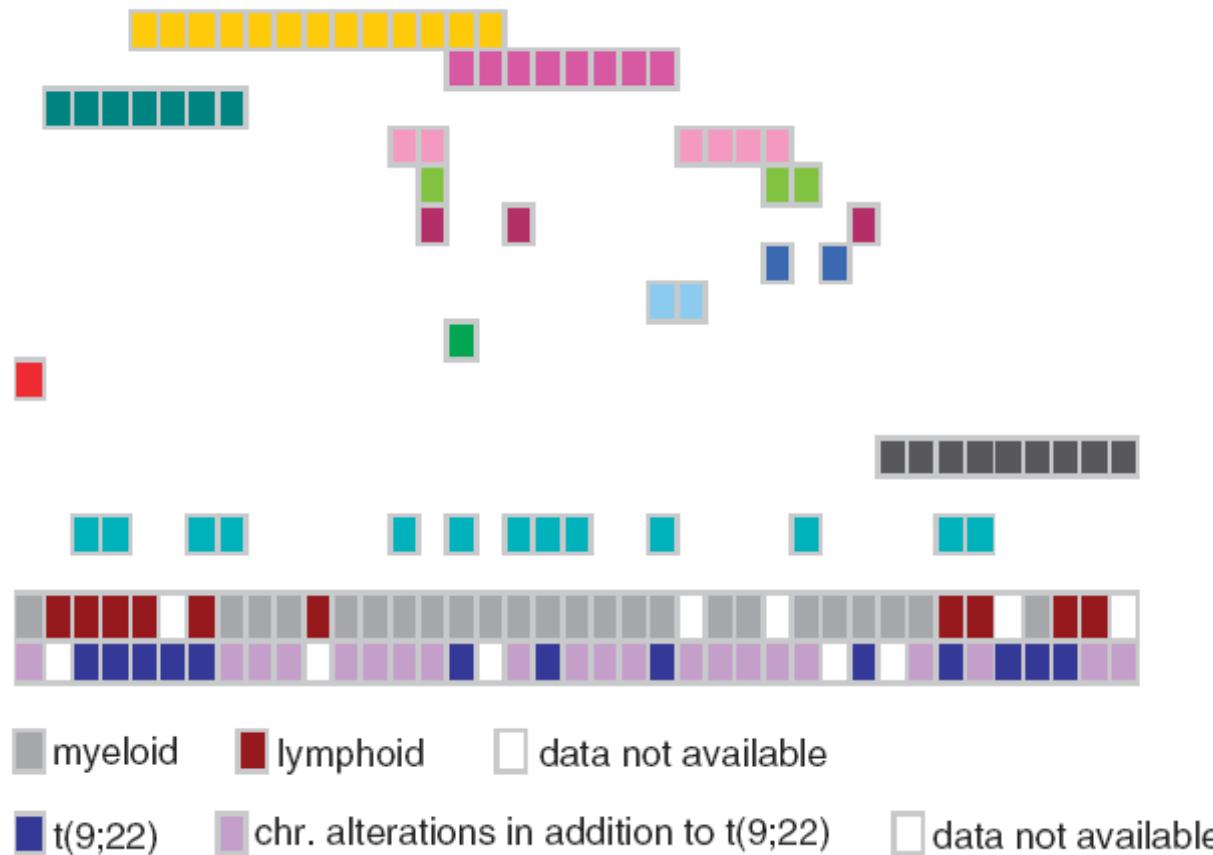




MLL

## Progression to BC in CML on the molecular level

<i>RUNX1</i>	[33.3%, 13/39]
<i>ASXL1</i>	[20.5%, 8/39]
<i>IKZF1</i>	[17.9%, 7/39]
<i>WT1</i>	[15.4%, 6/39]
<i>TET2</i>	[7.7%, 3/39]
<i>IDH1</i>	[7.7%, 3/39]
<i>NRAS</i>	[5.1%, 2/39]
<i>KRAS</i>	[5.1%, 2/39]
<i>CBL</i>	[2.6%, 1/39]
<i>TP53</i>	[2.6%, 1/39]



# Summary

- Aneuploidy is a frequent phenomenon in leukemia
- Different mechanisms lead to aneuploidy
- Aneuploidy contributes to malignancy by
  - deregulation of gene expression
  - loss of tumor suppressor genes
  - copy number increase of oncogenes