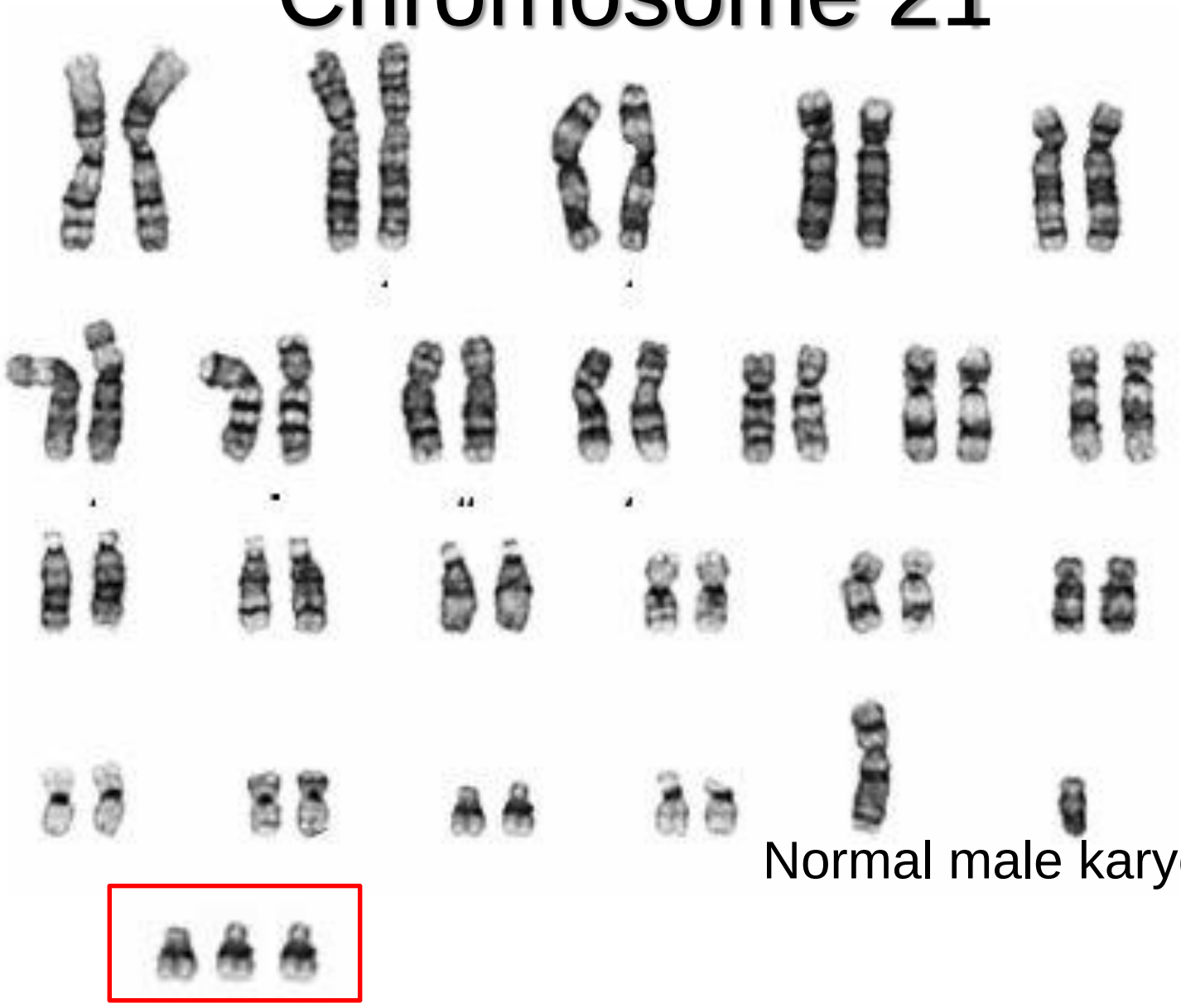
Constitutional and somatic rearrangement of chromosome 21 in acute lymphoblastic leukaemia (ALL)

Christine J Harrison PhD FRCPath FMedSci
Professor of Childhood Cancer Cytogenetics
Northern Institute for Cancer Research
Newcastle University, UK

Chromosome 21



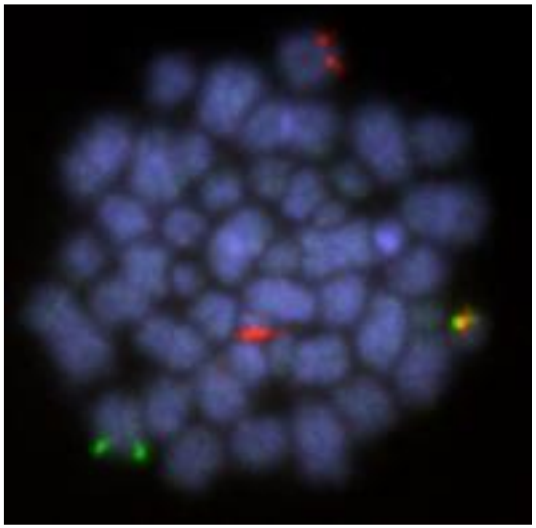
Normal male karyotype

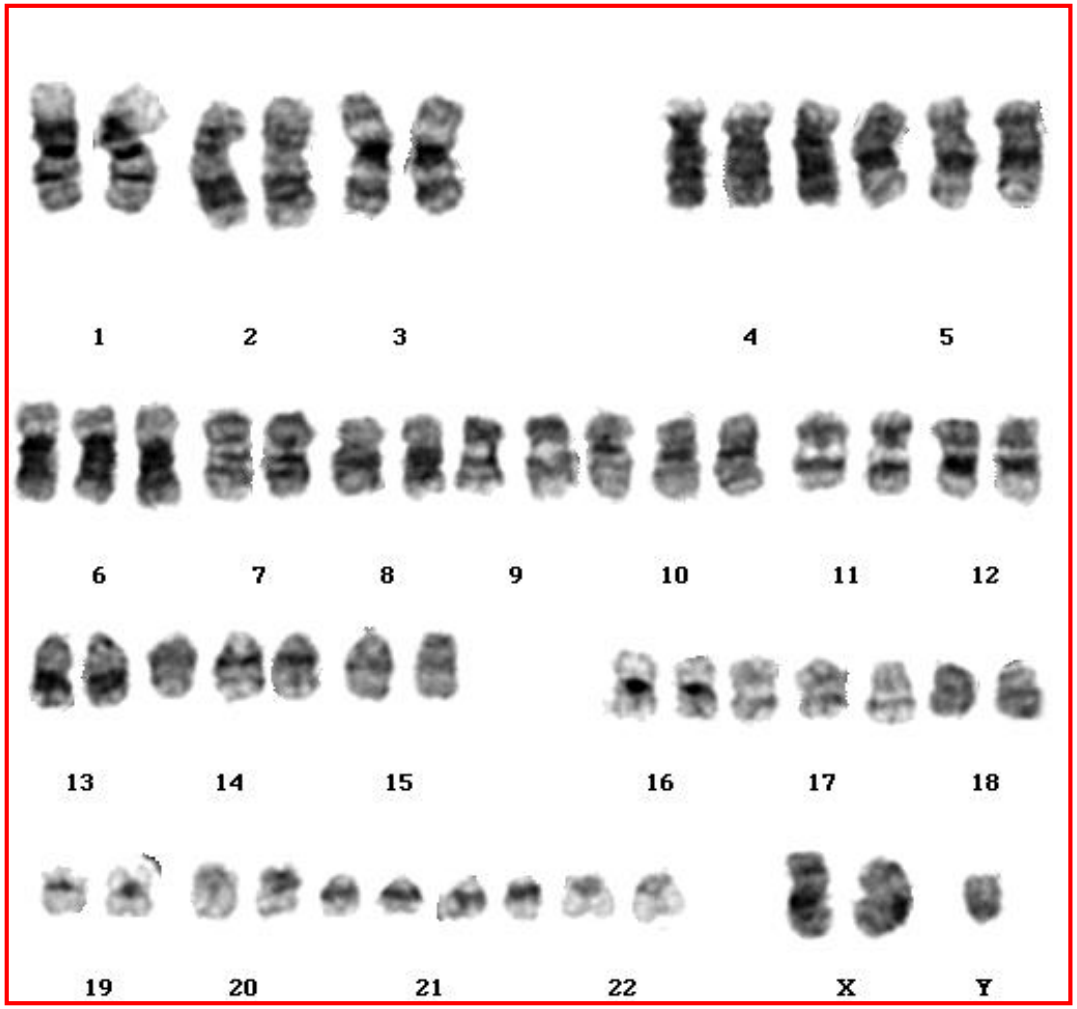
Constitutional gain of chromosome 21 in Down syndrome

Chromosome 21 in good risk ALL

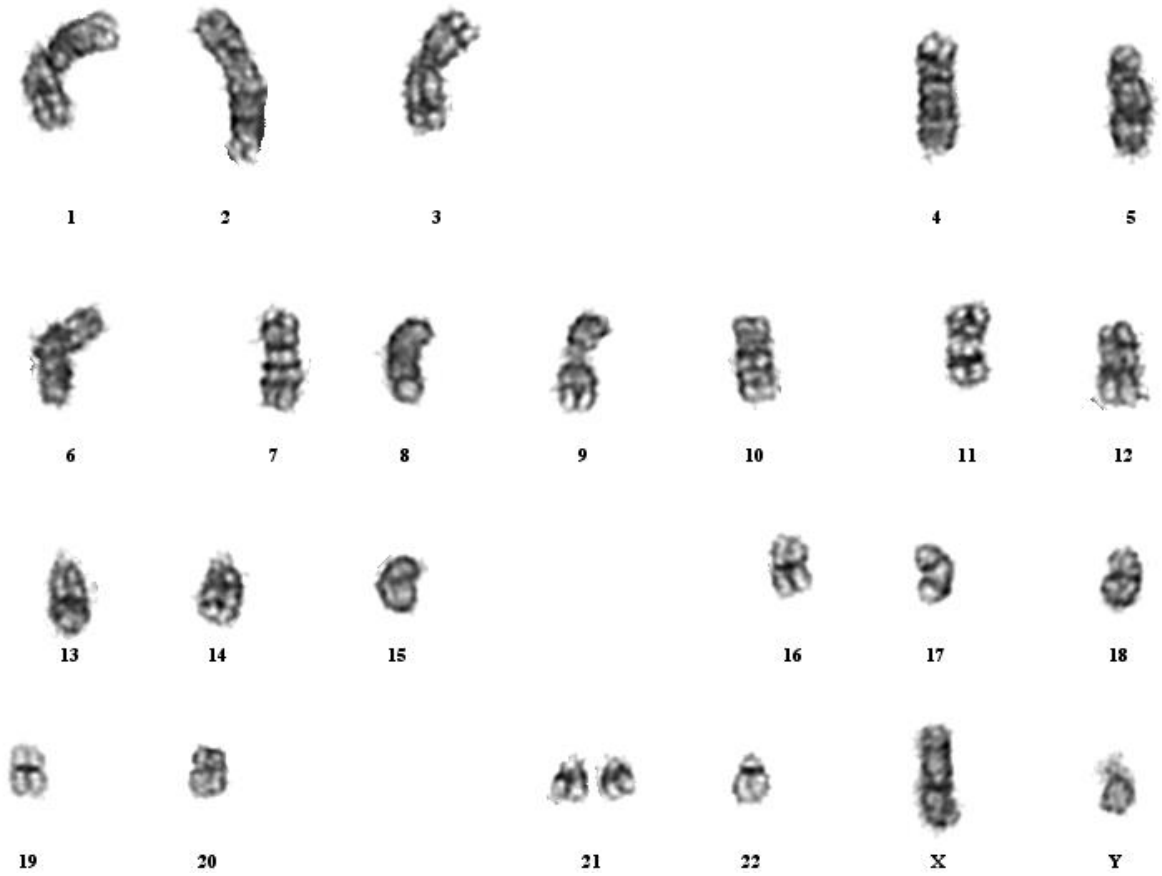
High hyperdiploidy
(51-65 chromosomes)

ETV6-RUNX1





Chromosome 21 in poor risk ALL

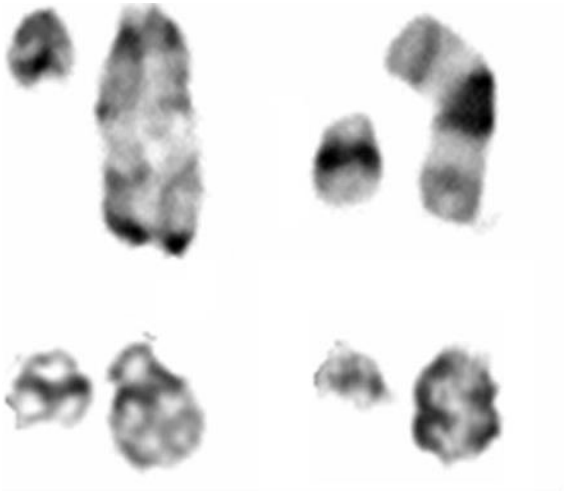


Near haploidy (23-29 chromosomes)

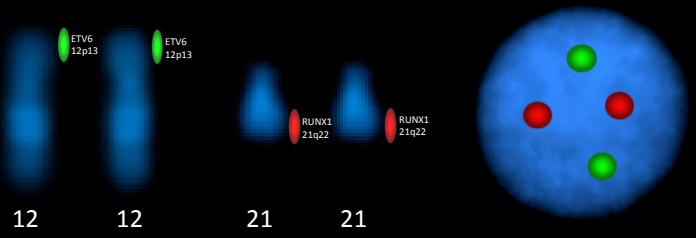
Poor risk cytogenetic abnormality

Intrachromosomal amplification of chromosome 21

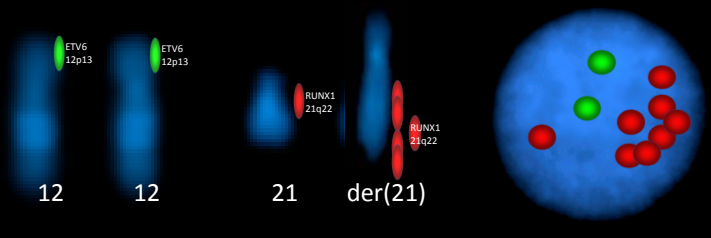
iAMP21



Intrachromosomal amplification of chromosome 21
iAMP21



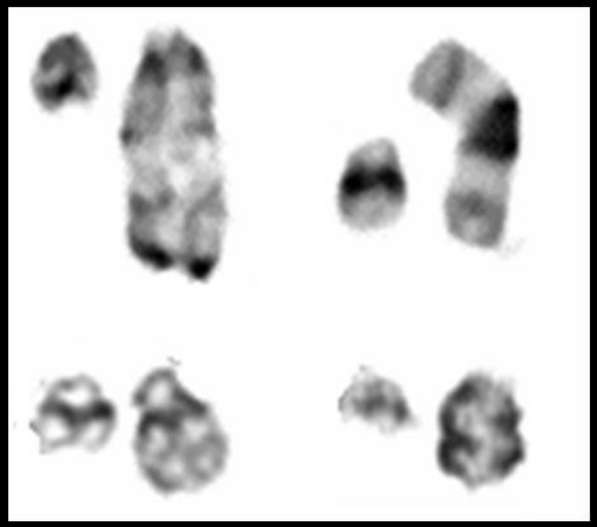
ETV6-RUNX1 extra signal

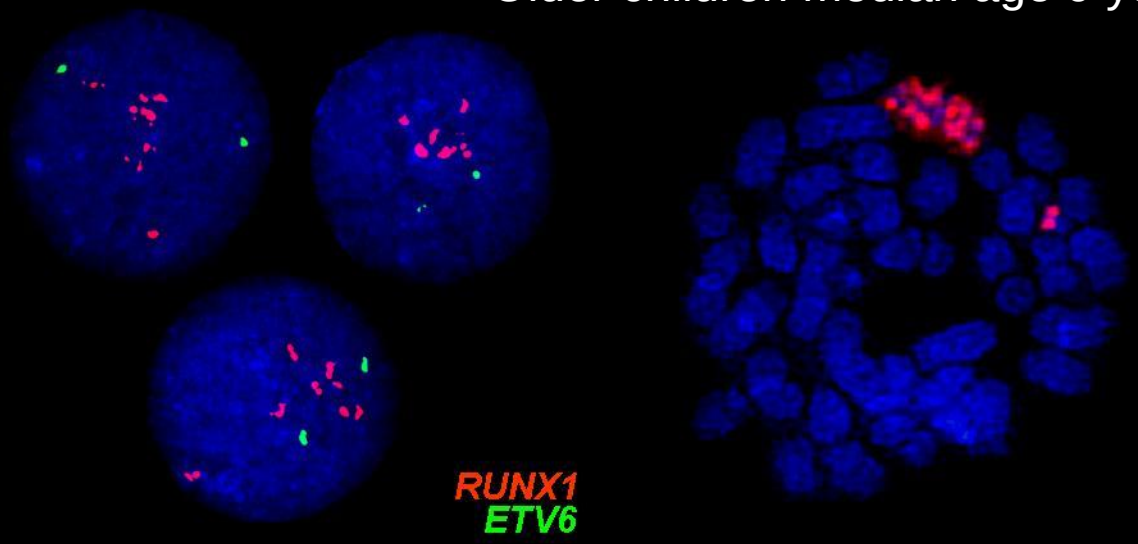


Normal signal pattern

Abnormal signal pattern

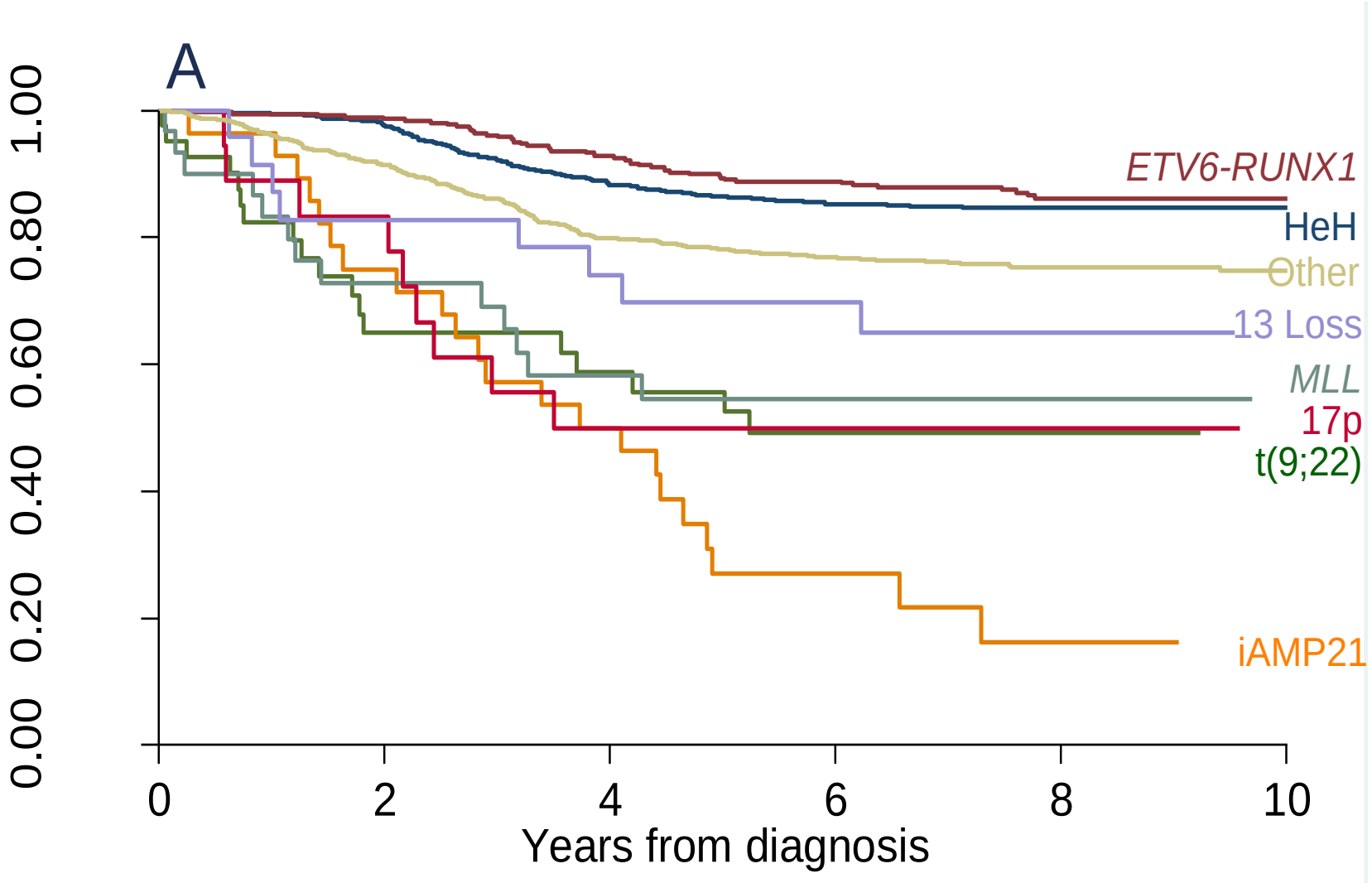
Incidence ~2%
Older children median age 9 years





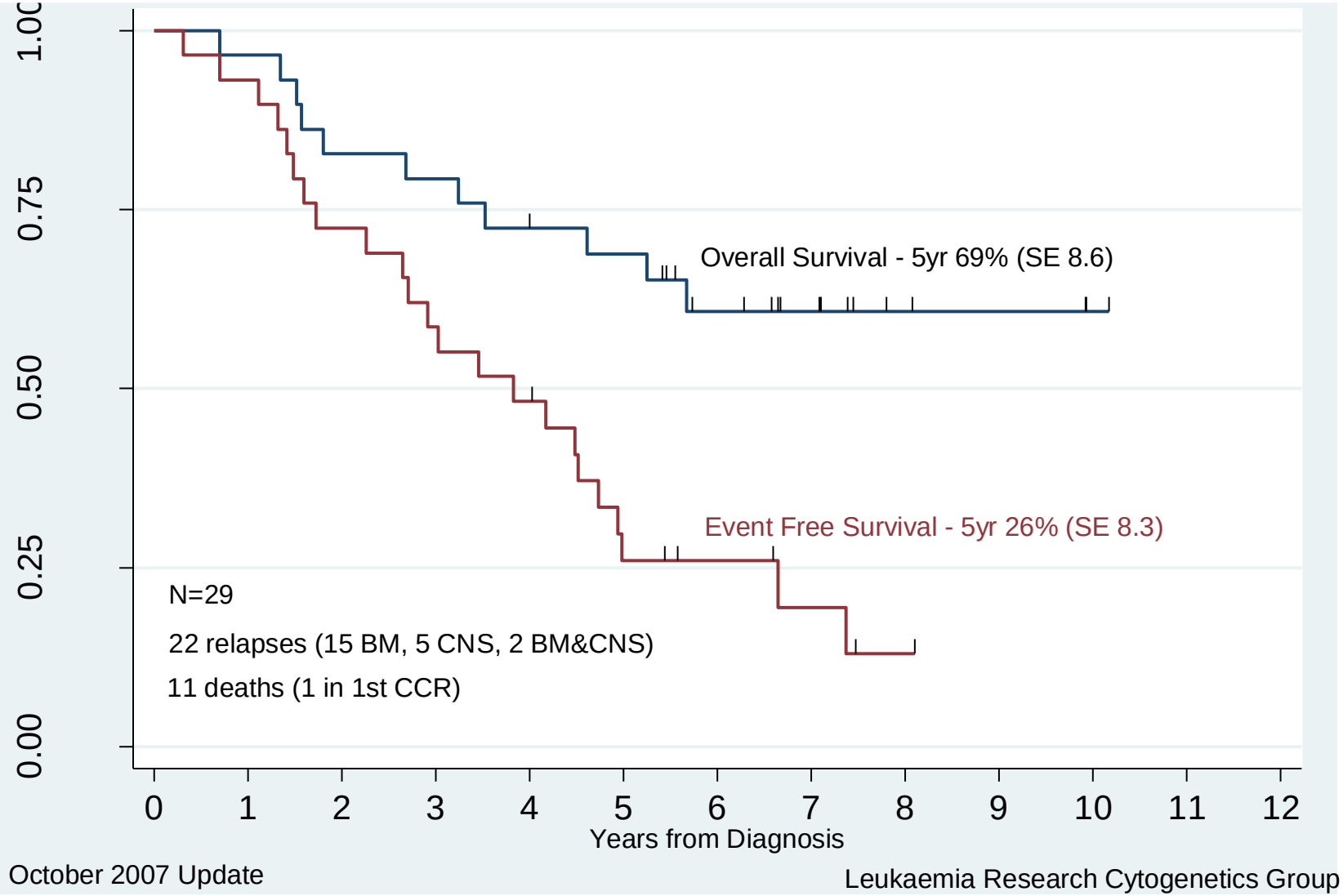
Harewood *et al* 2003 Leukemia 17: 547-53; Soulier *et al* 2003 Leukemia 17: 1679-82
Robinson *et al* 2003 Leukemia 17: 2249-50; Robinson *et al* 2007 Genes Chromos Cancer 46: 318-26

ALL97: Risk of relapse by cytogenetics

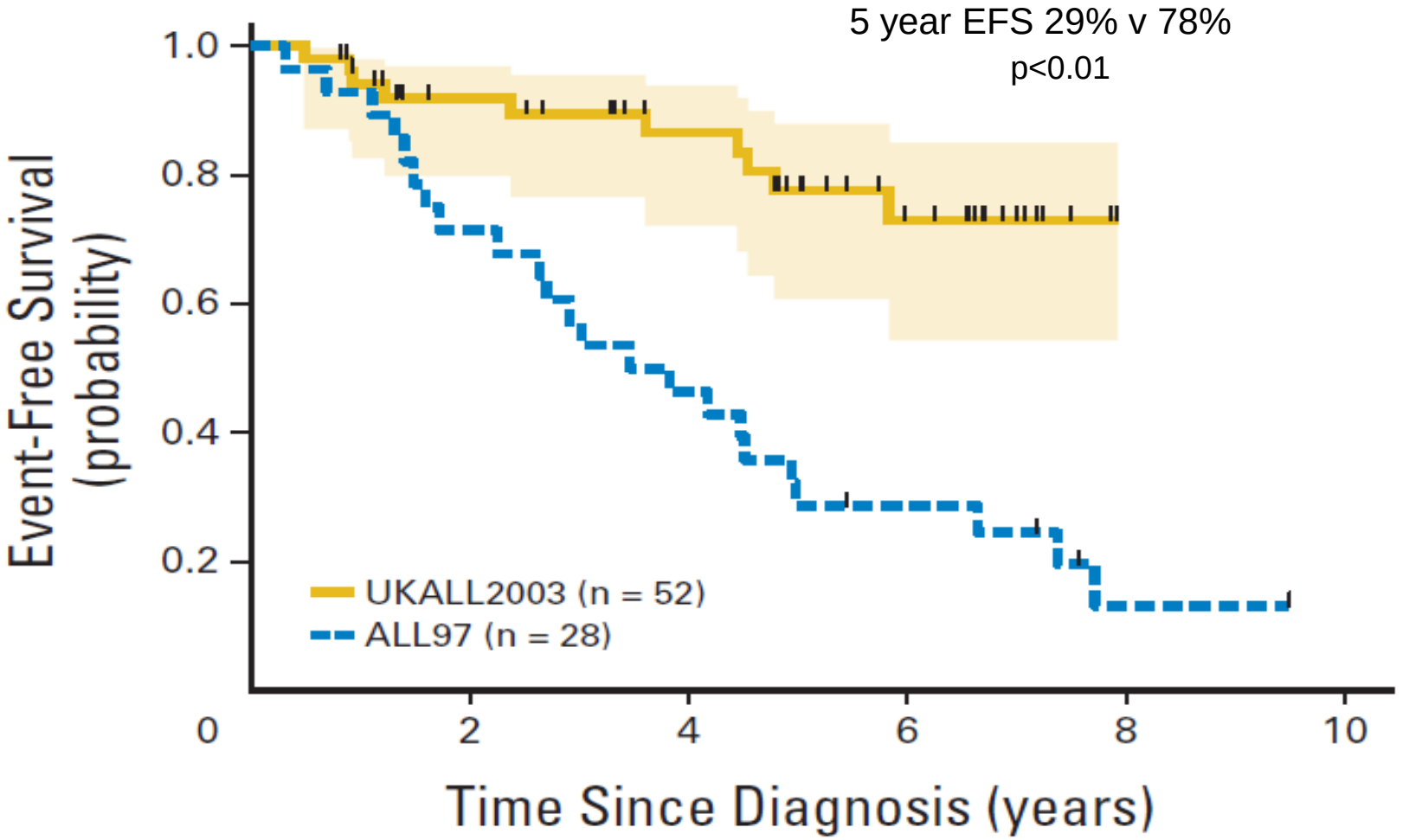


Moorman *et al*, 2010 Lancet Oncology

Outcome of iAMP21 patients on ALL97

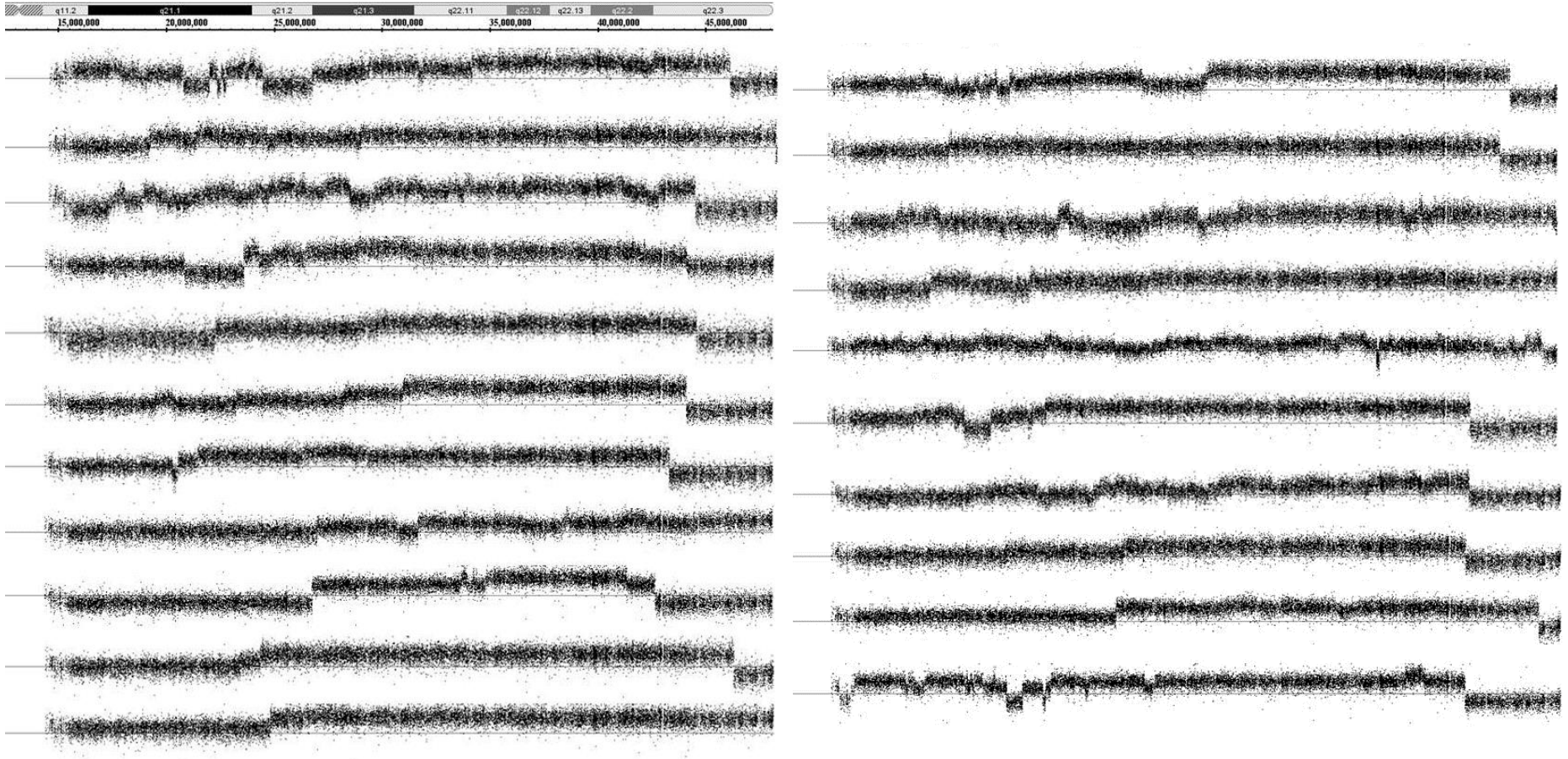


Intensive therapy improves outcome of iAMP21 patients

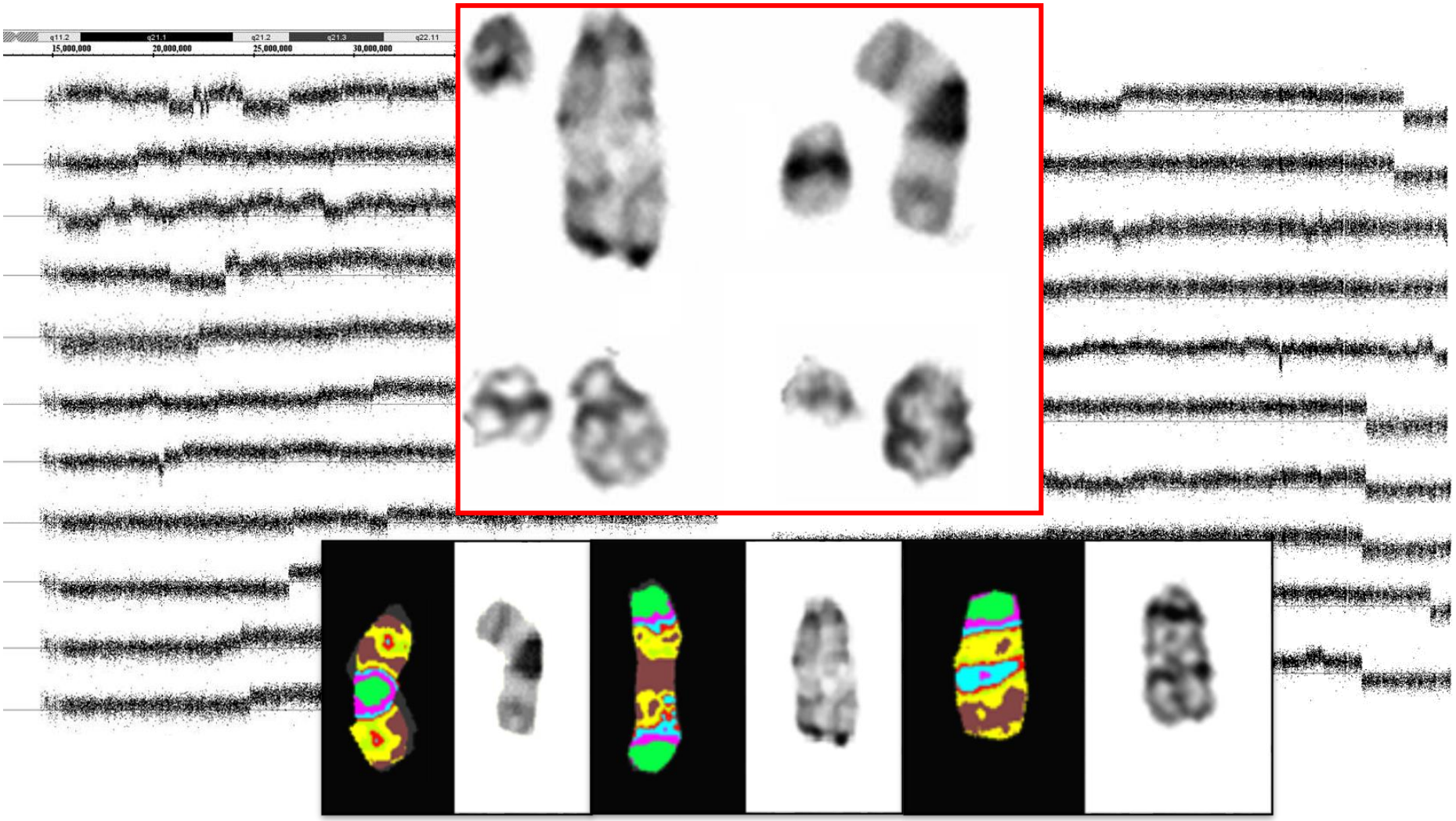


Moorman *et al* 2013 J Clin Oncol

SNP6.0 profiles of chromosome 21 in iAMP21 patients

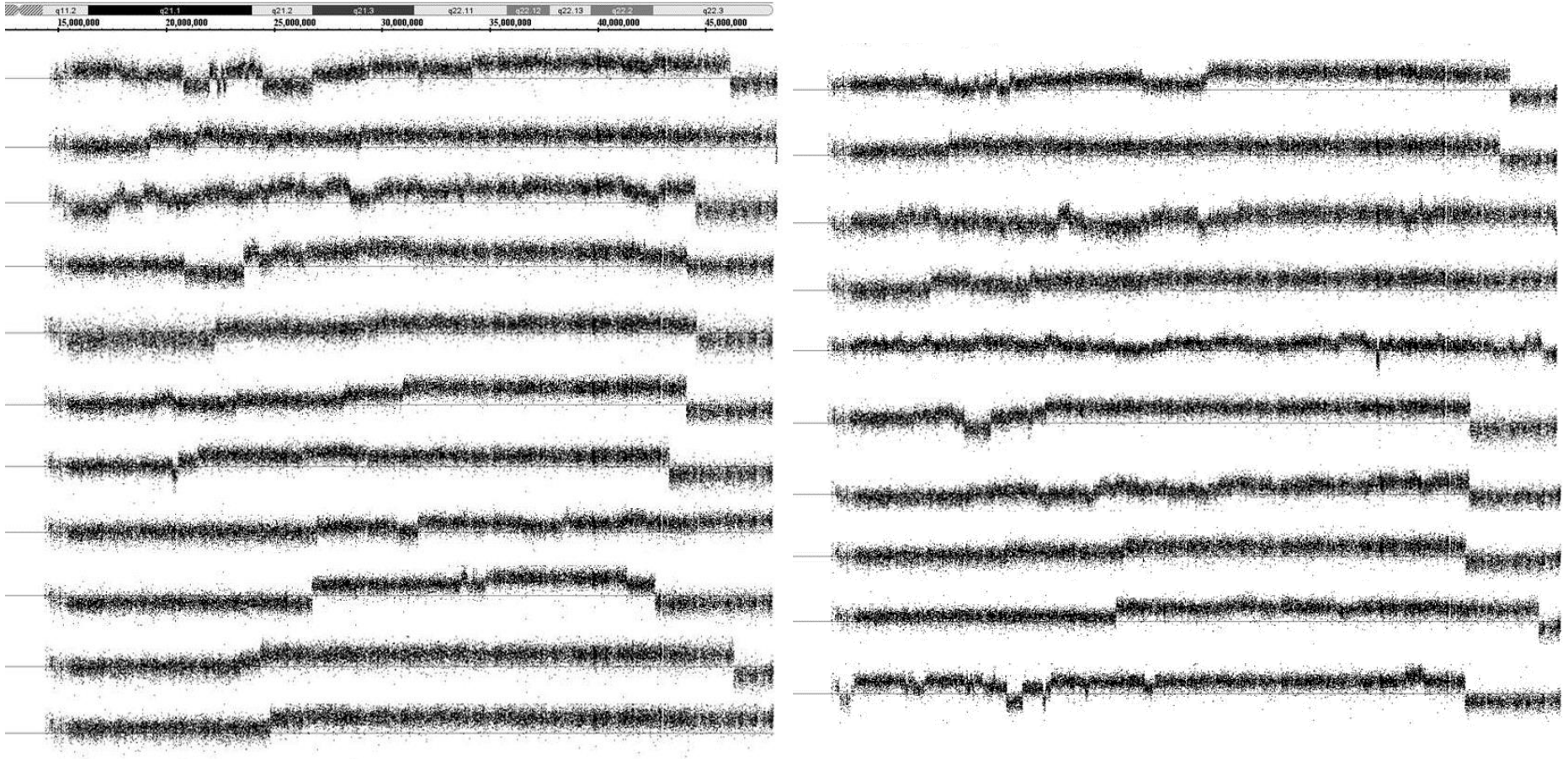


SNP6.0 profiles of chromosome 21 in iAMP21 patients



SNP6.0 profiles of chromosome 21 in iAMP21 patients

RUNX1

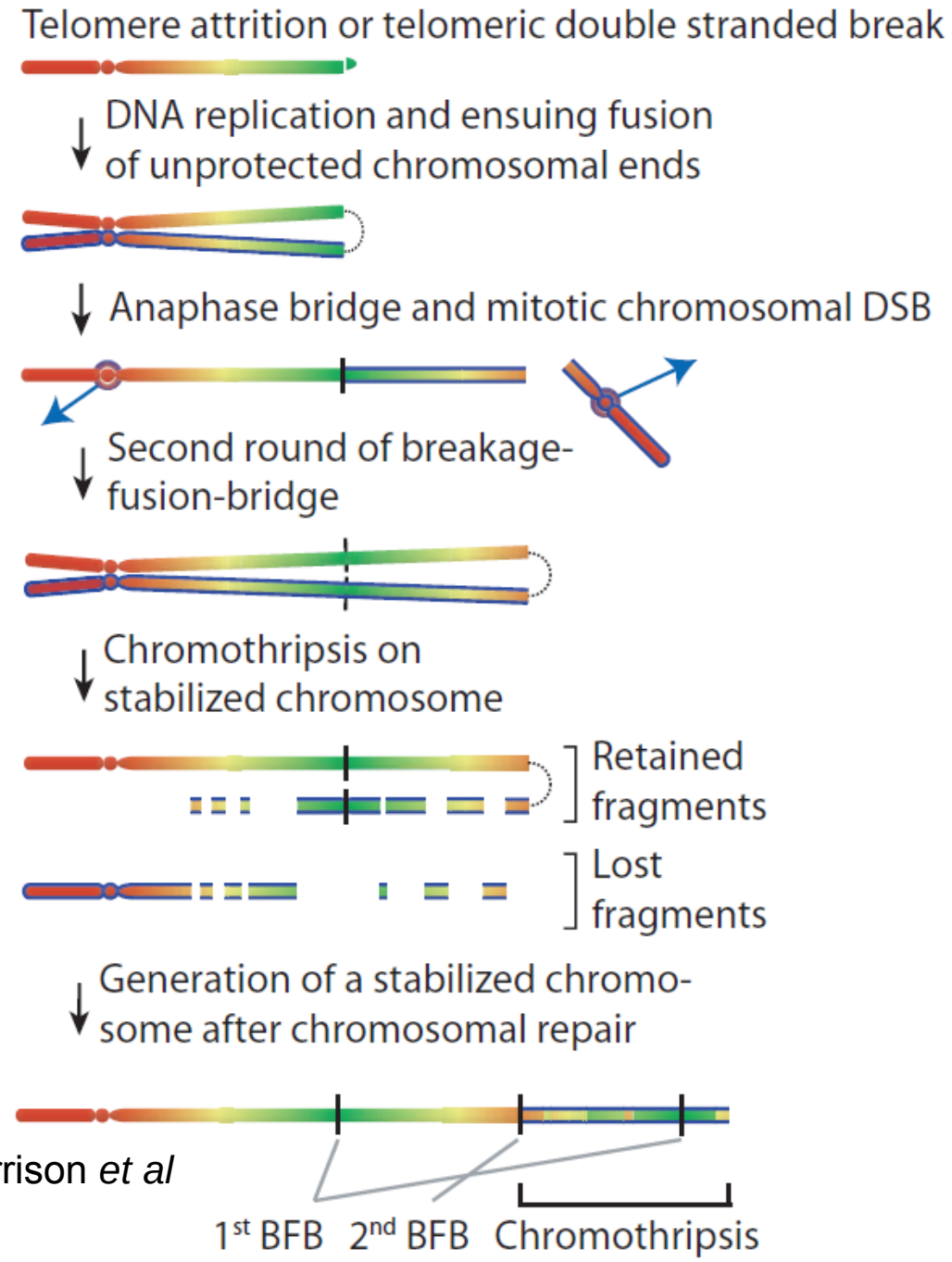


The mechanism

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

wellcome trust sanger institute

The Mechanism



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

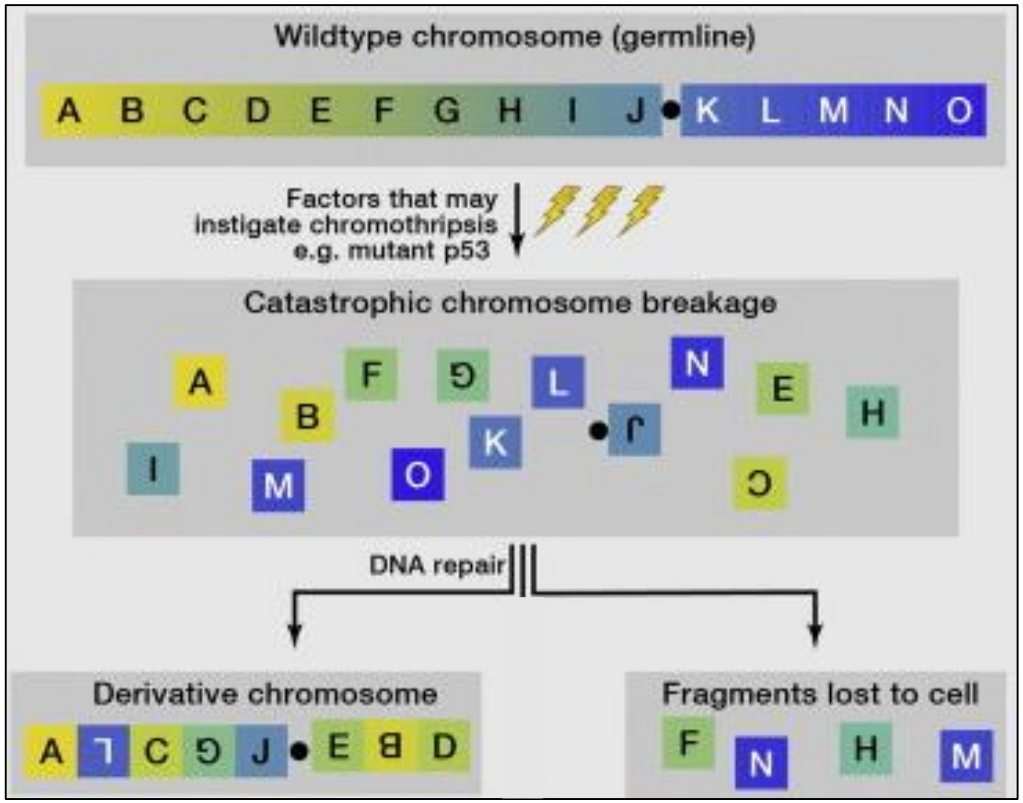
Chromothripsis

- 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

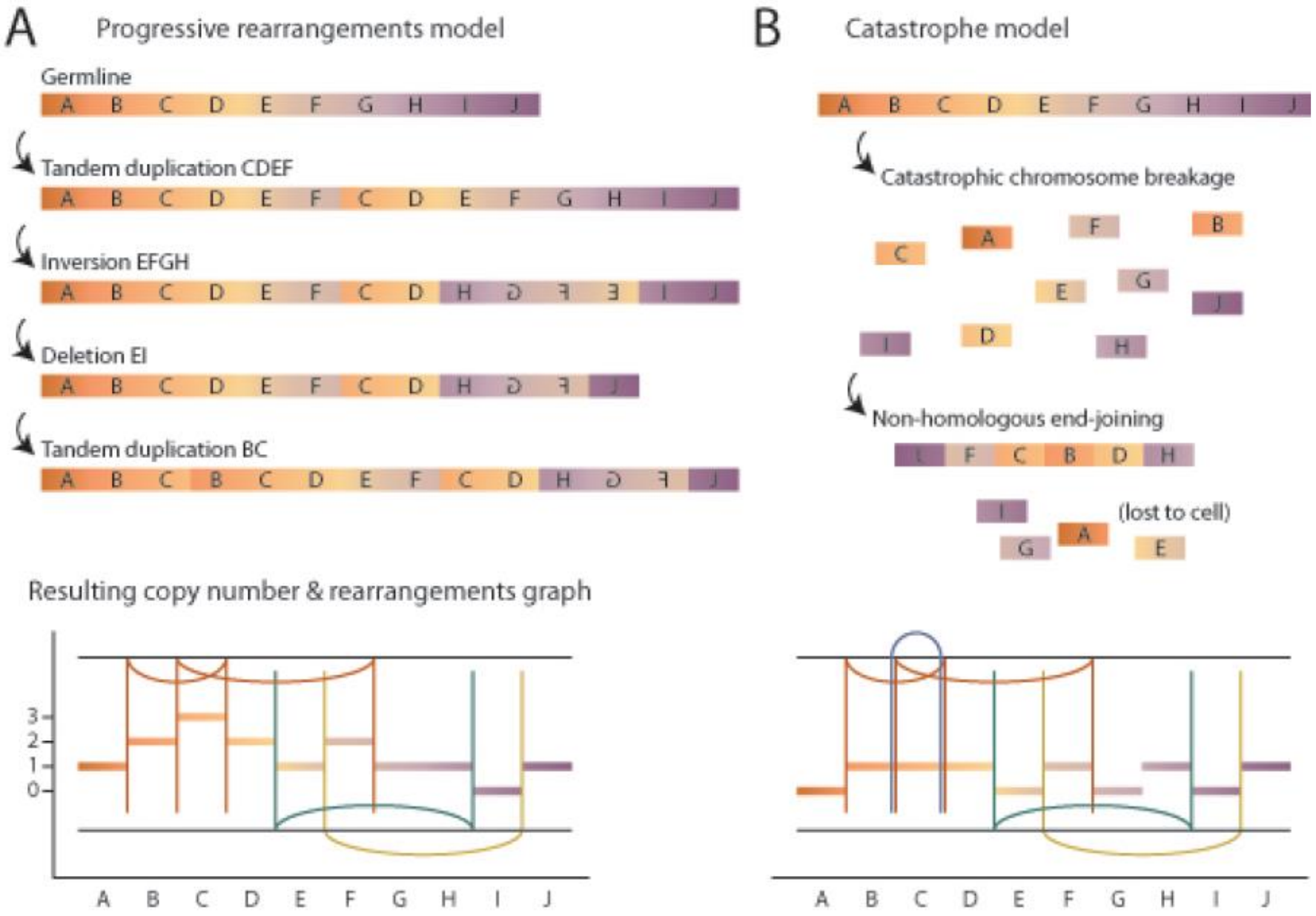
- Cell survives because one or more cancer causing lesion emerges from this genomic mayhem
- Common in cancer (2-3% of all cancers)
- Enriched in certain cancers (~25% bone cancers)
- Rare in acute lymphoblastic leukaemia (ALL)

Chromothripsis



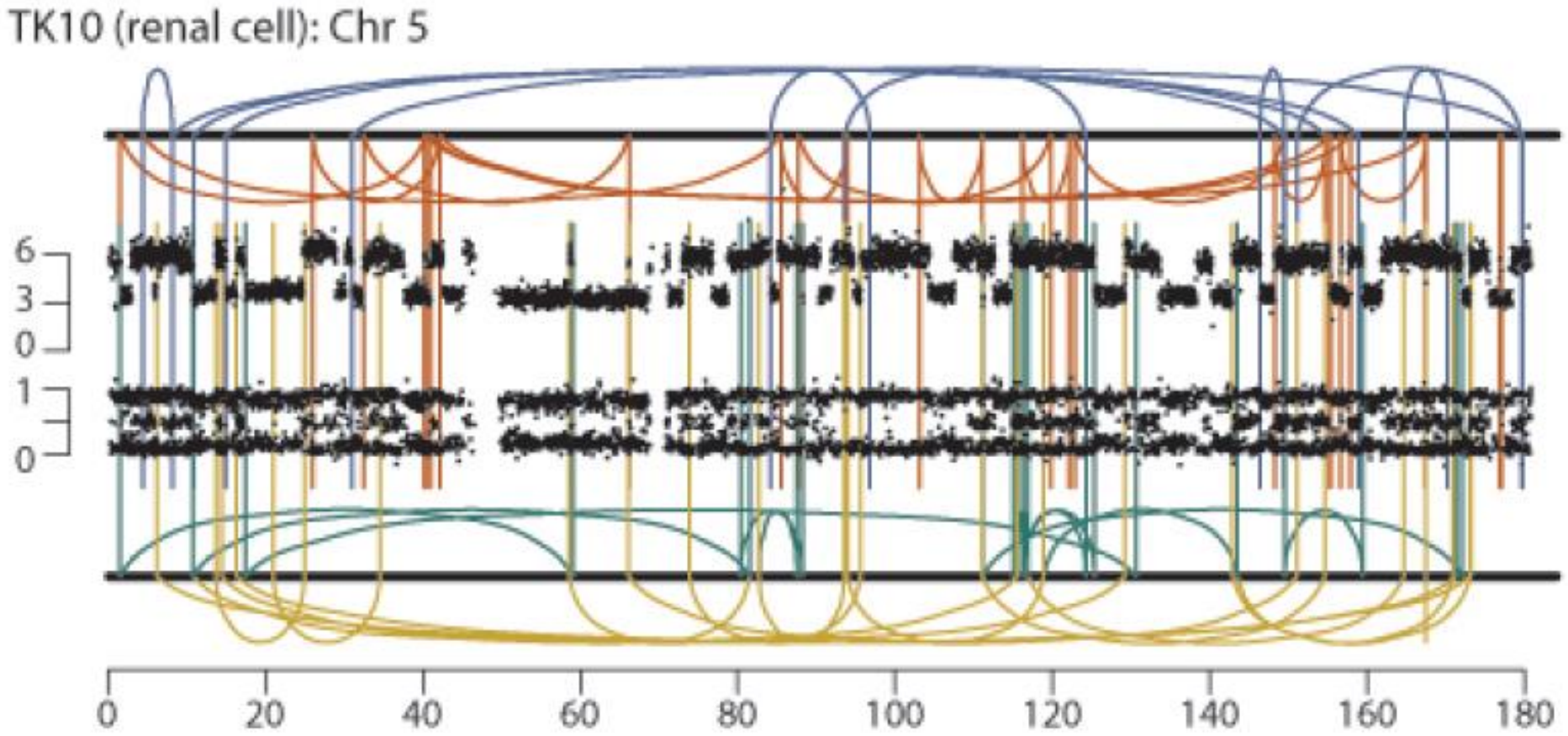
Tumour progression and development

Stephens et al 2010 Cell
Korbel and Campbell, 2013 Cell

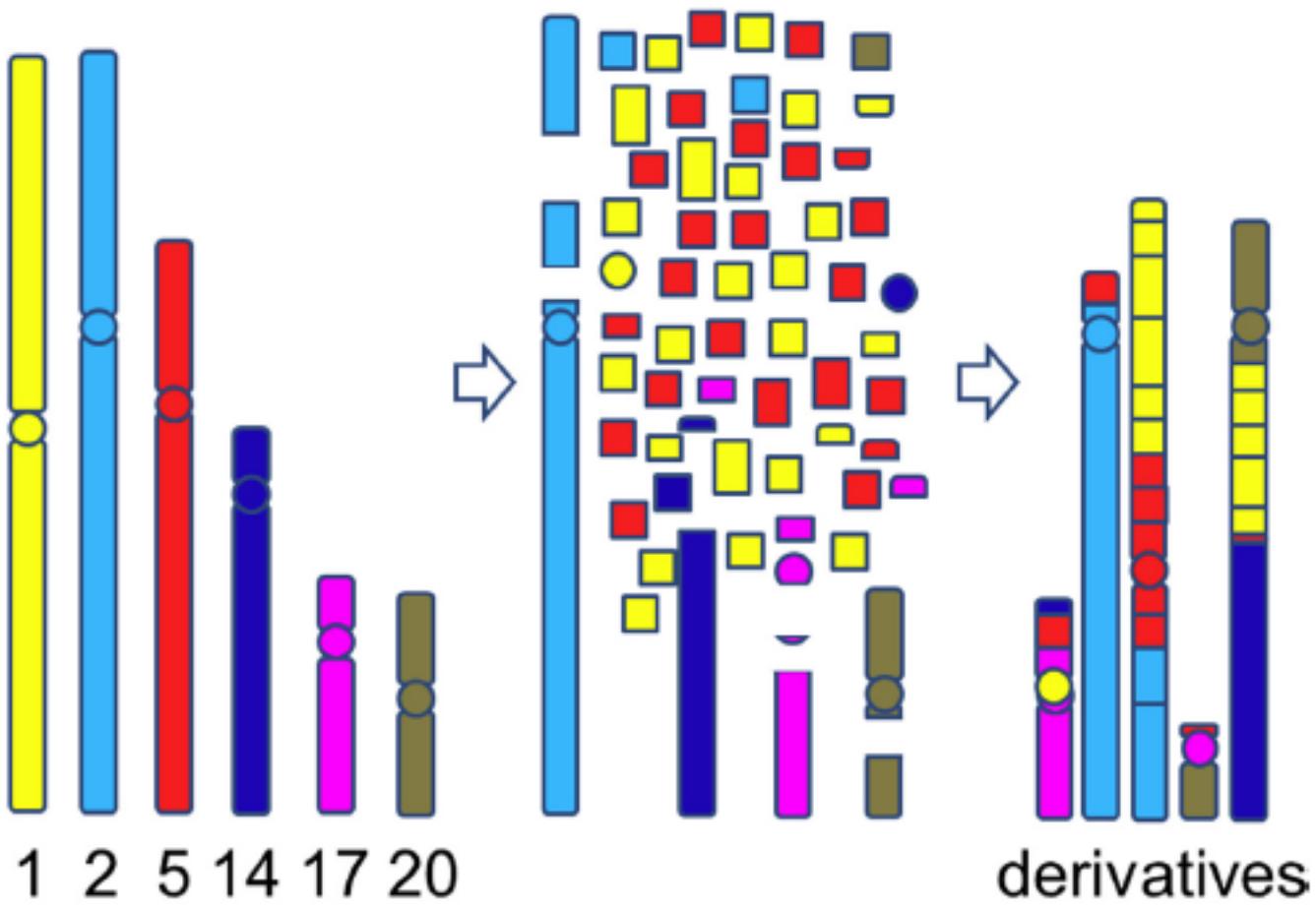


Stephens et al 2010 Cell

Chromothripsis involving a single chromosome

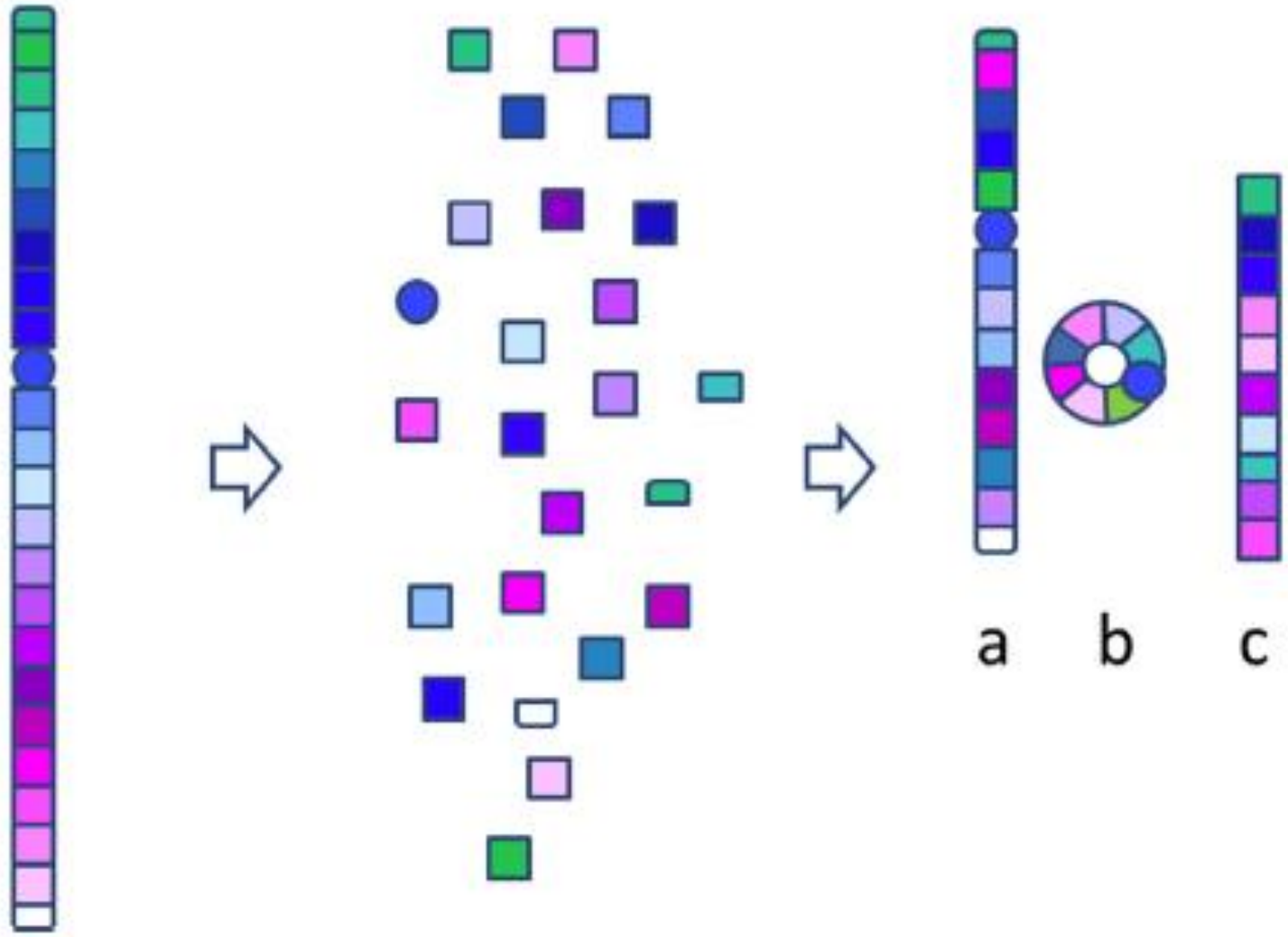


Chromothripsis involving multiple chromosomes

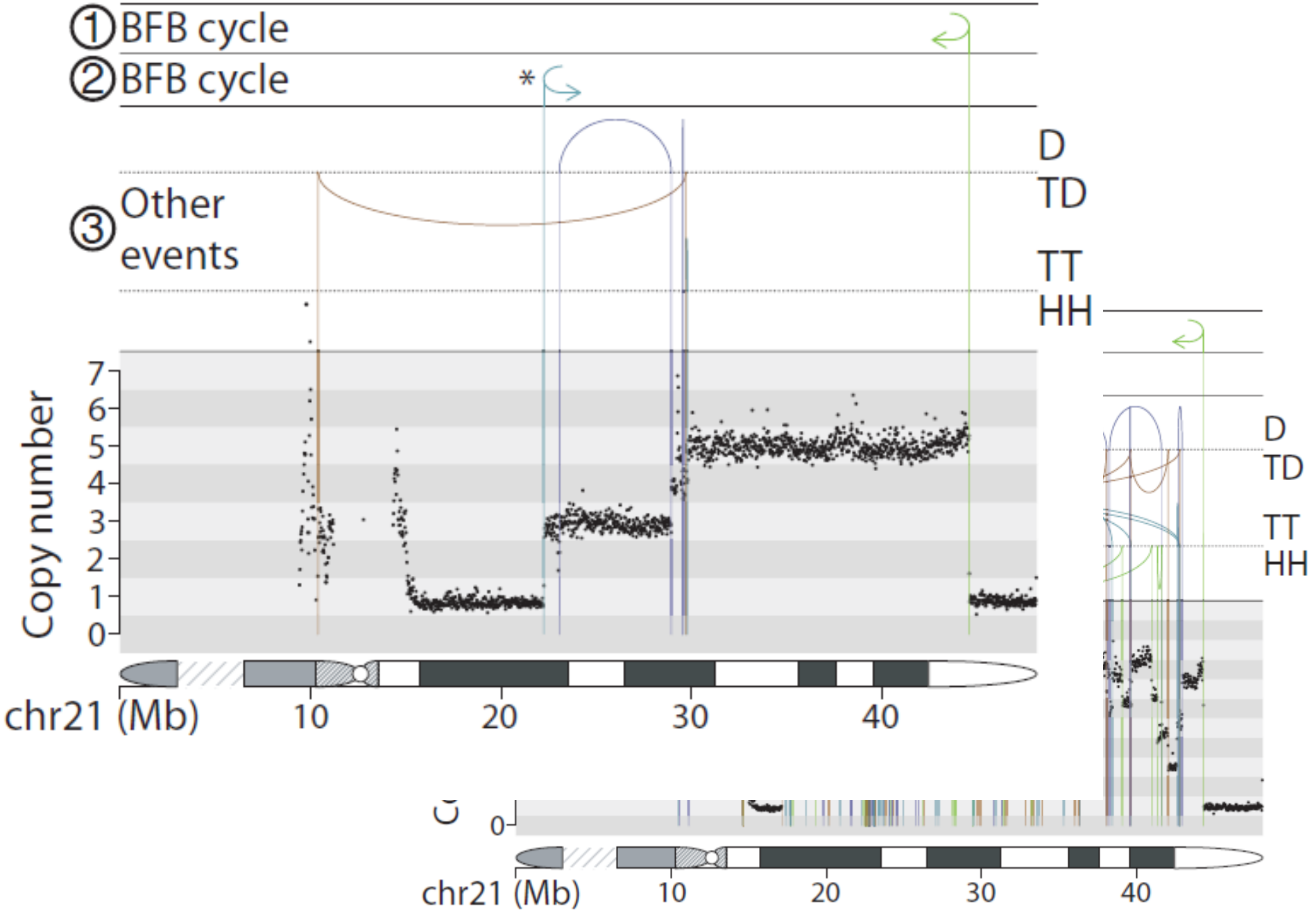


MacKinnon and Campbell 2013 Cancer Genetics

Centromere protects segments

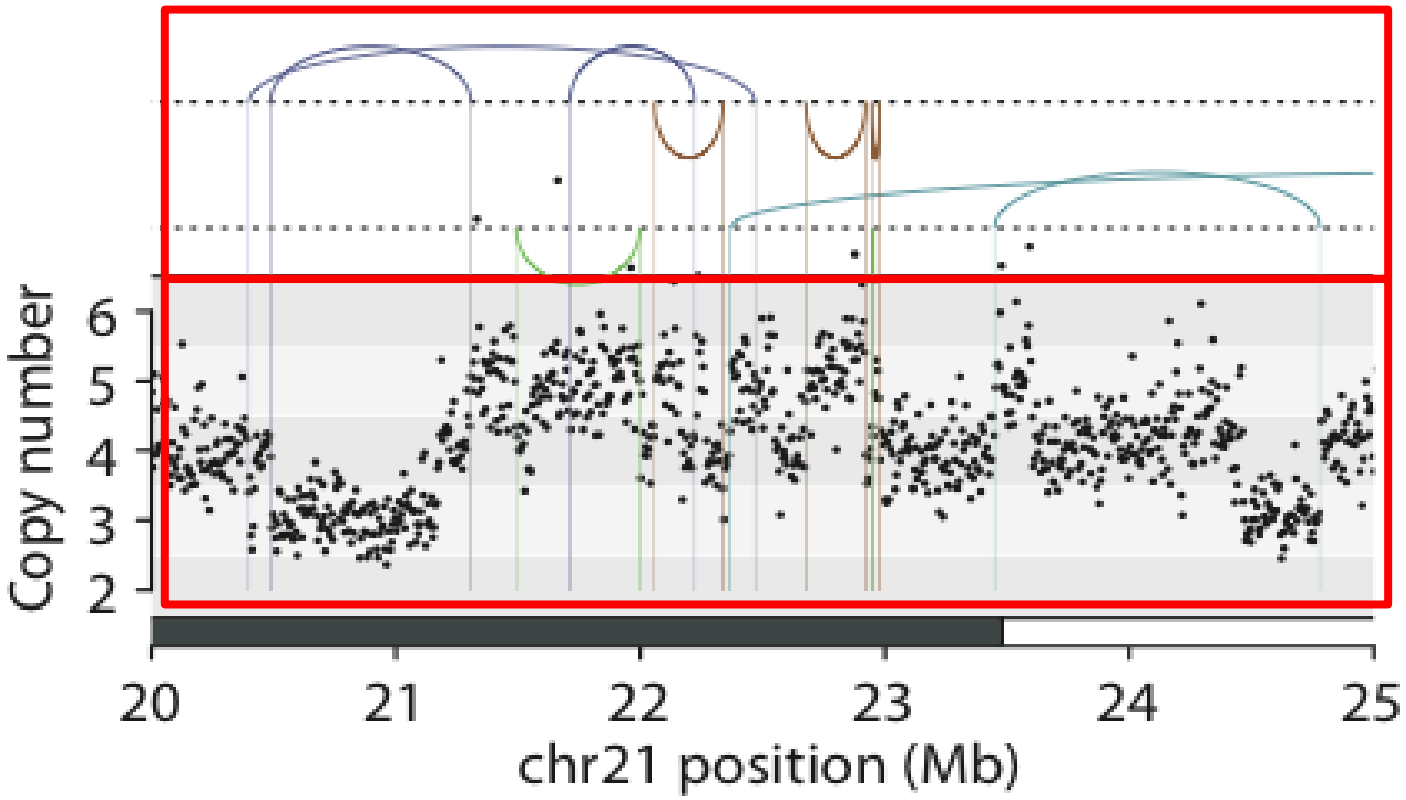


MacKinnon and Campbell 2013 Cancer Genetics

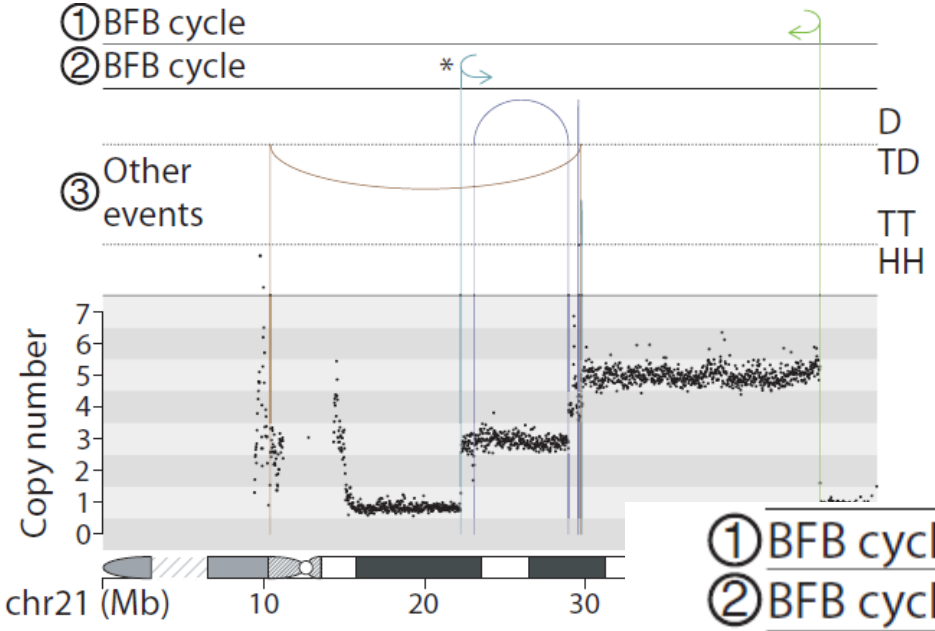

①BFB cycle
②BFB cycle
③Other events
*
D
TD
TT
HH
Copy number
7
6
5
4
3
2
1
0
chr21 (Mb)
10
20
30
40
D
TD
TT
HH
0
chr21 (Mb)
10
20
30
40

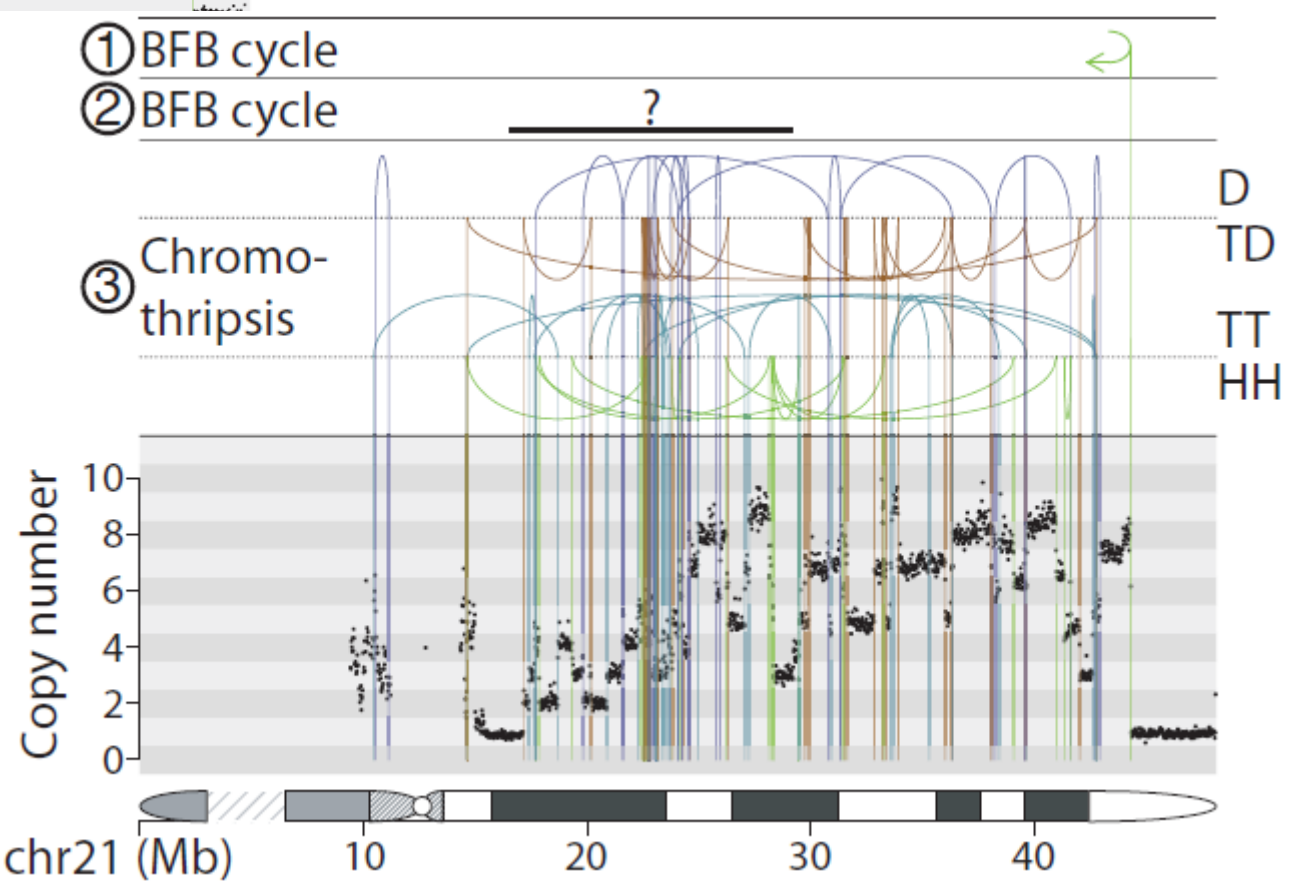
Evidence of chromothripsis in iAMP21

Rearrangements in equal numbers
in all possible orientations



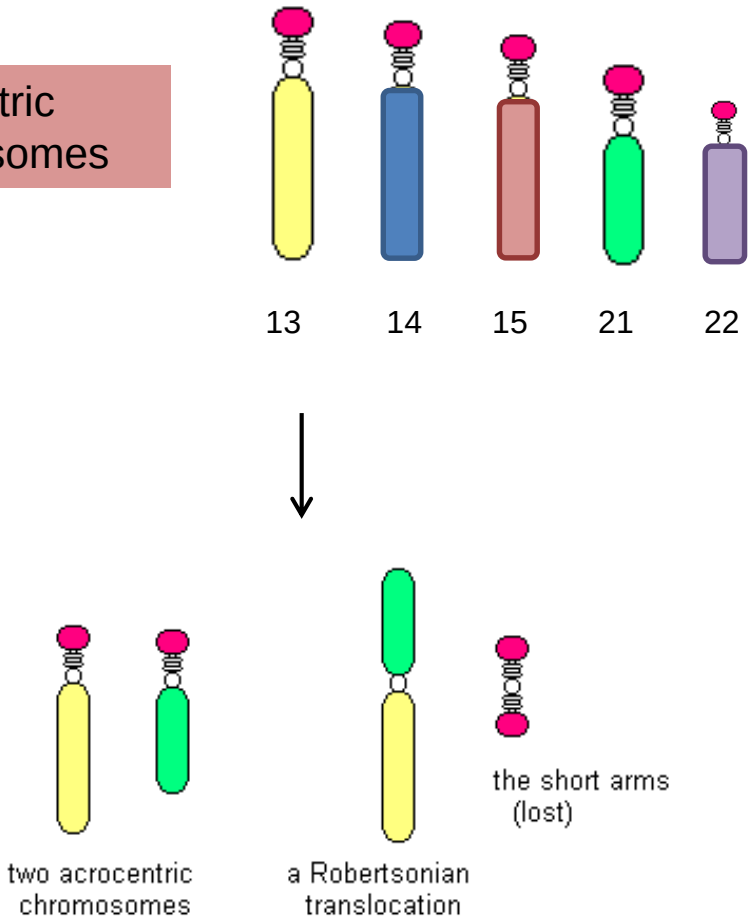
Many copy number changes alternating between two or three states


①BFB cycle
②BFB cycle
*
D
TD
③Other events
TT
HH
Copy number
7
6
5
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



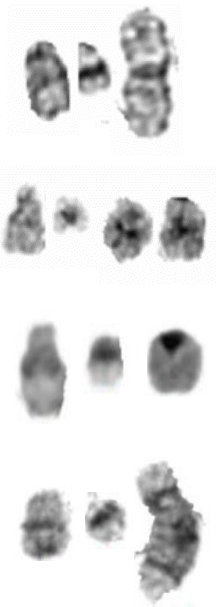
Robertsonian translocation	Incidence
rob(13;14)c	1 in 1300
rob(14;21)c	1 : 12,500
rob(14;15)c	1 : 20,000
rob(13;13)c rob(13;15)c rob(13;22)c rob(14;22)c	1 :50,000
rob(13;21)c rob(15;22)c	1 : 100,000
rob(15;21)c rob(21;21)c rob(21;22)c	1 :100,000-200,000

Prevalence of 1 in 1000

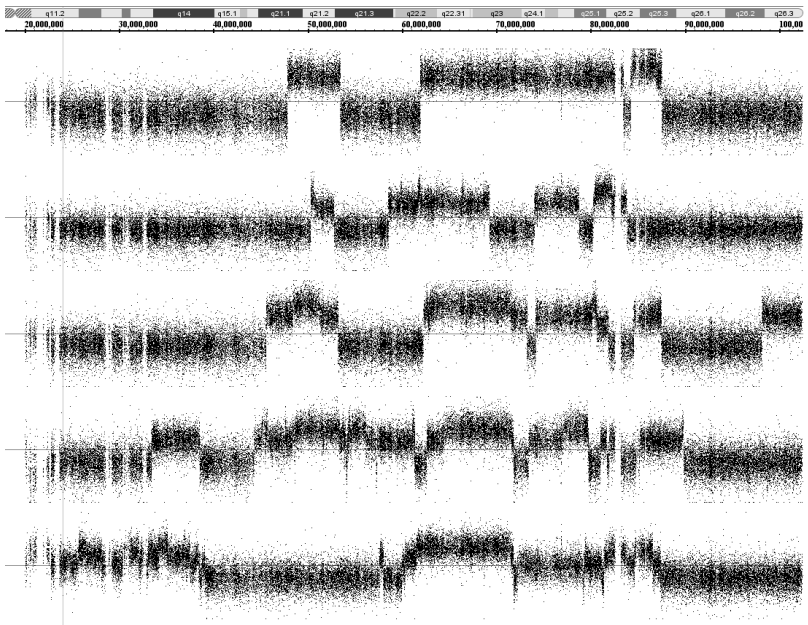
2,700 x increased risk of ALL

Genomic characterisation of rob(15;21)c cases

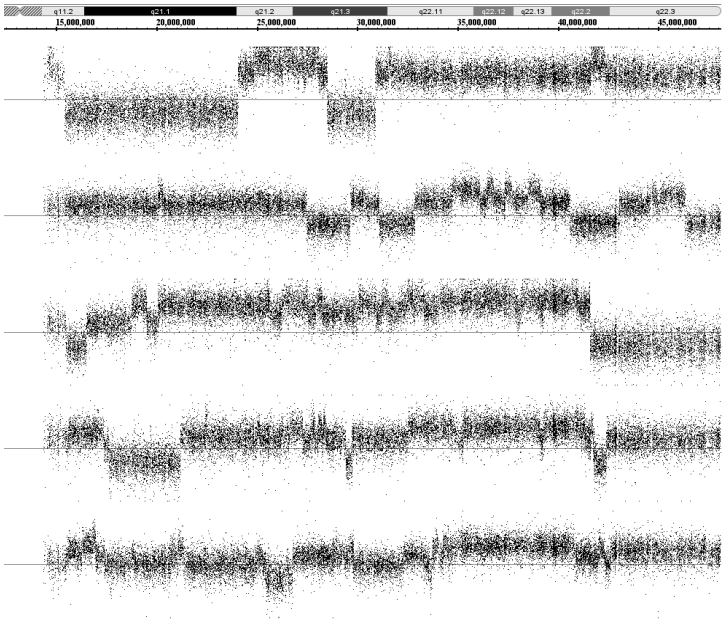
G-banding



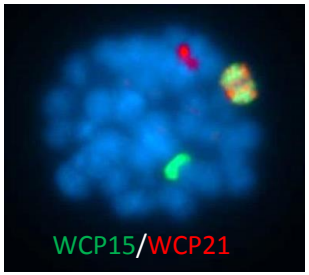
Chromosome 15

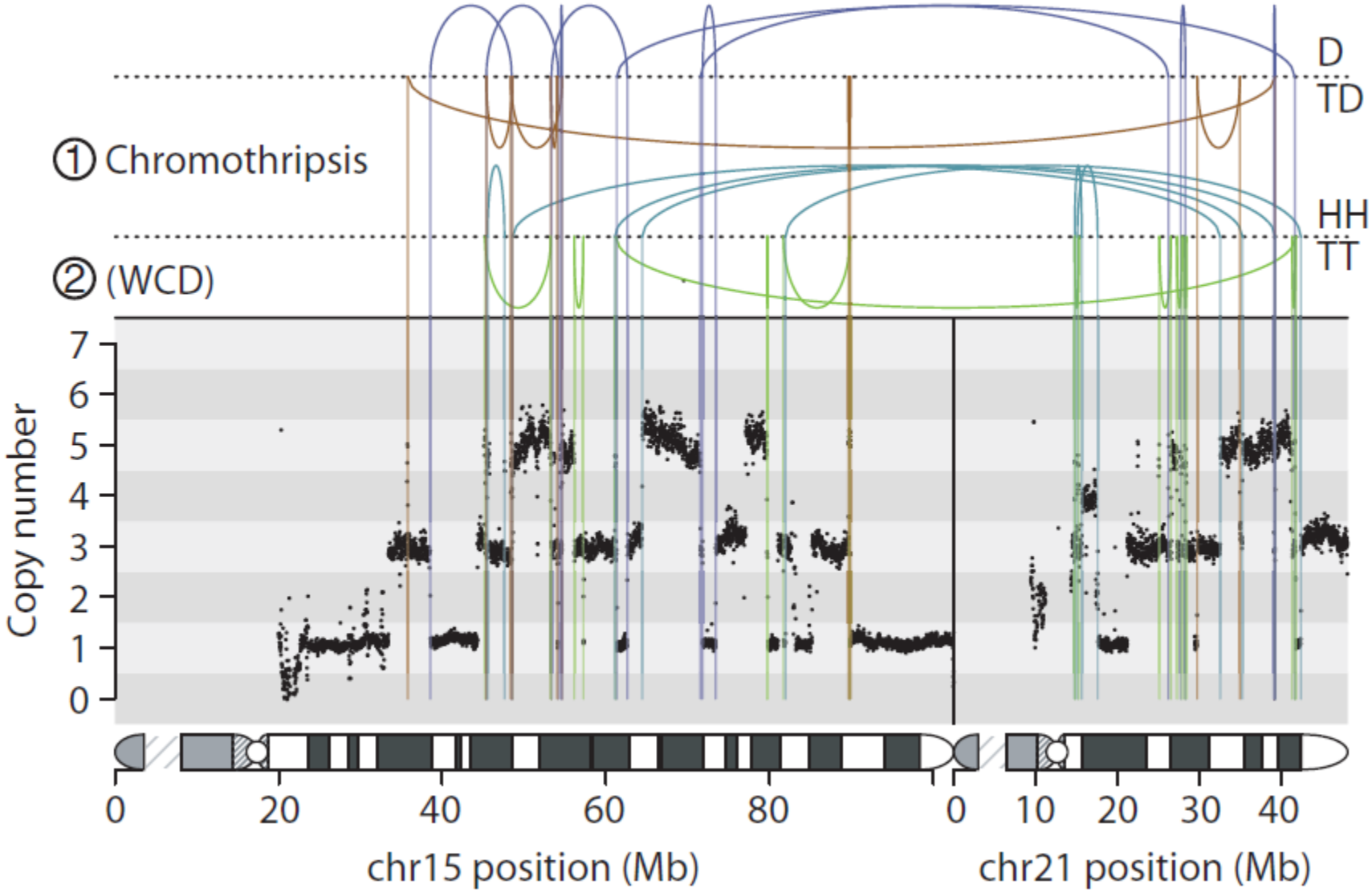


Chromosome 21

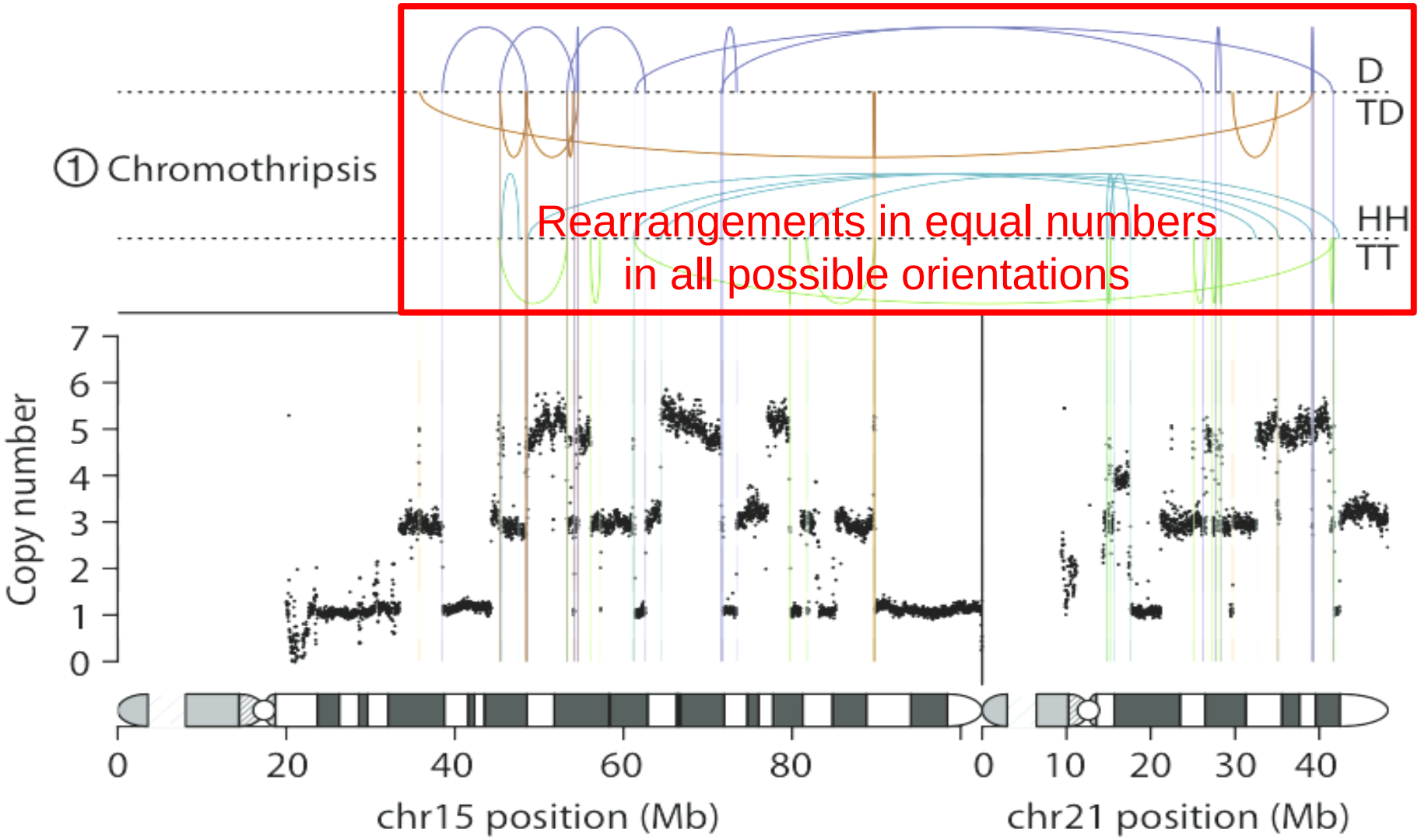


FISH studies confirmed iAMP21 was derived from rob(15;21)c

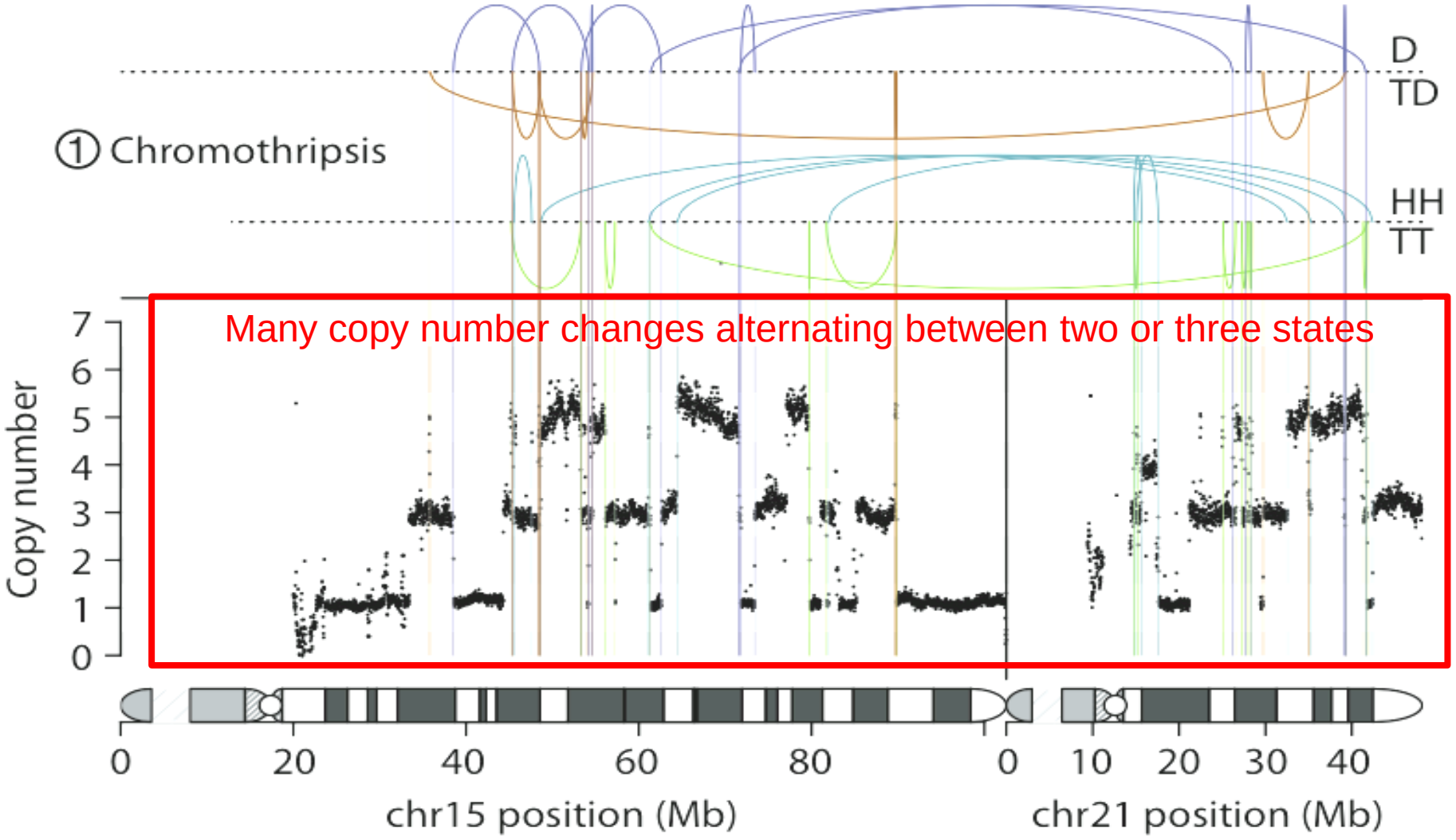



① Chromothripsis
② (WCD)
D
TD
HH
TT
Copy number
7
6
5
4
3
2
1
0
0
20
40
60
80
chr15 position (Mb)
0
10
20
30
40
chr21 position (Mb)

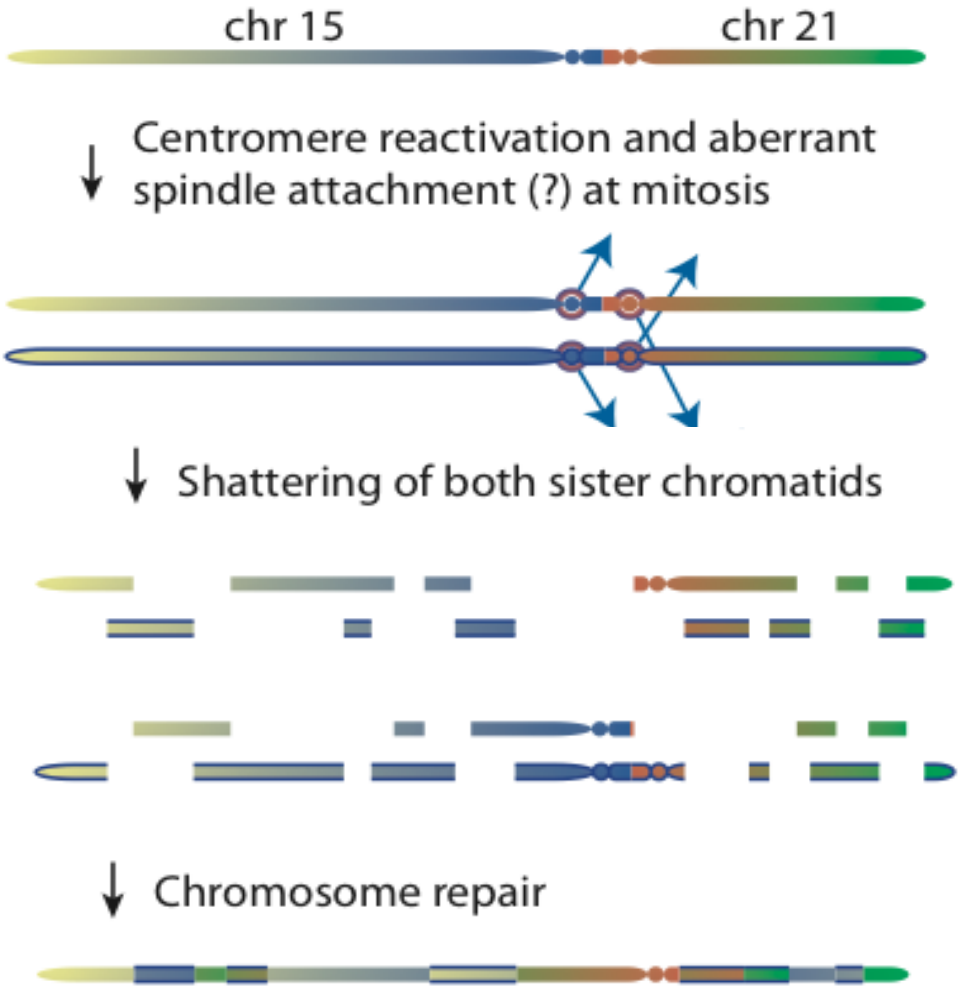
Criteria for Chromothripsis



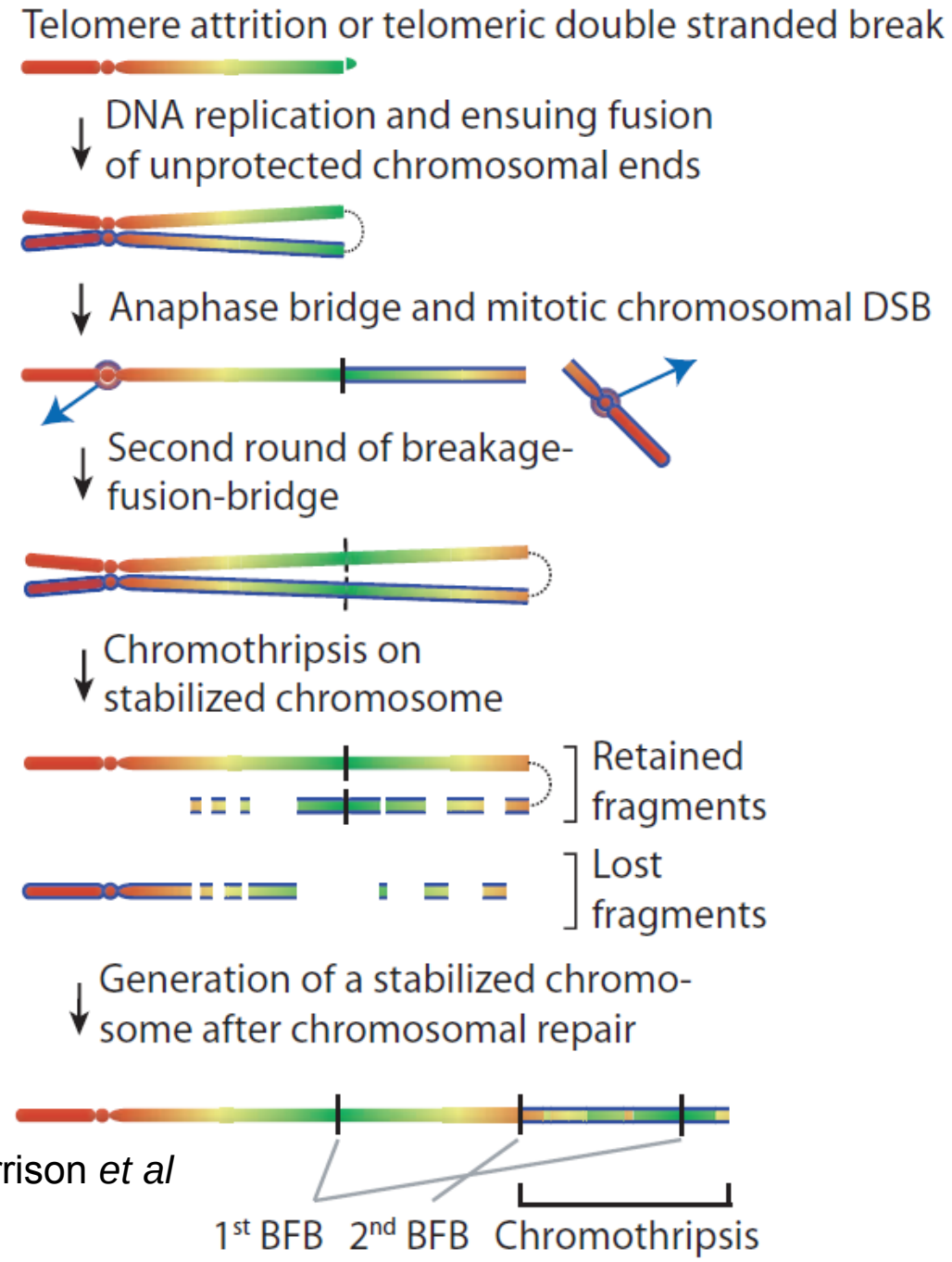
Criteria for Chromothripsis



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

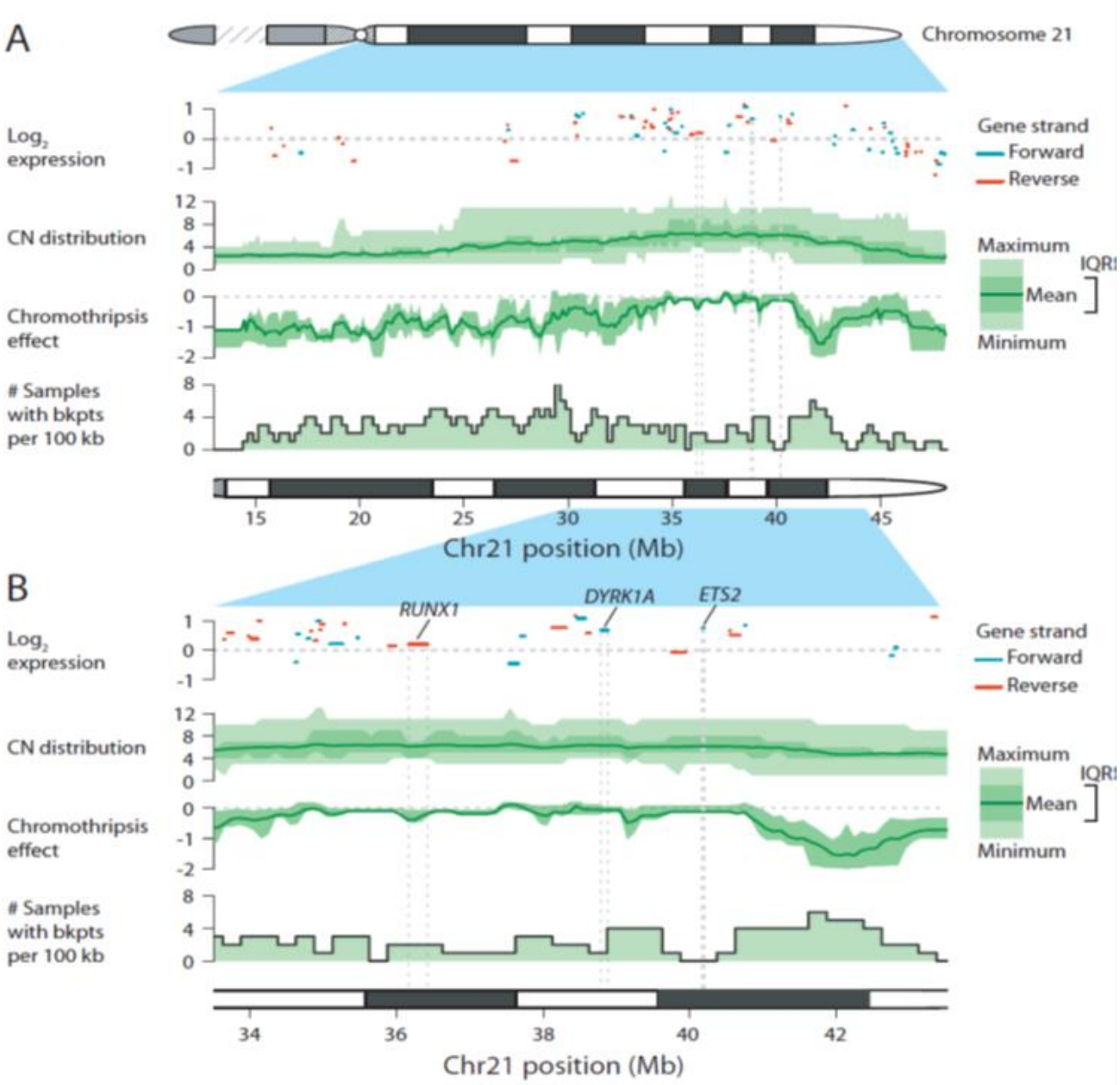
Genetic alterations behind der(15;21) iAMP21

Constitutional dicentric chromosome

Chromothripsis

Stabilisation of the derivative chromosome

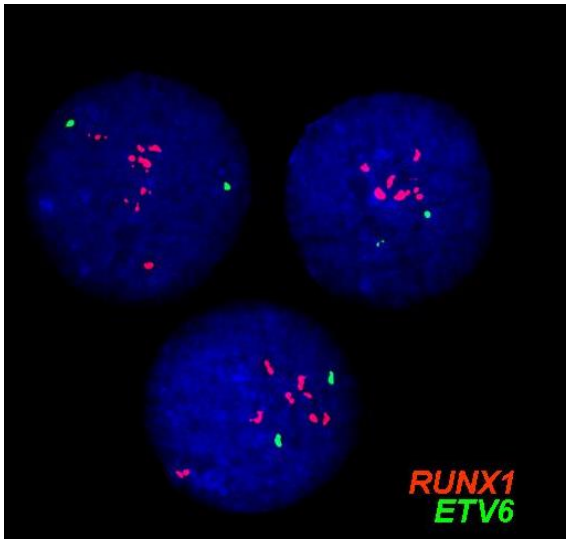
Highly amplified region is protected from chromothripsis



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

wellcome trust sanger institute

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