Constitutional and somatic rearrangement of chromosome 21 in acute lymphoblastic leukaemia (ALL)

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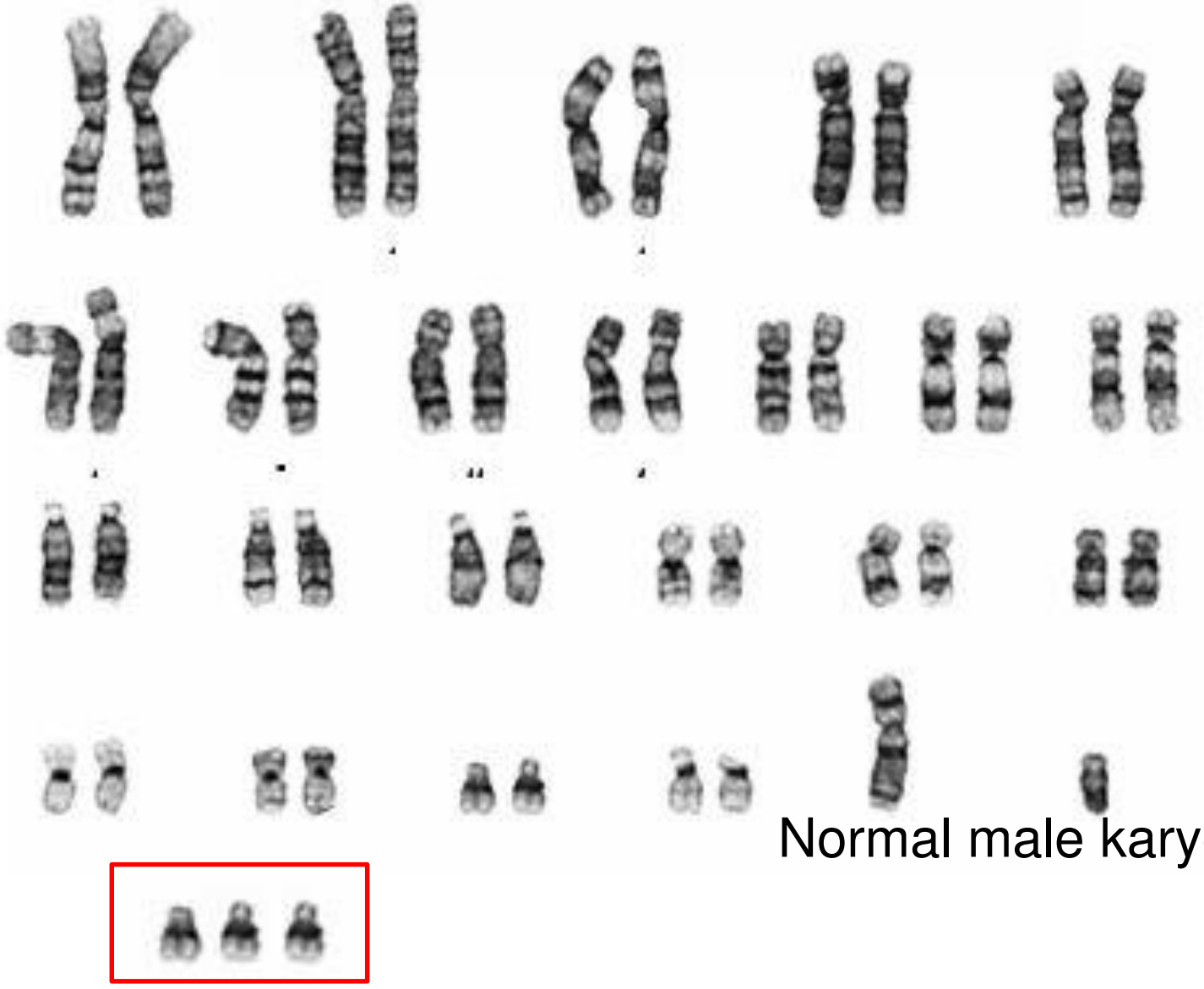
Chromosome 21



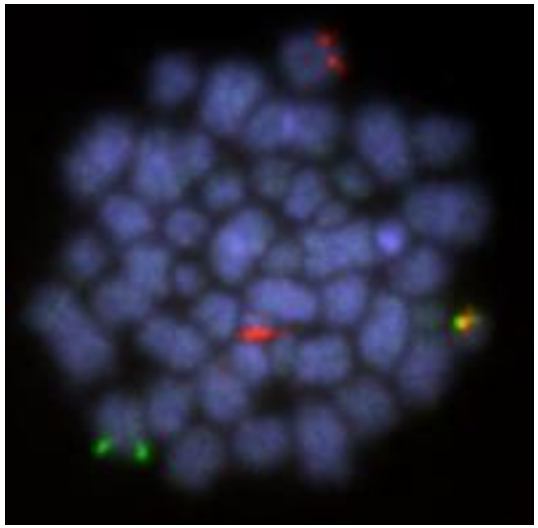
Normal male karyotype

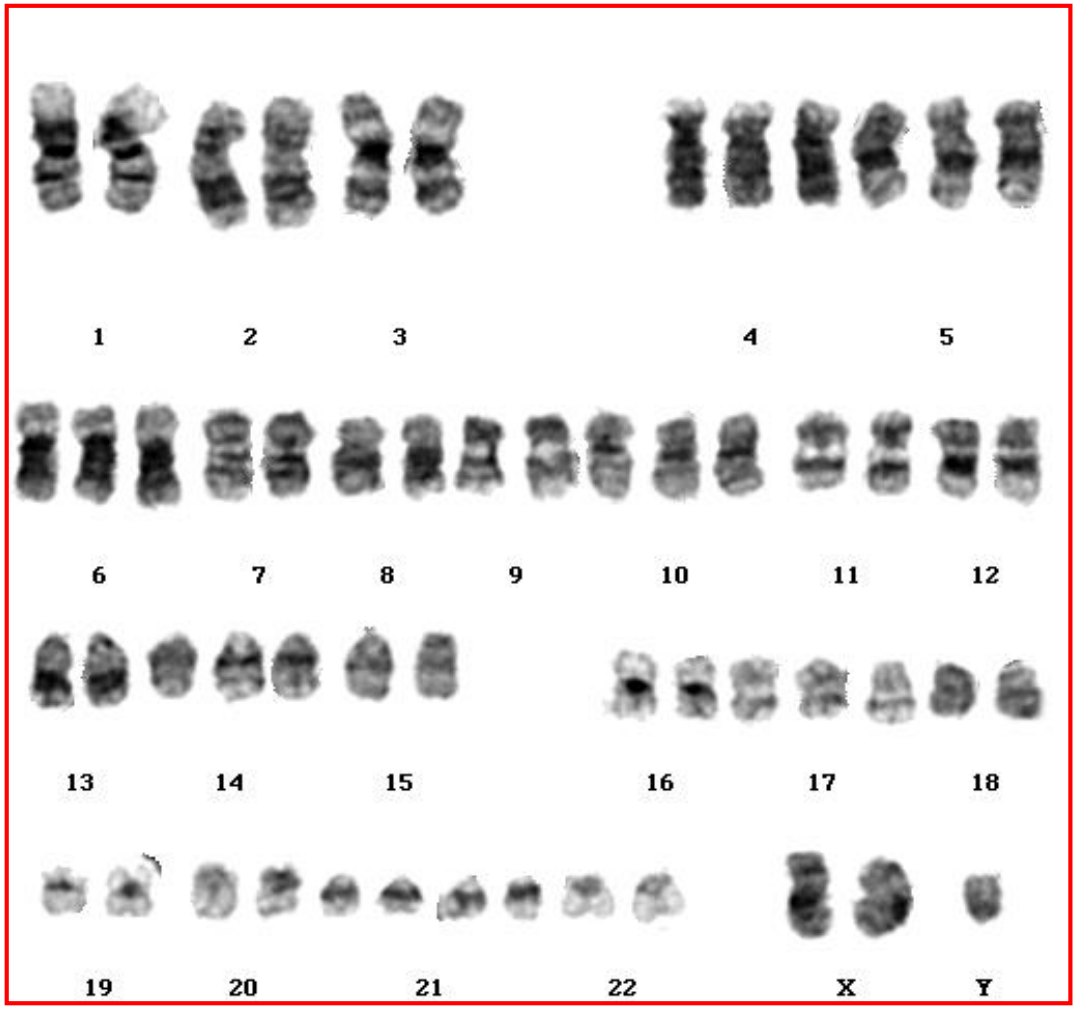
Constitutional gain of chromosome 21 in Down syndrome

Chromosome 21 in good risk ALL

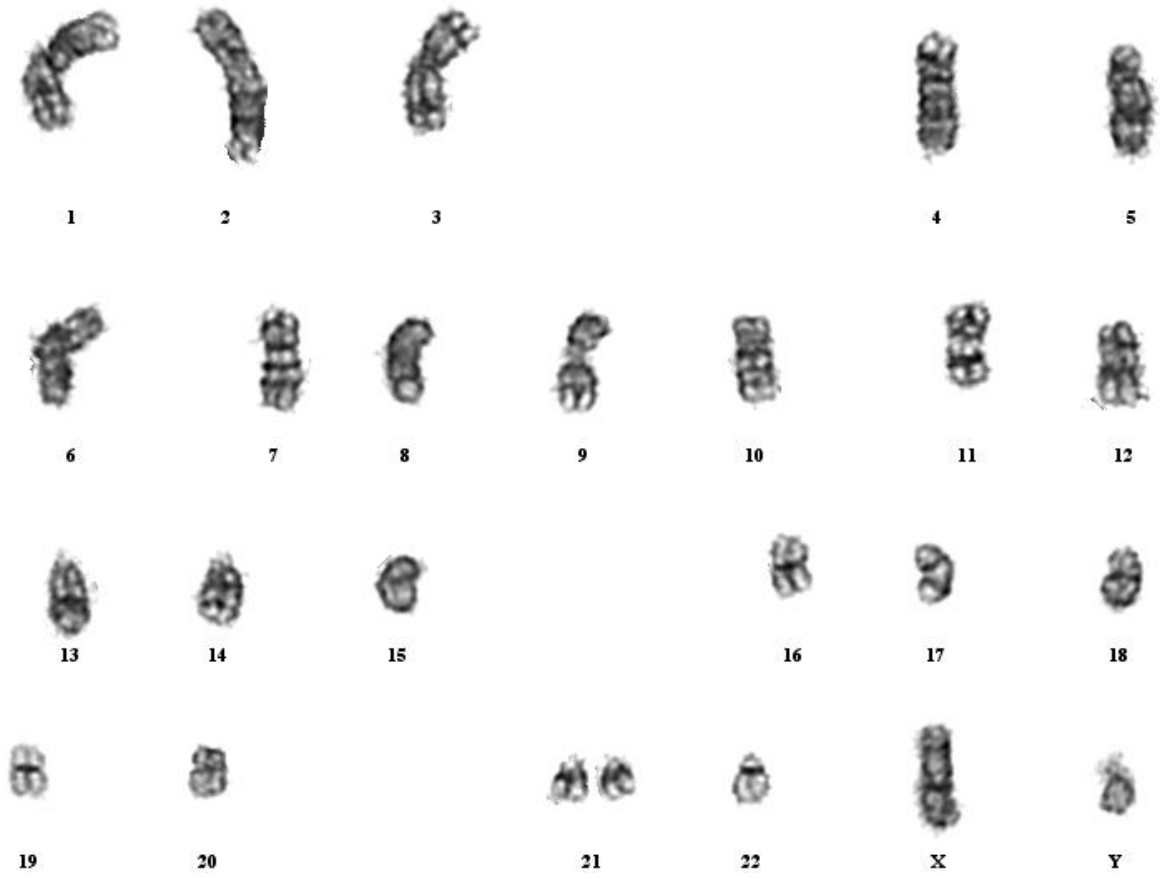
High hyperdiploidy
(51-65 chromosomes)

ETV6-RUNX1





Chromosome 21 in poor risk ALL

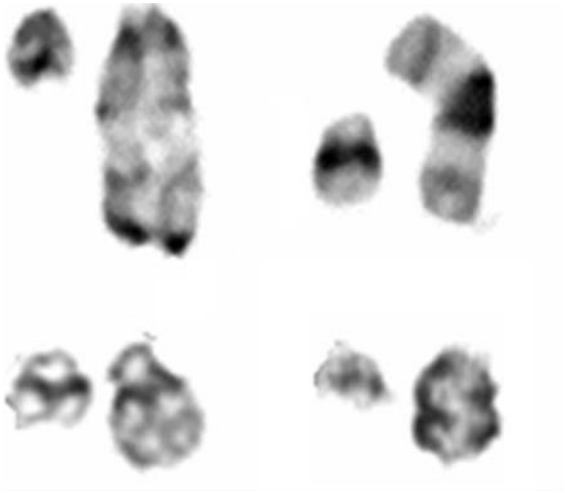


Near haploidy (23-29 chromosomes)

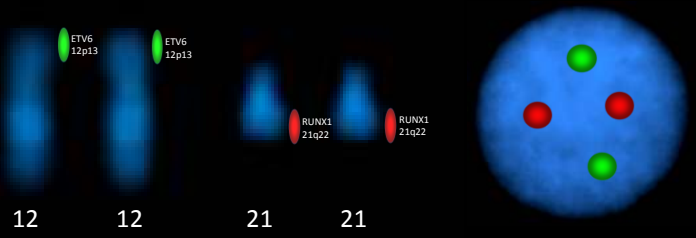
Poor risk cytogenetic abnormality

Intrachromosomal amplification of chromosome 21

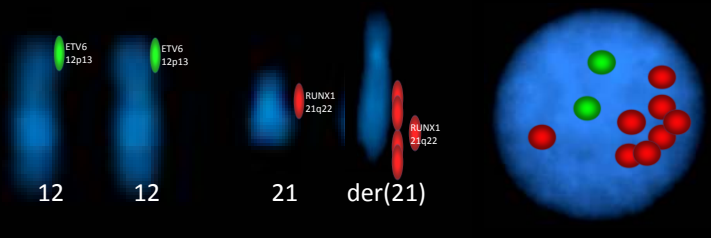
iAMP21



Intrachromosomal amplification of chromosome 21
iAMP21



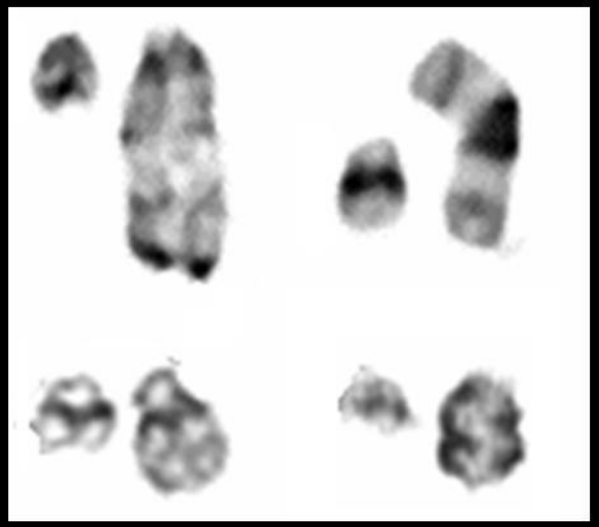
ETV6-RUNX1 extra signal

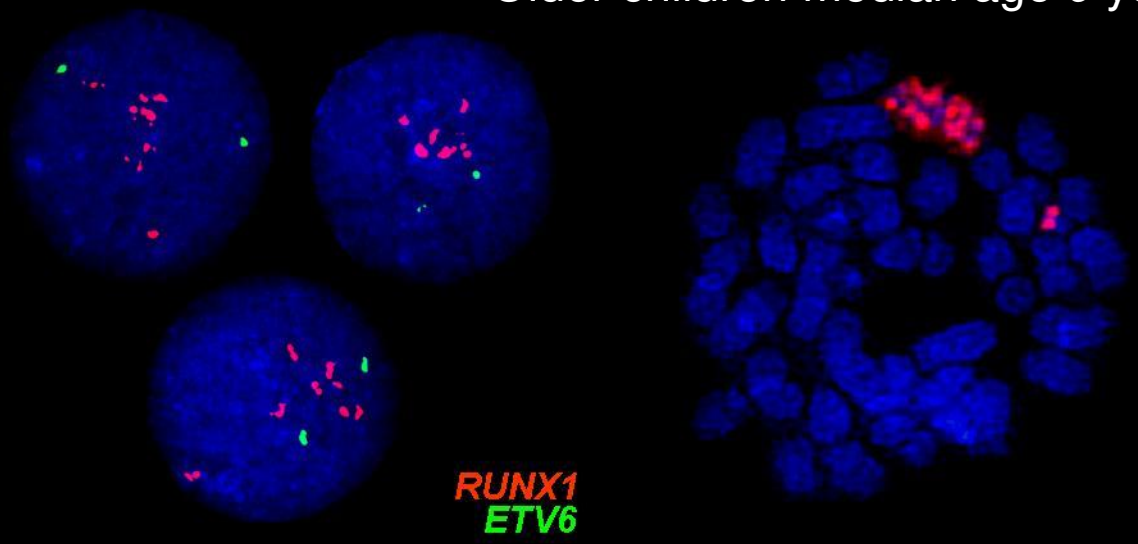


Normal signal pattern

Abnormal signal pattern

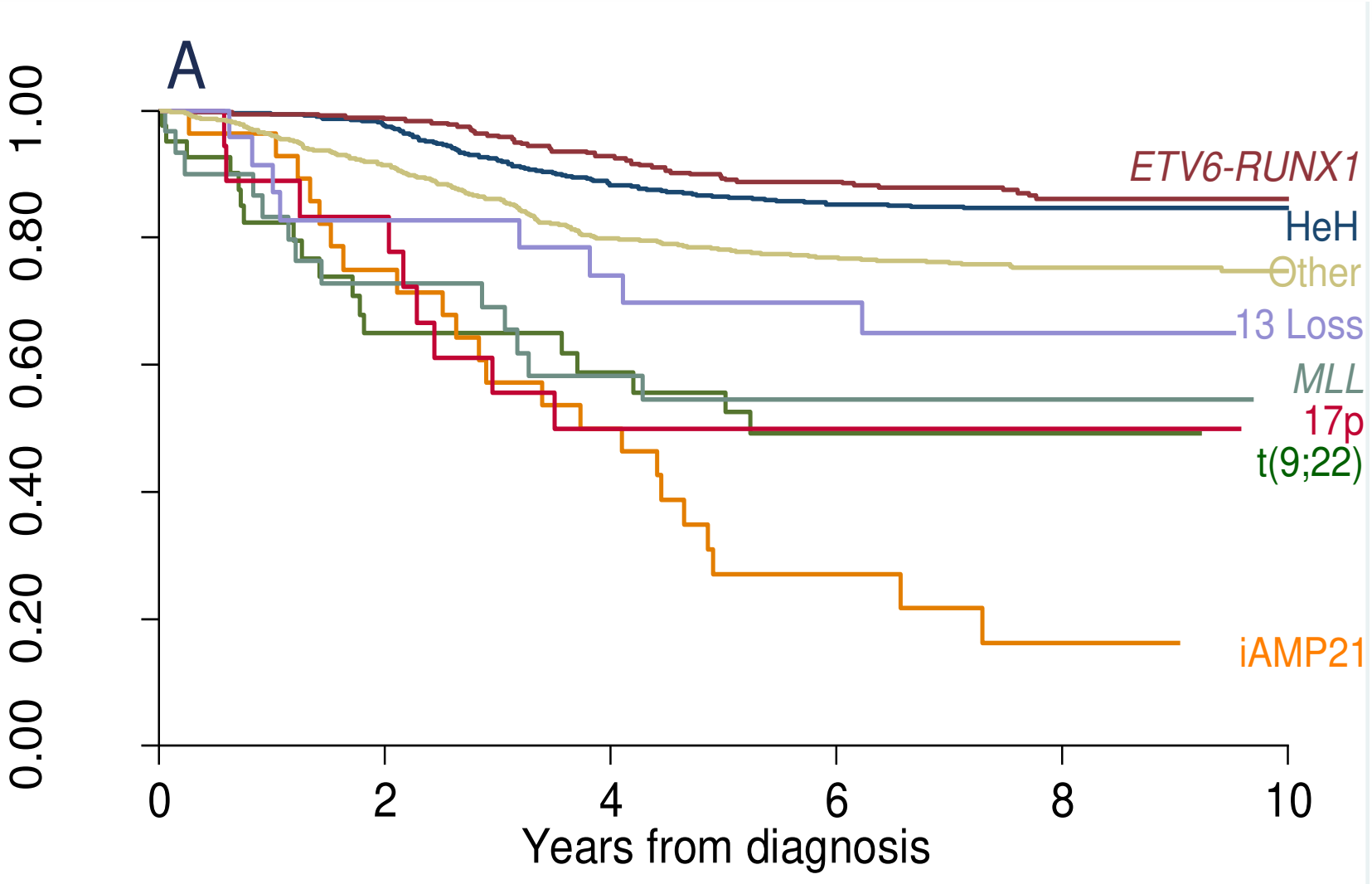
Incidence ~2%
Older children median age 9 years





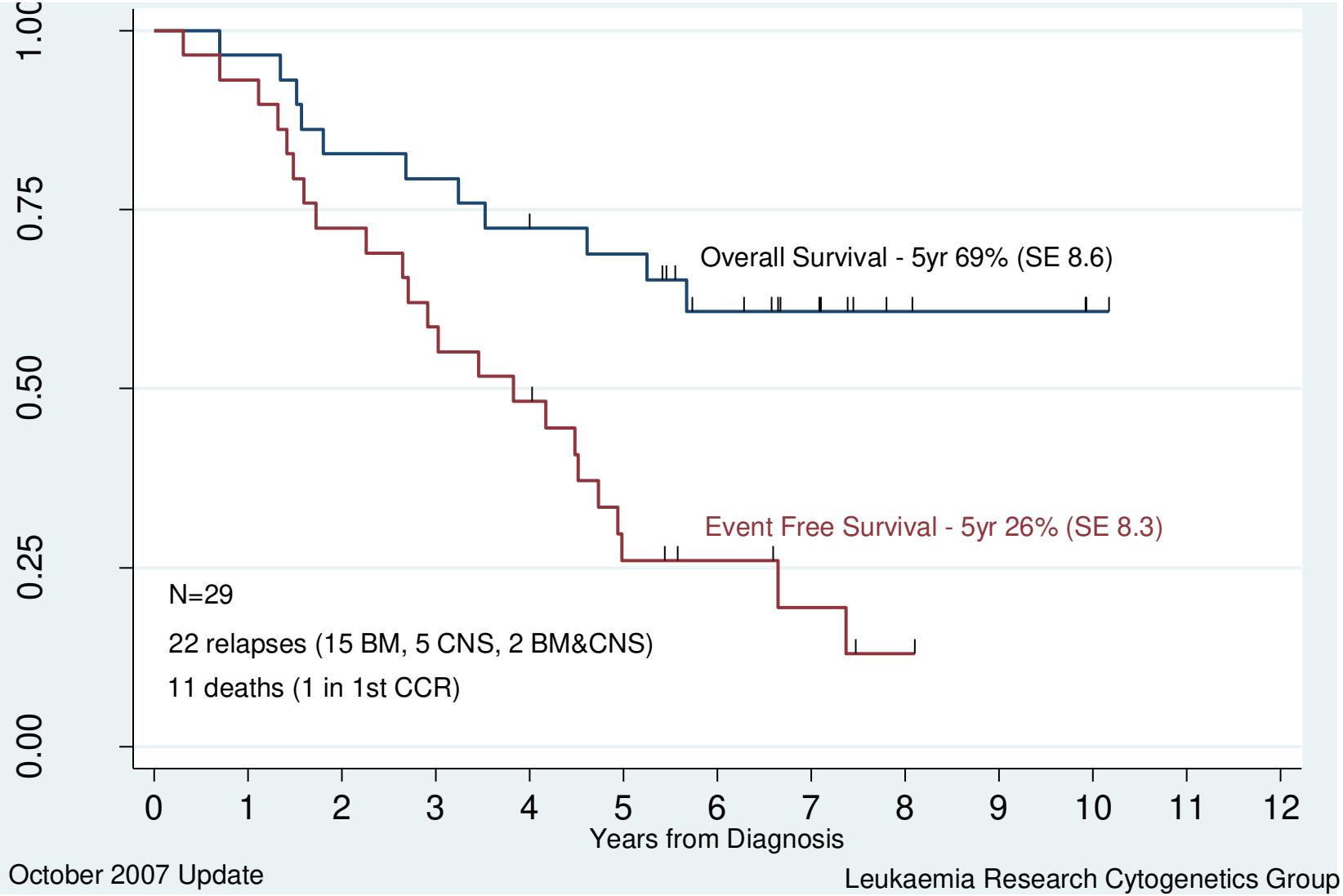
Harewood *et al* 2003 Leukemia 17: 547-53; Soulier *et al* 2003 Leukemia 17: 1679-82
Robinson *et al* 2003 Leukemia 17: 2249-50; Robinson *et al* 2007 Genes Chromos Cancer 46: 318-26

ALL97: Risk of relapse by cytogenetics

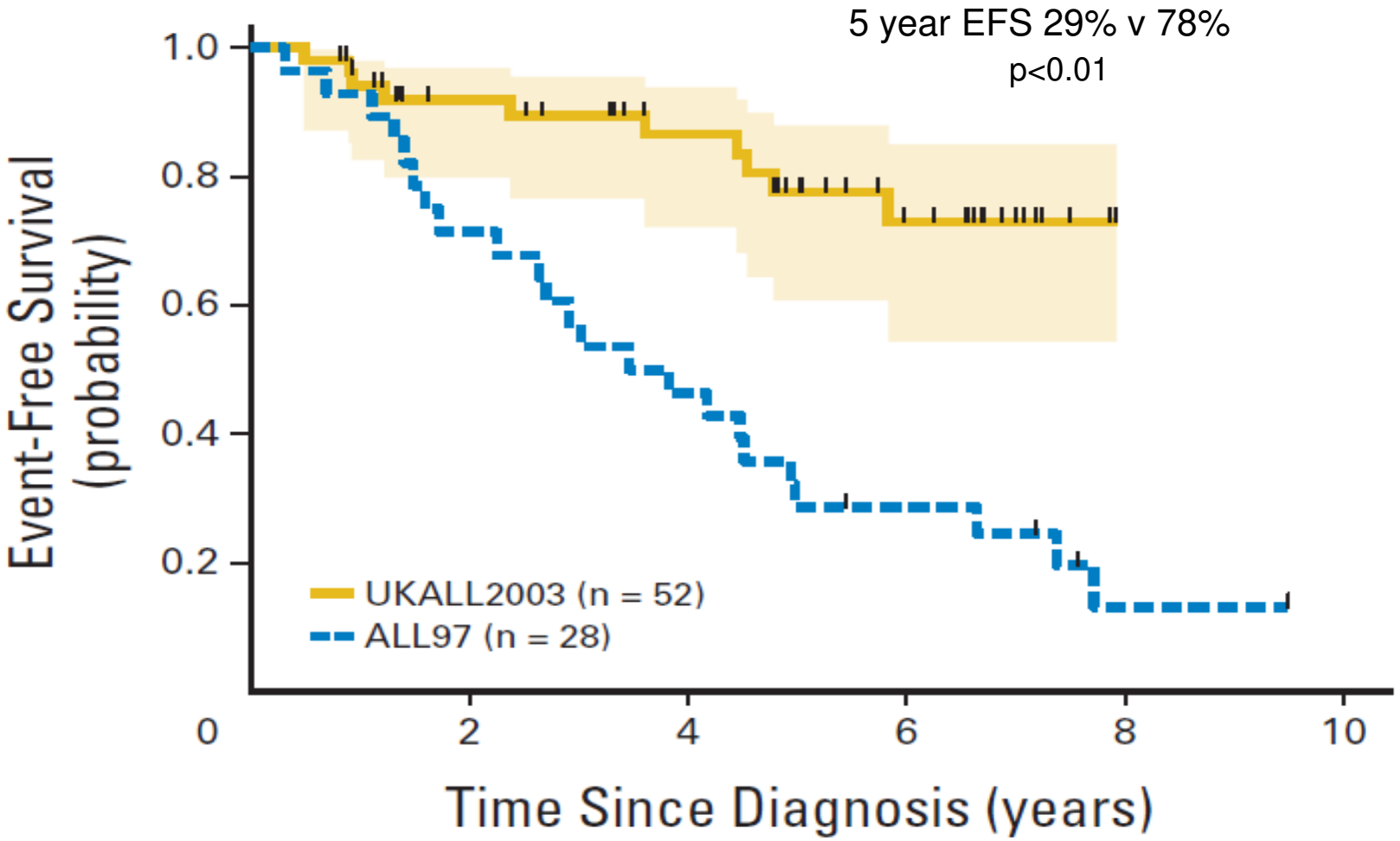


Moorman *et al*, 2010 Lancet Oncology

Outcome of iAMP21 patients on ALL97

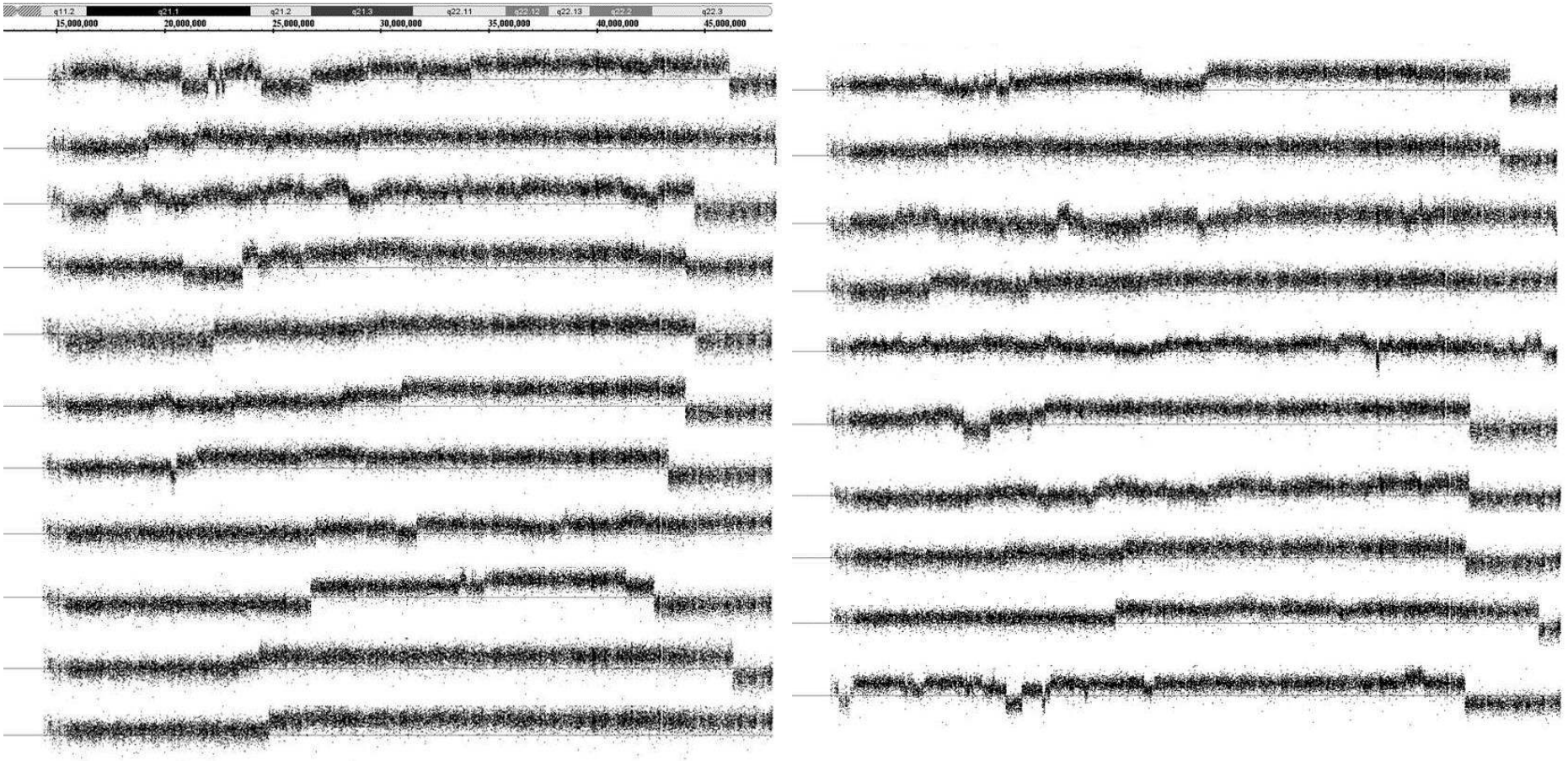


Intensive therapy improves outcome of iAMP21 patients

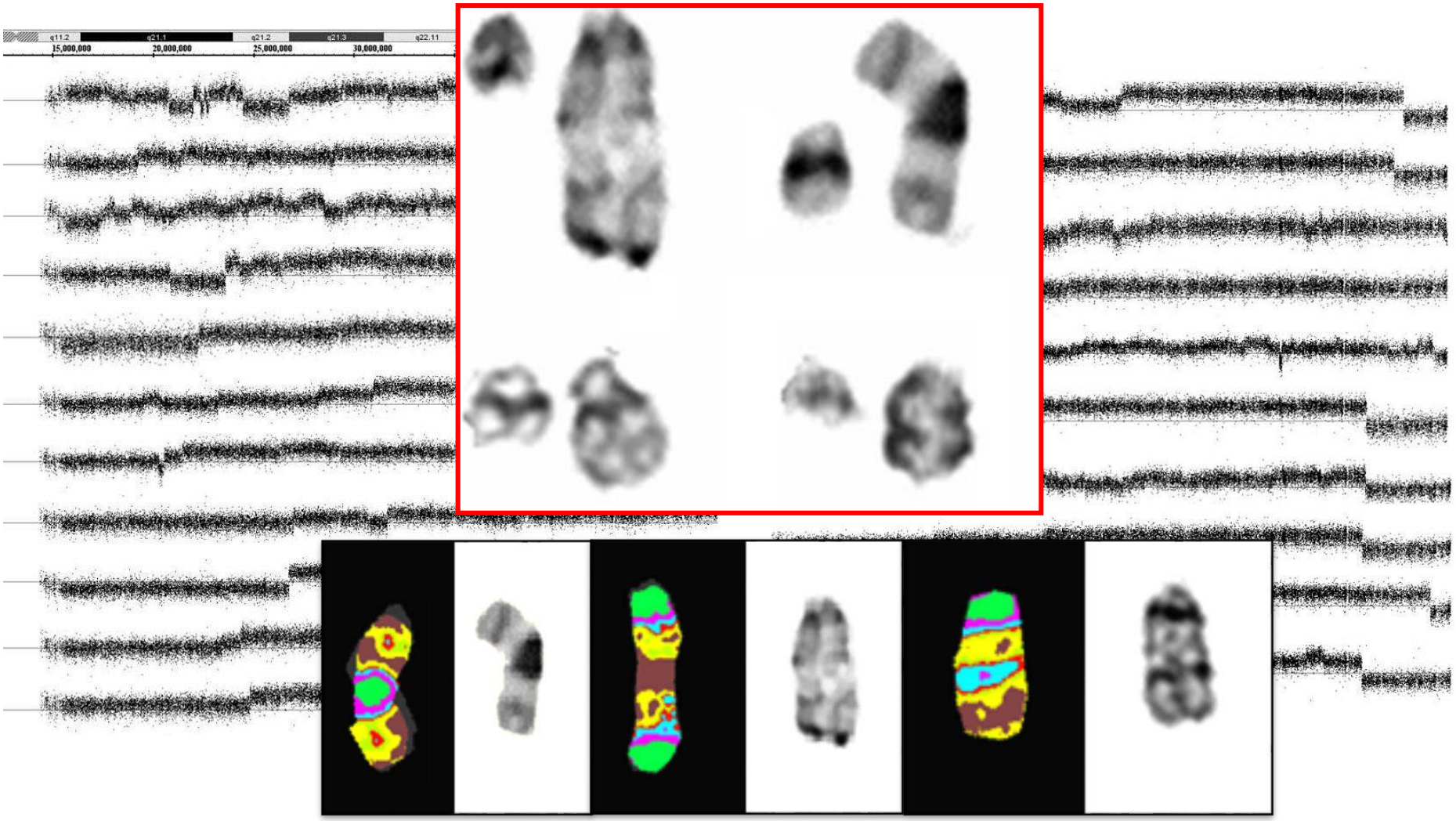


Moorman *et al* 2013 J Clin Oncol

SNP6.0 profiles of chromosome 21 in iAMP21 patients

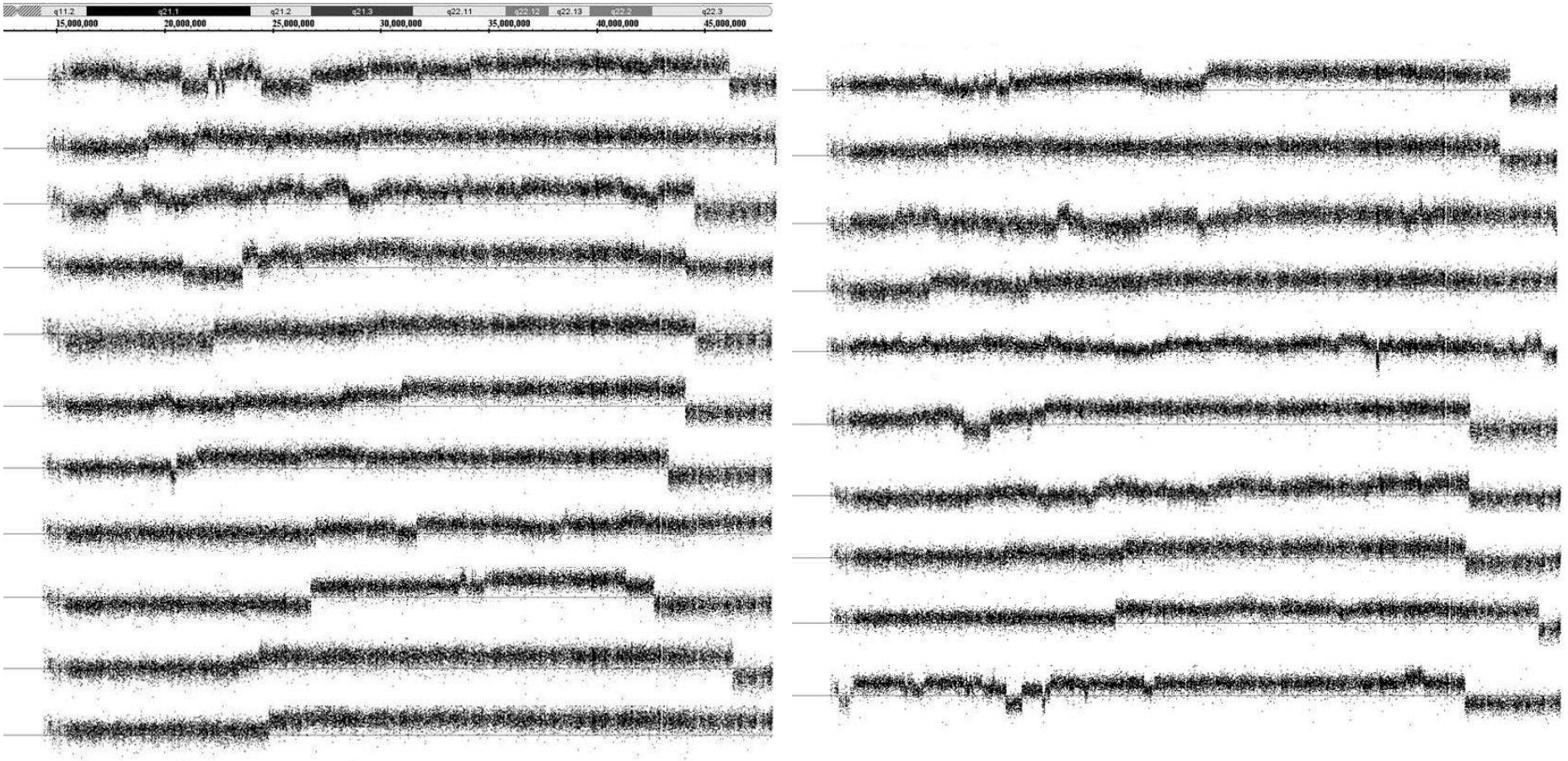


SNP6.0 profiles of chromosome 21 in iAMP21 patients



SNP6.0 profiles of chromosome 21 in iAMP21 patients

RUNX1



The mechanism

- Cytogenetics
- Fluorescence *in situ* hybridization (FISH)
- Next generation sequencing
- Novel bioinformatics approaches
- Computer simulation

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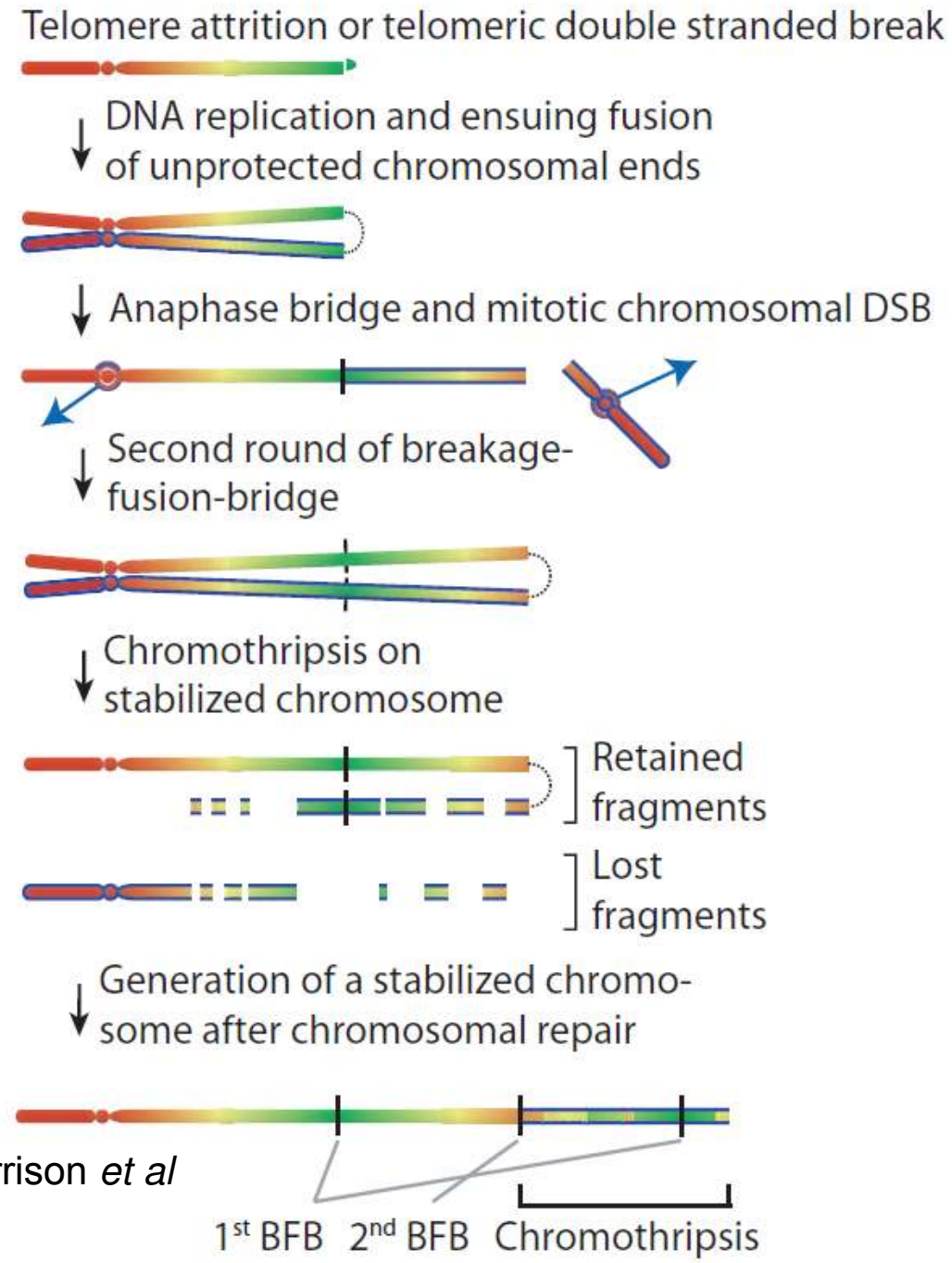
The Mechanism



Li, Schwab, Ryan……..Campbell, Harrison *et al*
Nature 2014

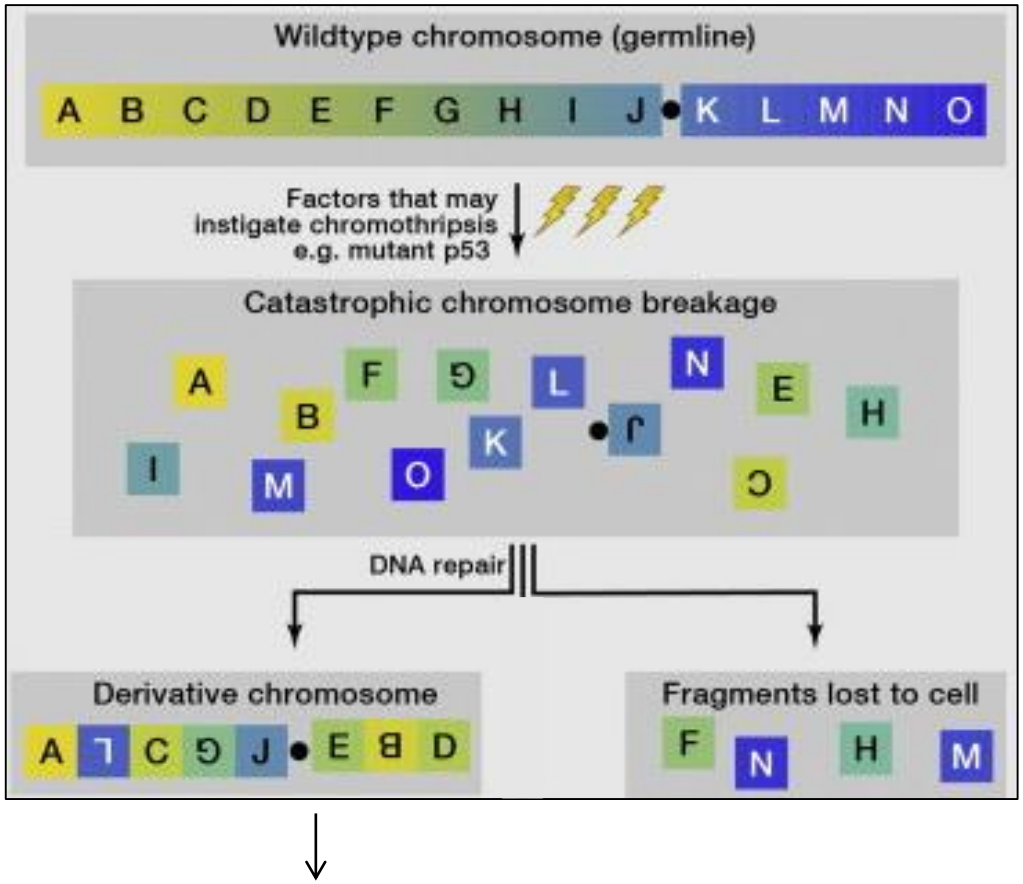
Chromothripsis

- First described by Stephens et al 2010, Cell.
- Greek: chromosome, shattering to pieces
- 10s to 100s of genomic rearrangements occurring in a one-off cellular crisis
- Rearrangements show tight localization
- Oscillate between 2 copy number states

Chromothripsis

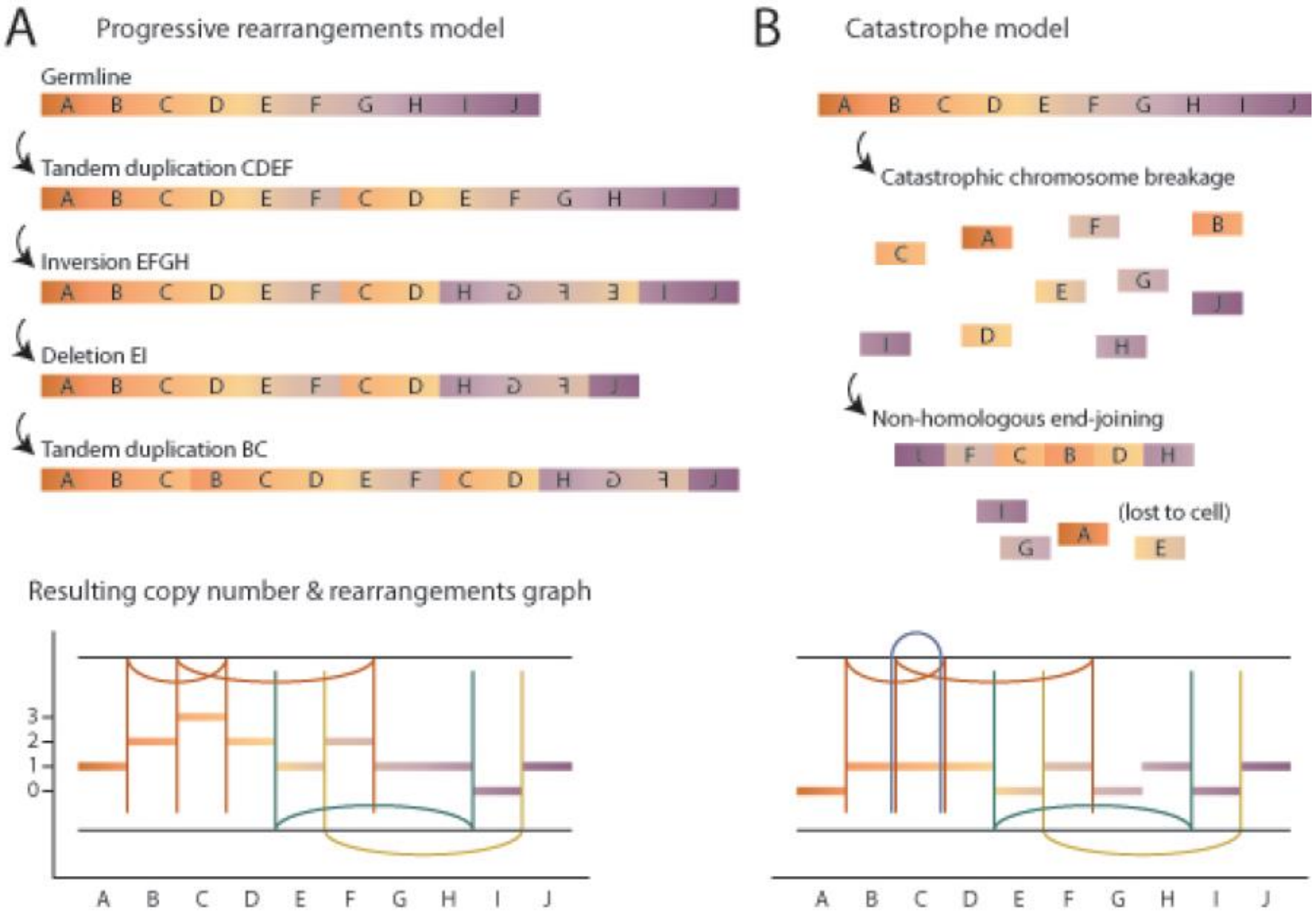
- Cell survives because one or more cancer causing lesion emerges from this genomic mayhem
- Common in cancer (2-3% of all cancers)
- Enriched in certain cancers (~25% bone cancers)
- Rare in acute lymphoblastic leukaemia (ALL)

Chromothripsis



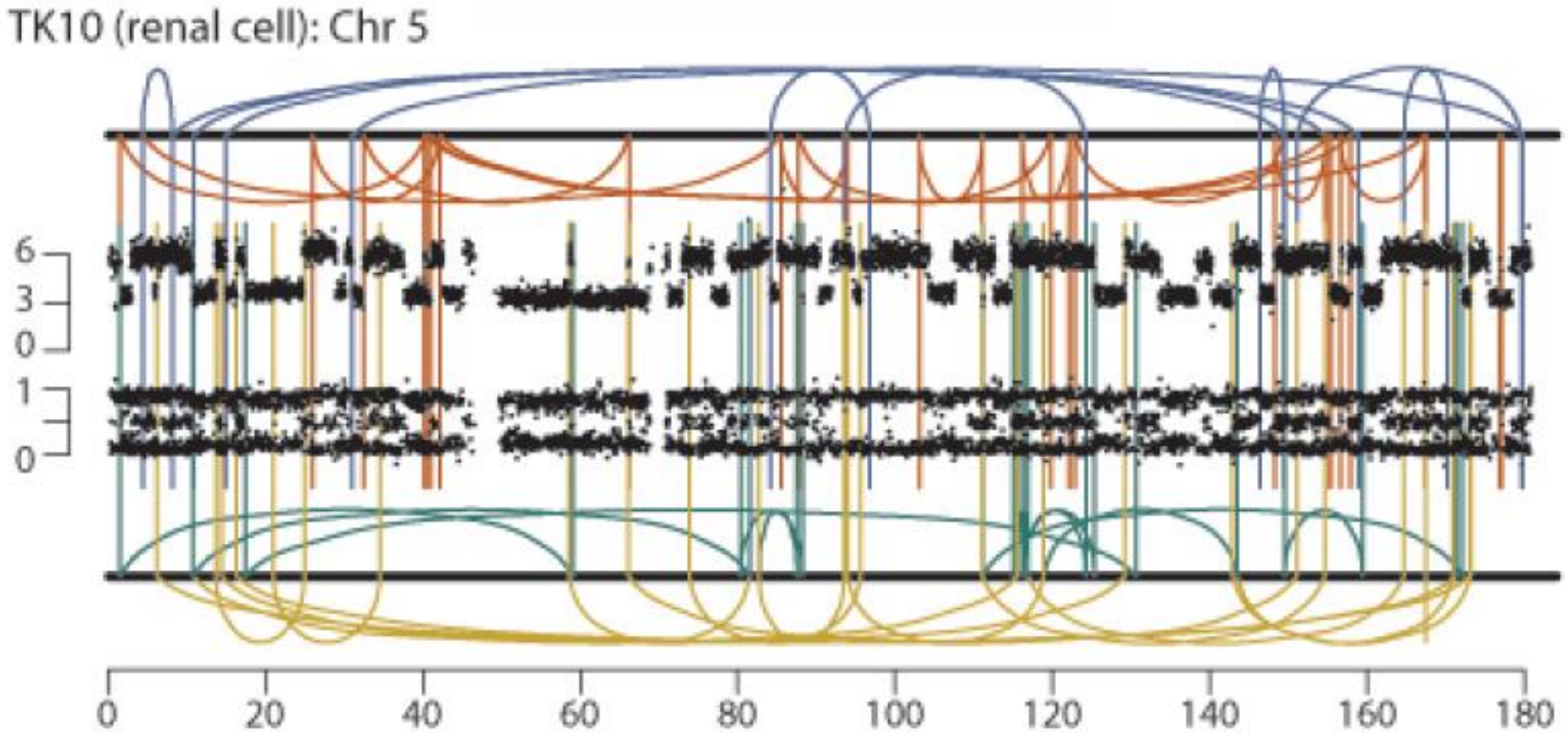
Tumour progression and development

Stephens et al 2010 Cell
Korbel and Campbell, 2013 Cell

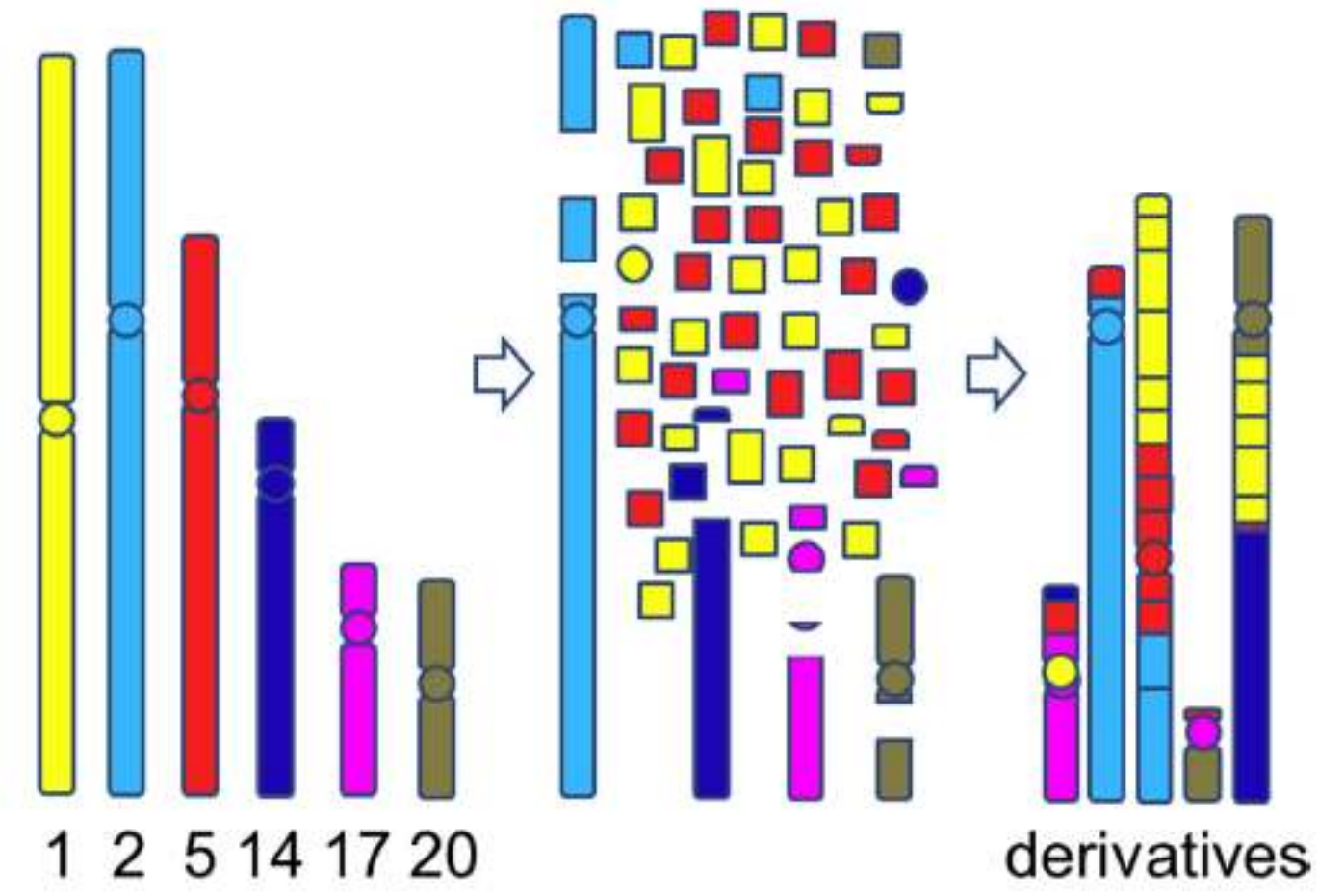


Stephens et al 2010 Cell

Chromothripsis involving a single chromosome

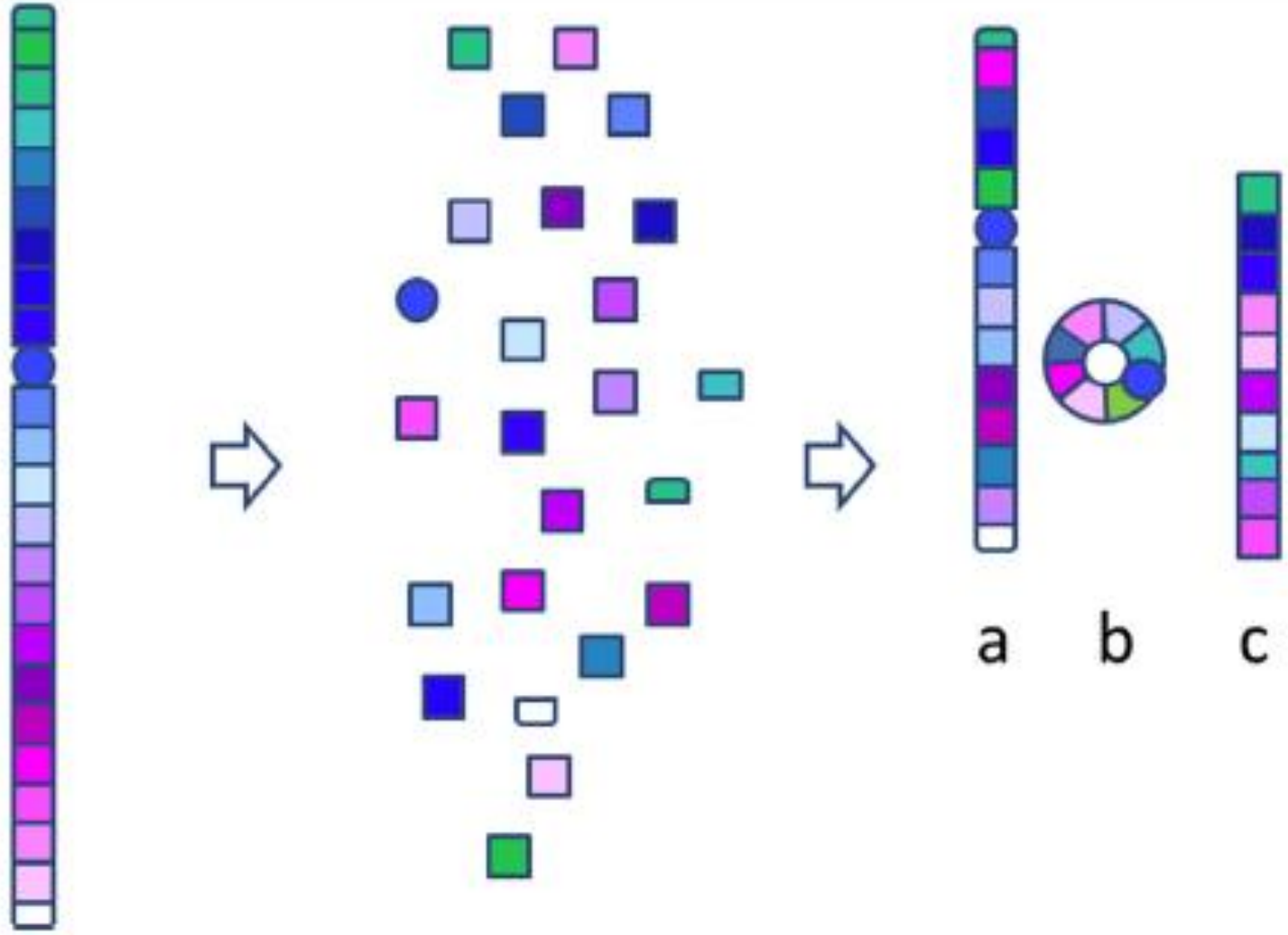


Chromothripsis involving multiple chromosomes

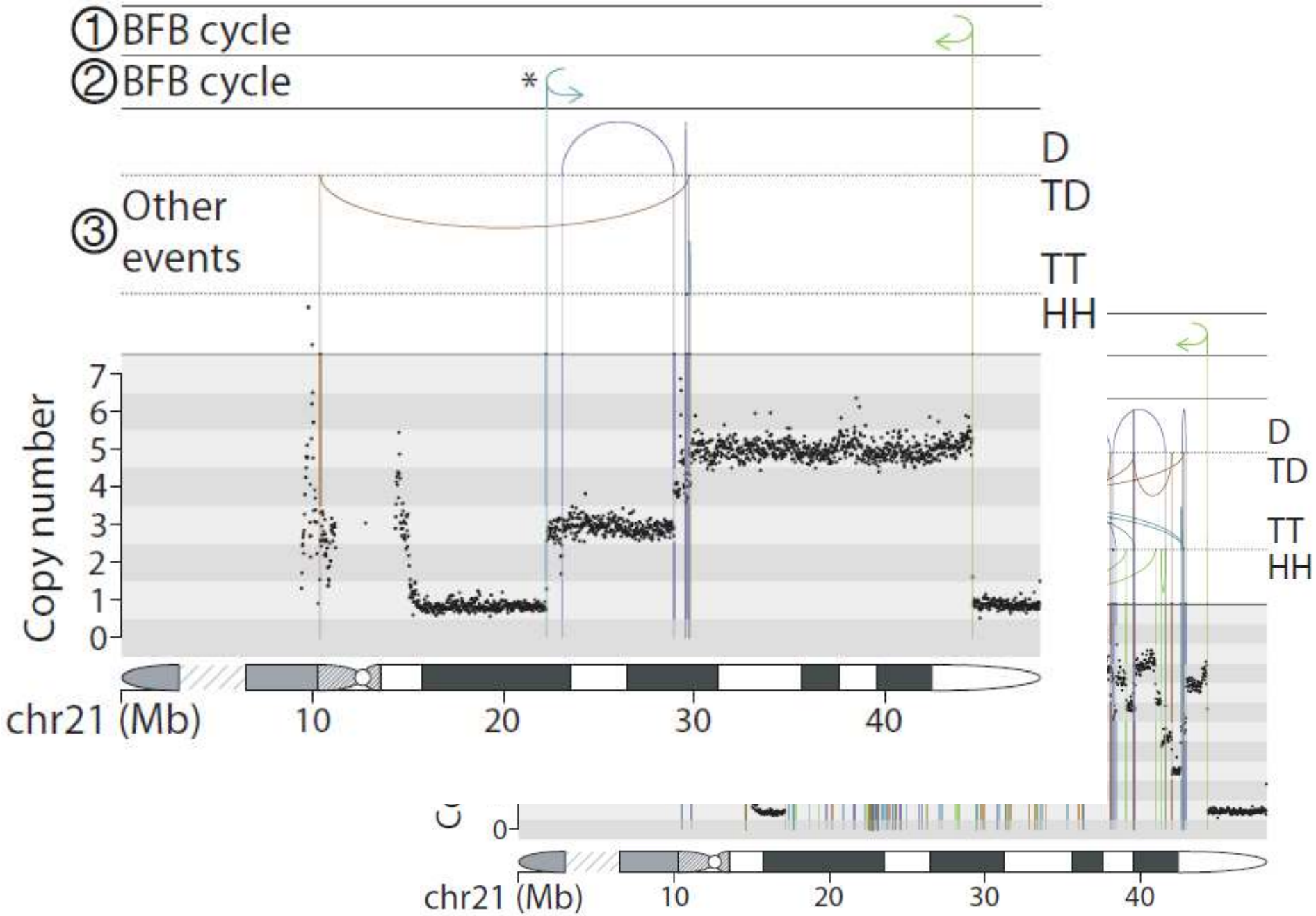


MacKinnon and Campbell 2013 Cancer Genetics

Centromere protects segments

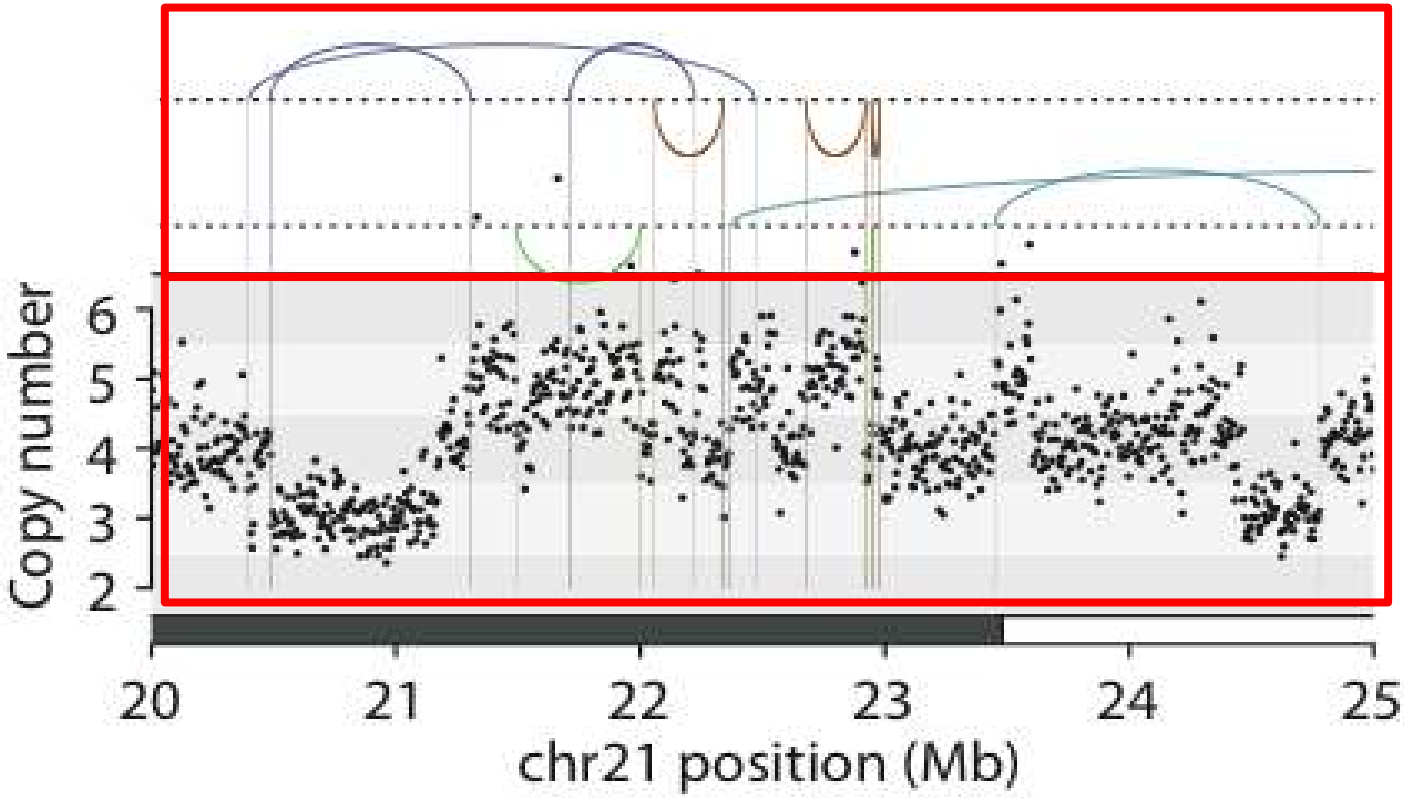


MacKinnon and Campbell 2013 Cancer Genetics

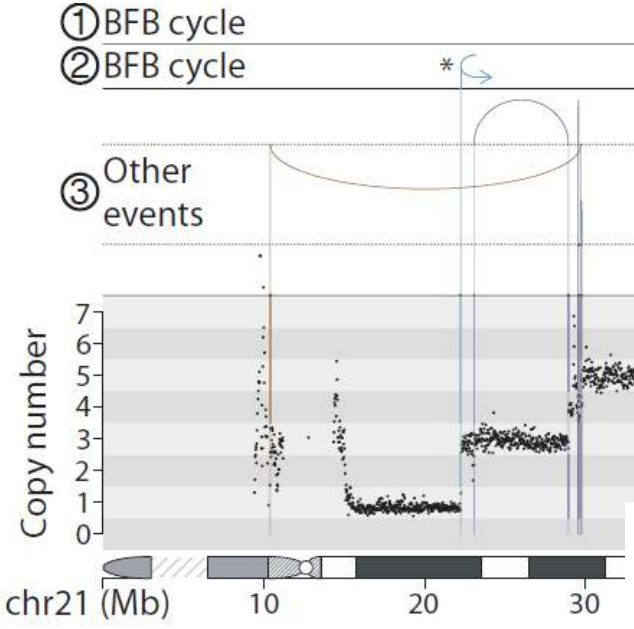

①BFB cycle
②BFB cycle
③Other events
*
D
TD
TT
HH
Copy number
7
6
5
4
3
2
1
0
chr21 (Mb)
10
20
30
40
D
TD
TT
HH
0
chr21 (Mb)
10
20
30
40

Evidence of chromothripsis in iAMP21

Rearrangements in equal numbers
in all possible orientations



Many copy number changes alternating between two or three states


①BFB cycle
②BFB cycle
*
D
TD
③Other events
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Copy number
7
6
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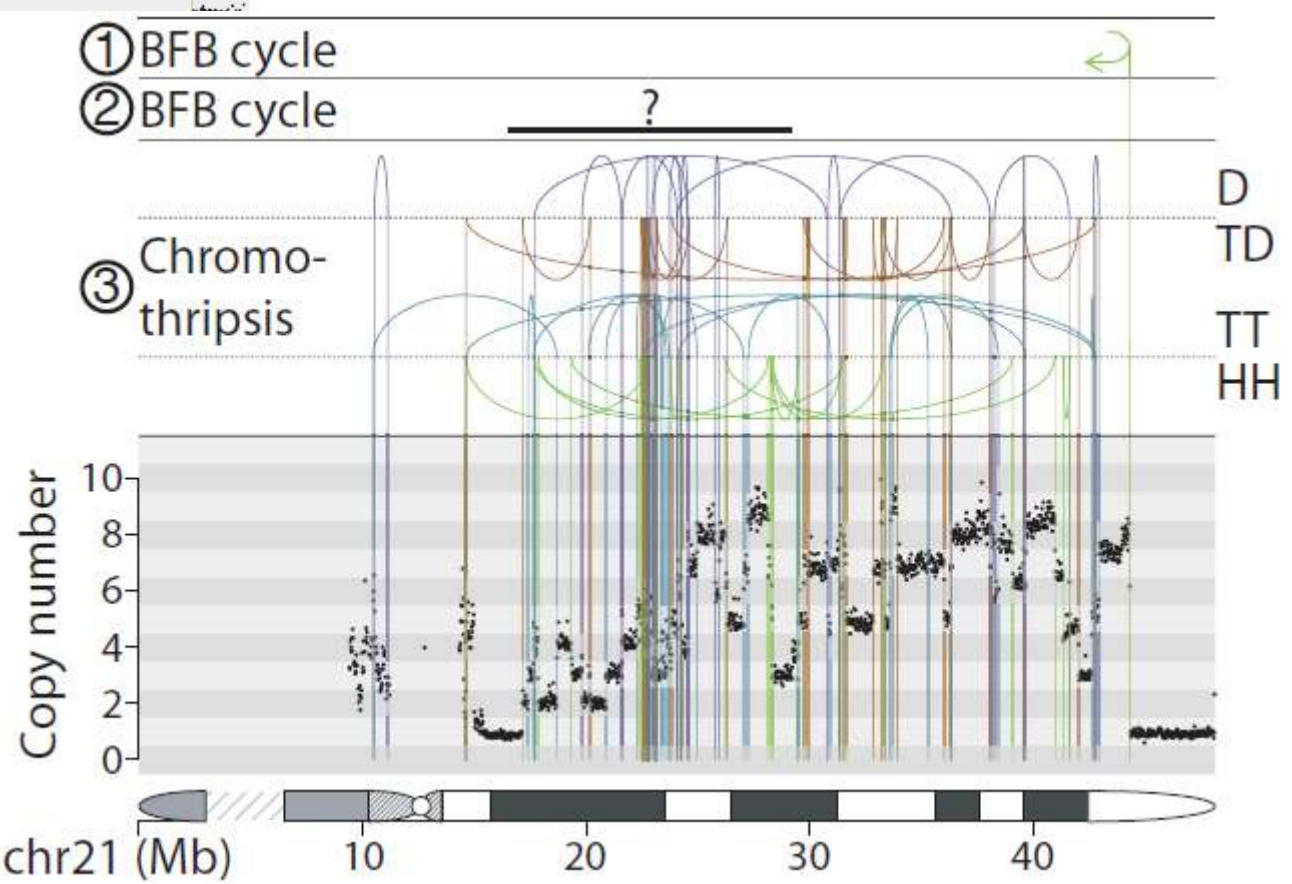
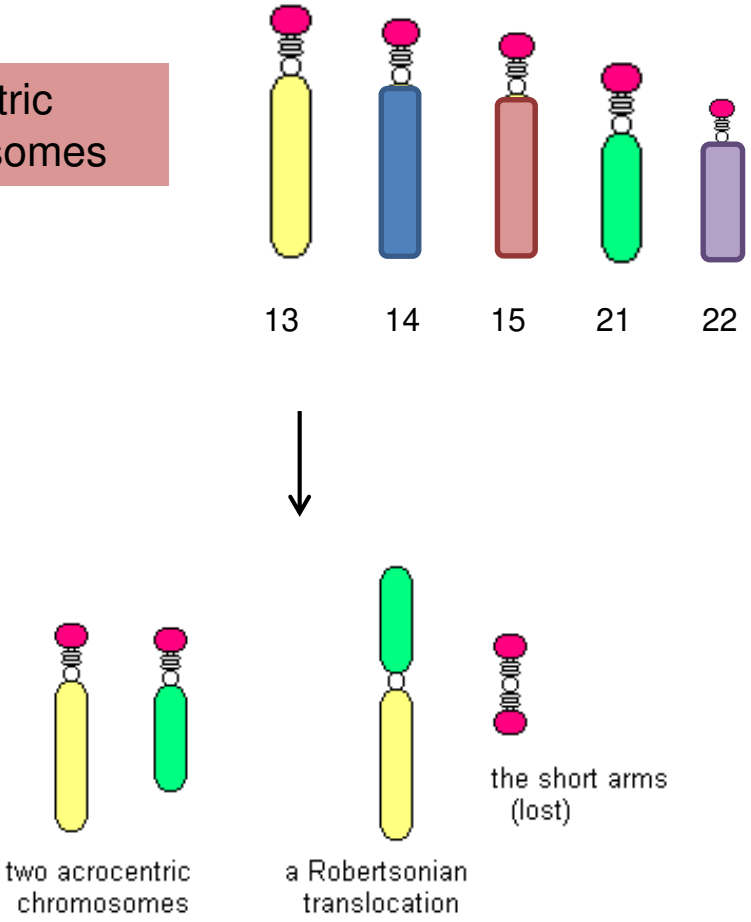
4
3
2
1
0
chr21 (Mb)
10
20
30


①BFB cycle
②BFB cycle
?
D
TD
③Chromo-thripsis
TT
HH
Copy number
10
8
6
4
2
0
chr21 (Mb)
10
20
30
40

Robertsonian translocations

Acrocentric chromosomes



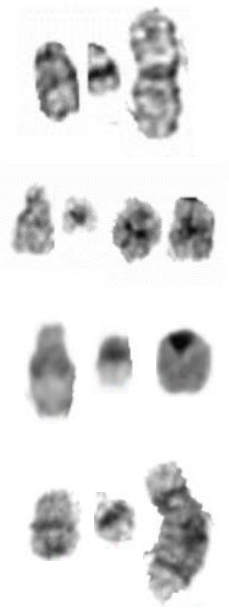
Robertsonian translocation	Incidence
rob(13;14)c	1 in 1300
rob(14;21)c	1 : 12,500
rob(14;15)c	1 : 20,000
rob(13;13)c rob(13;15)c rob(13;22)c rob(14;22)c	1 :50,000
rob(13;21)c rob(15;22)c	1 : 100,000
rob(15;21)c rob(21;21)c rob(21;22)c	1 :100,000-200,000

Prevalence of 1 in 1000

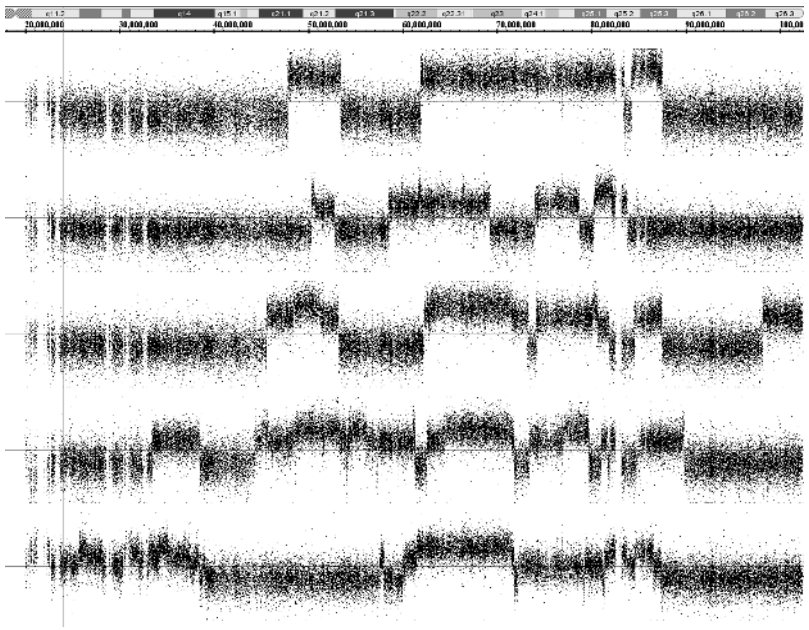
2,700 x increased risk of ALL

Genomic characterisation of rob(15;21)c cases

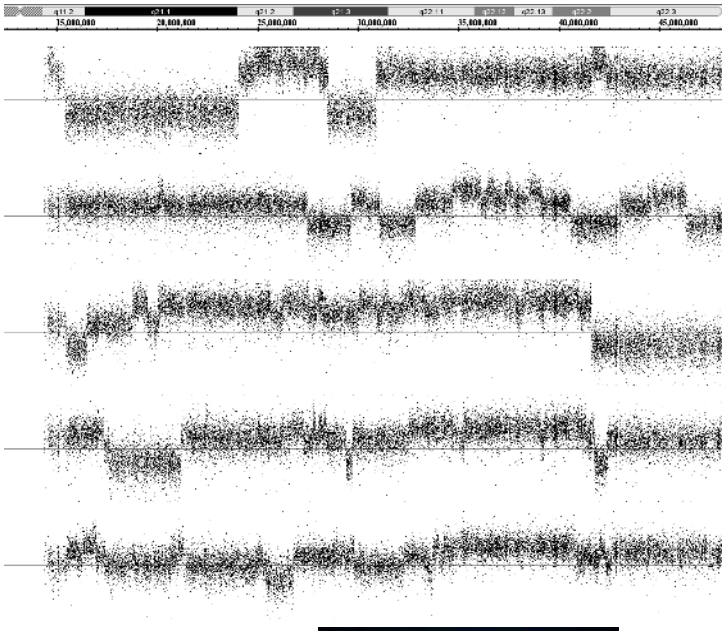
G-banding



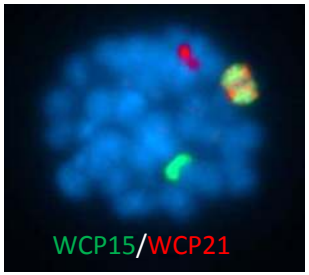
Chromosome 15

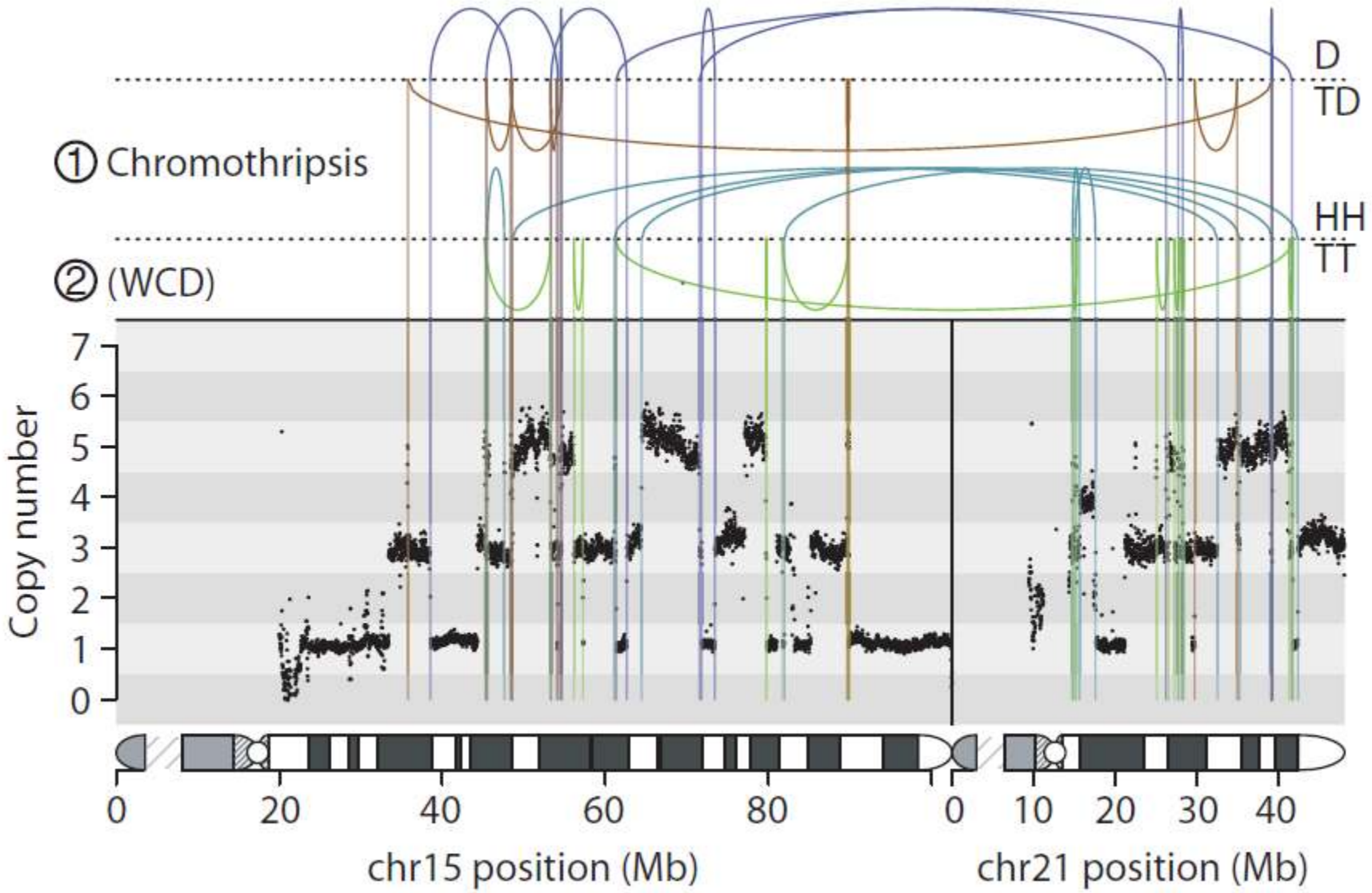


Chromosome 21

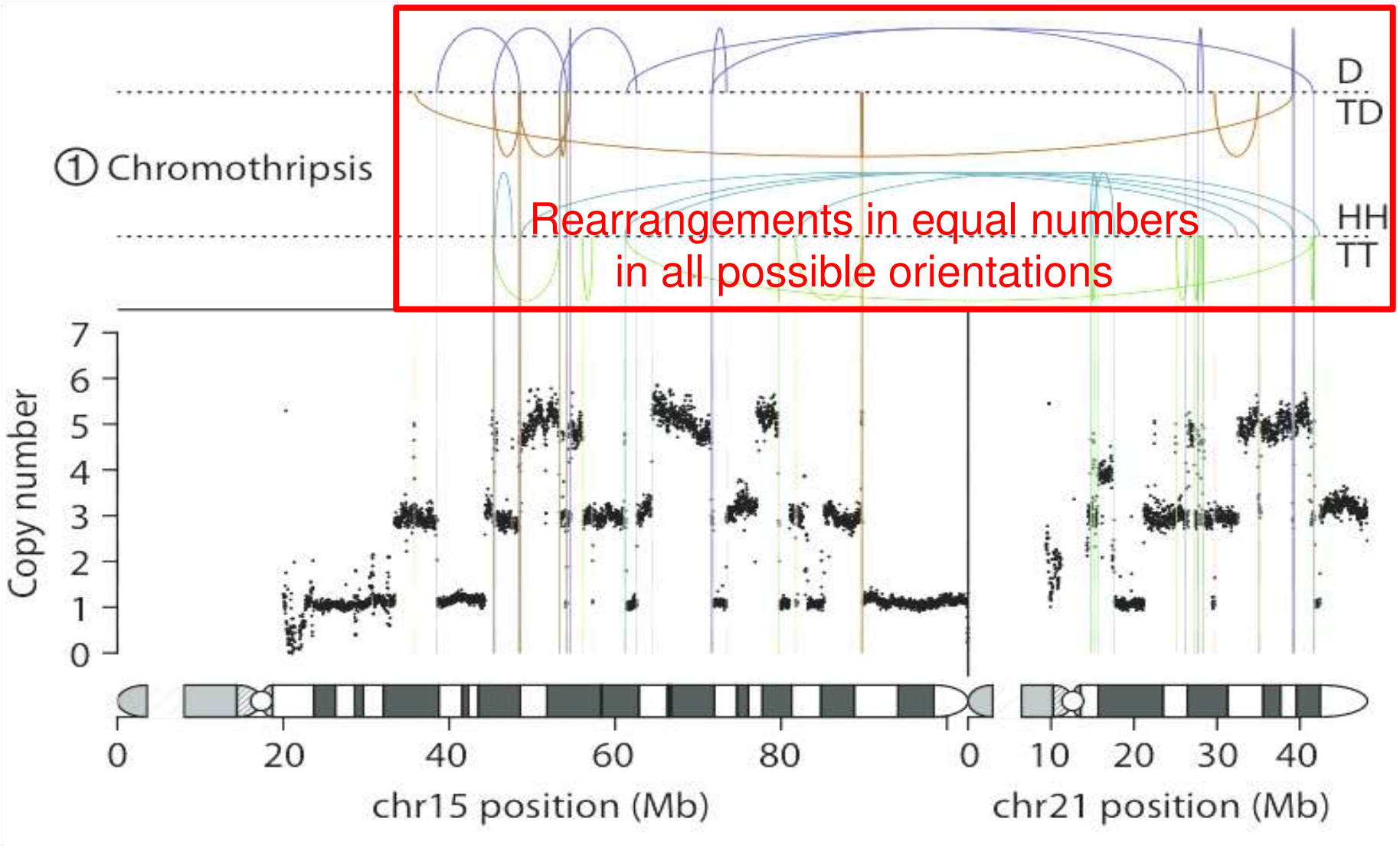


FISH studies confirmed iAMP21 was derived from rob(15;21)c

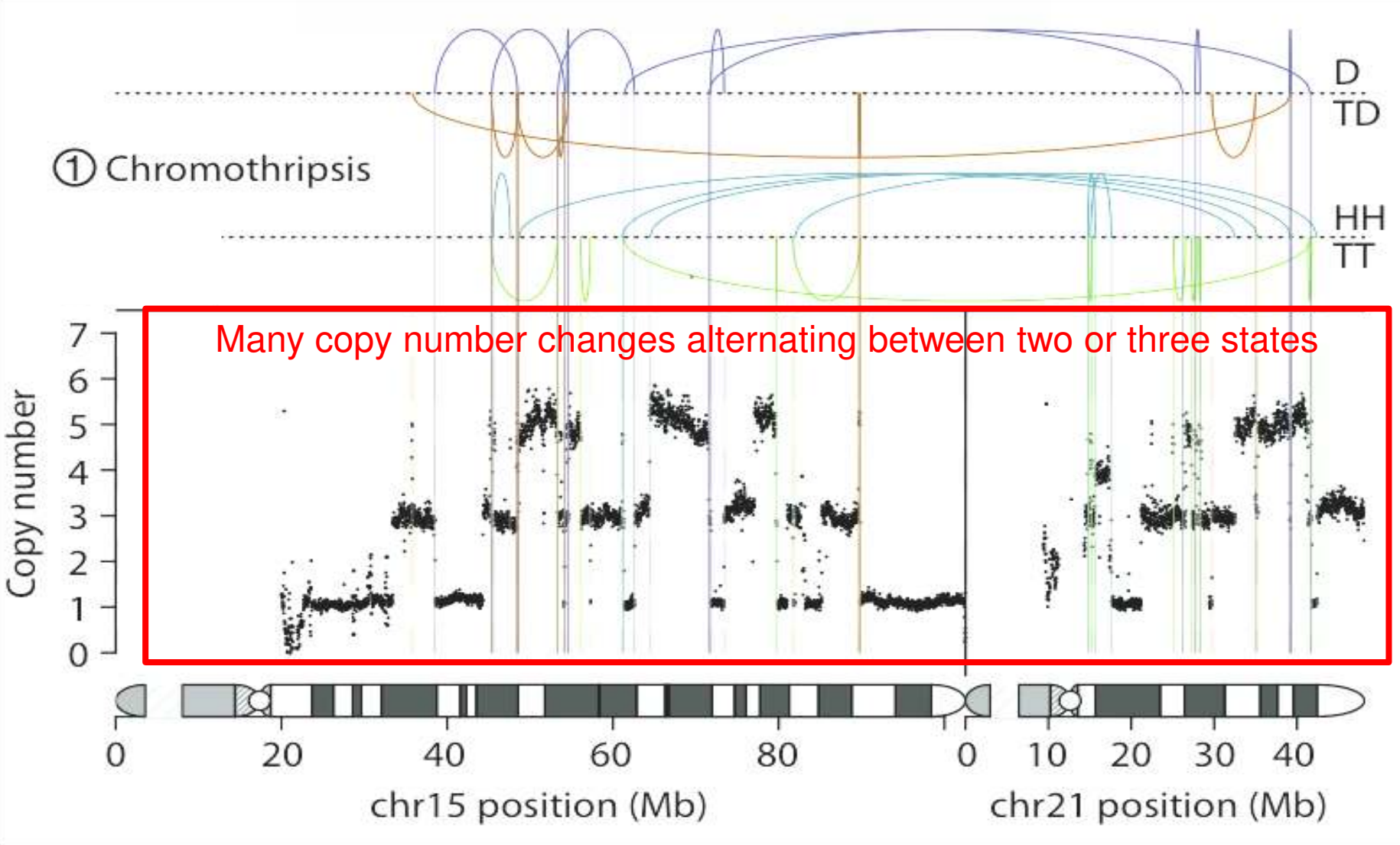



① Chromothripsis
② (WCD)
D
TD
HH
TT
Copy number
7
6
5
4
3
2
1
0
0
20
40
60
80
chr15 position (Mb)
0
10
20
30
40
chr21 position (Mb)

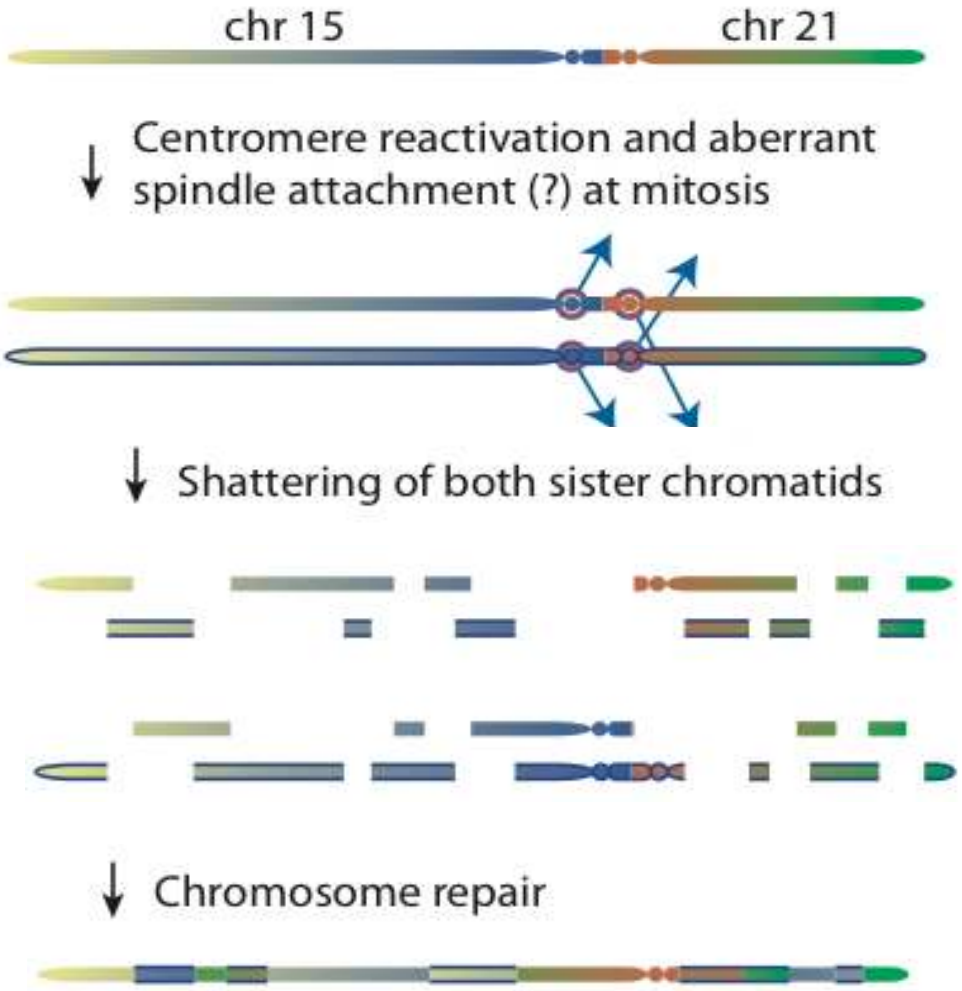
Criteria for Chromothripsis



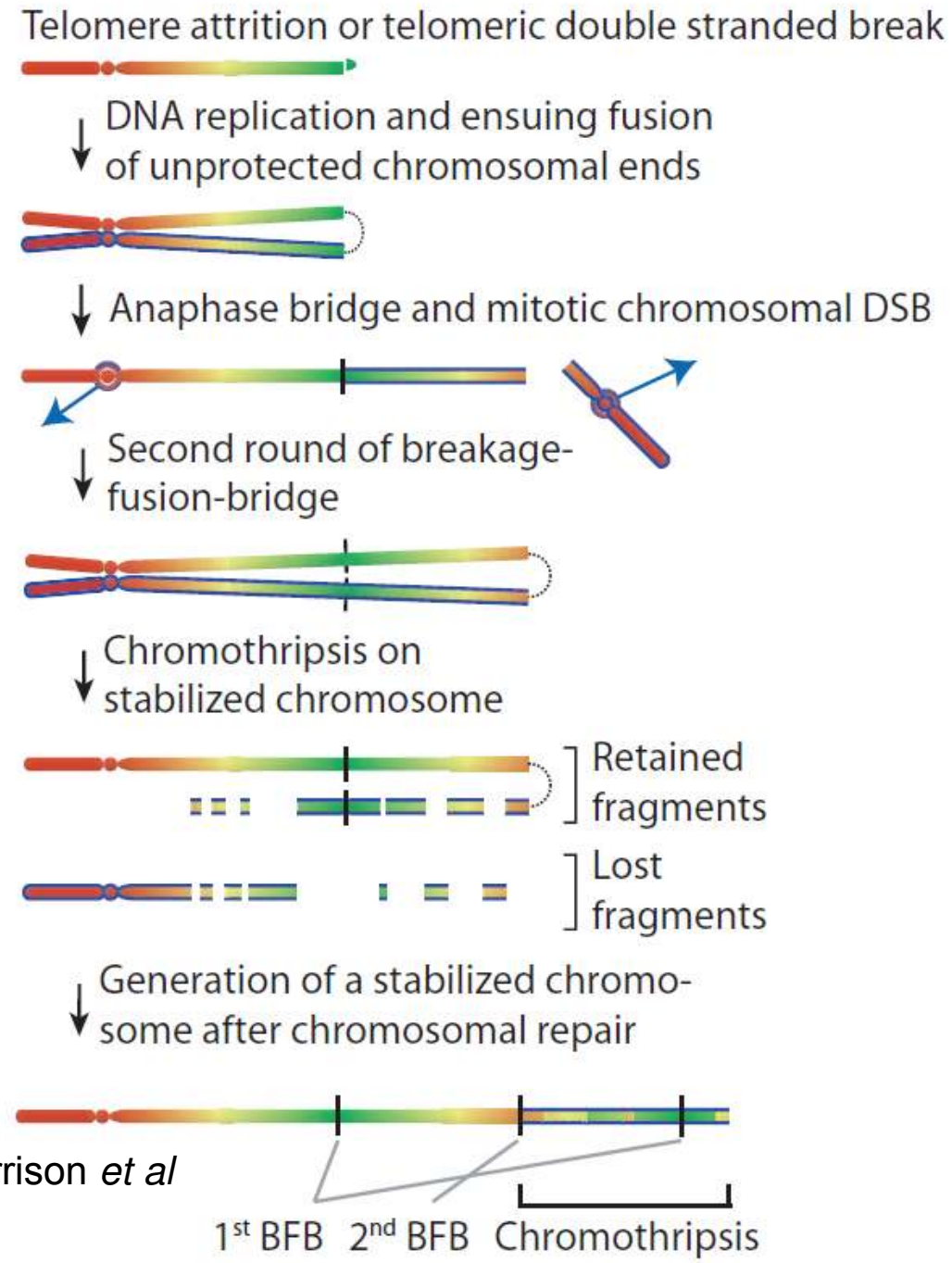
Criteria for Chromothripsis



Mechanism of der(15;21) iAMP21



The Mechanism



Li, Schwab, Ryan……..Campbell, Harrison *et al*
Nature 2014

Genetic alterations behind sporadic iAMP21

Breakage-fusion-bridge cycle - dicentric chromosome

↓

Chromothripsis

↓

Stabilisation of the derivative chromosome

Genetic alterations behind der(15;21) iAMP21

Constitutional dicentric chromosome

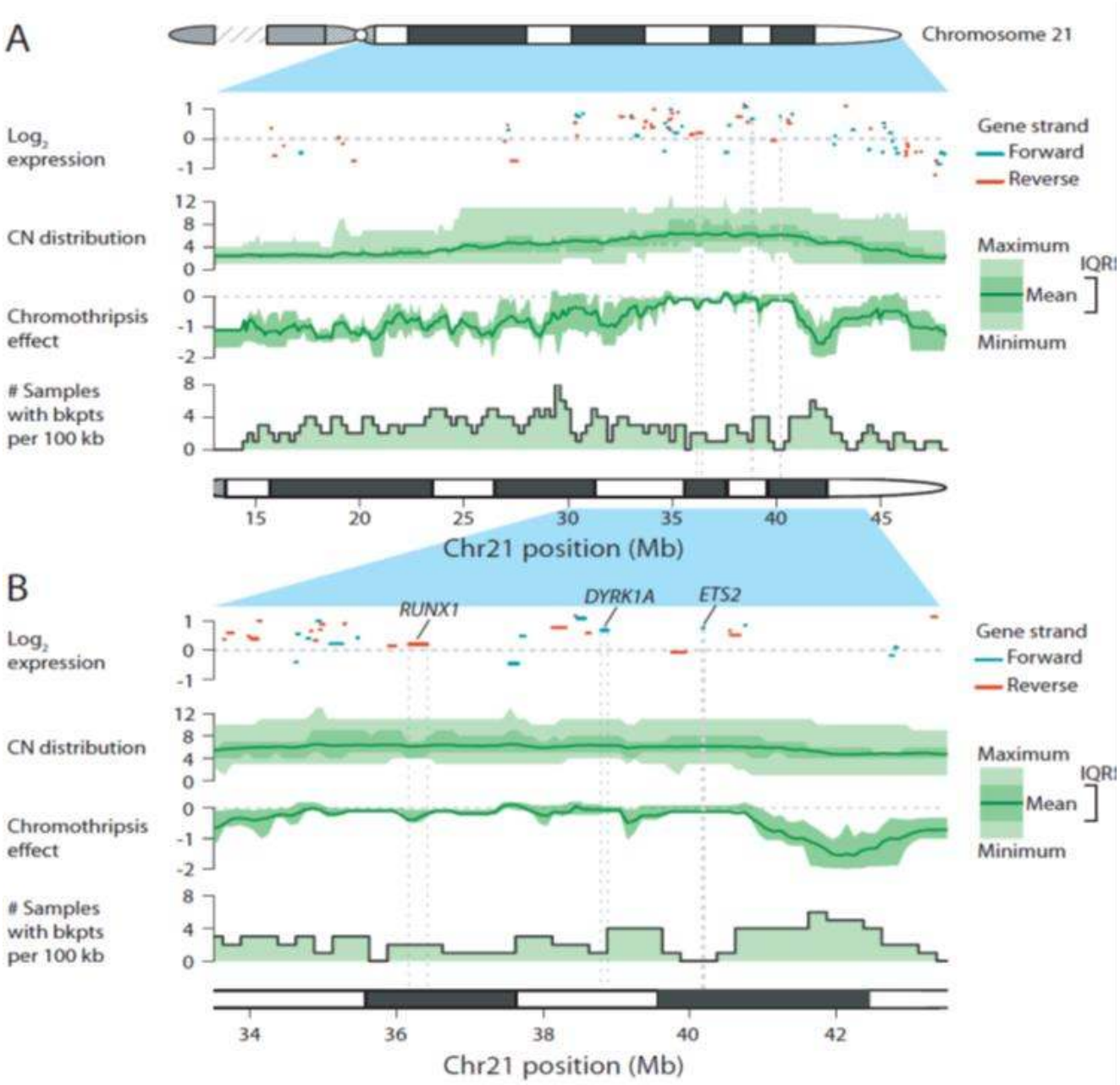
↓

Chromothripsis

↓

Stabilisation of the derivative chromosome

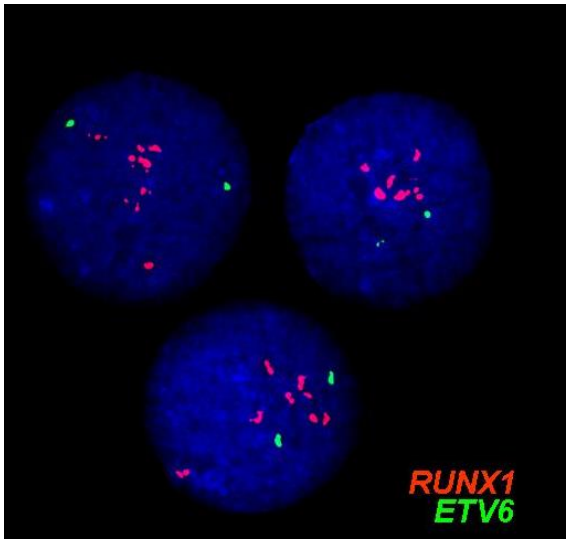
Highly amplified region is protected from chromothripsis



Conclusions

- Chromothripsis is common in cancer, but rare in ALL
- This is the first report of chromothripsis temporally and spatially controlled and restricted to a specific chromosome
- In iAMP21 ALL the significant genes protected from chromothripsis lead to leukaemia progression
- There is evidence of inherited predisposition
- This mechanism could apply to karyotype complexity in a range of cancer types

Identification of iAMP21



- While the initiating mechanism is unravelled

- FISH with probes directed to *RUNX1* remain the best detection method
  (SNP arrays)

- Intensive therapy is recommended

Thanks to …

LEUKAEMIA & LYMPHOMA RESEARCH

Beating Blood Cancers

erc

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- Past and present member of the Leukaemia Research Cytogenetics Group
- UK Cancer Cytogenetics Group
- Peter Cambell
- Yilong Li
- Sanger Institute