Jumping Translocations 1q12 Contribute to Copy Number (CN) Variations in Multiple Myeloma (MM): Unexpected CN Gains Involving Duplications and Translocations of Receptor Chromosomes

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Jumping Translocations 1q12

- Jumping 1q translocations (JT1q12) occur when the whole 1q acts as a donor chromosome and translocates to different receptor chromosomes (RC)

- Two types of JT1q12:
  - Telomeric JT1q12: translocates to the telomere of a RC
  - Whole-arm JT1q12: translocates to the pericentromeric region of RC causing a deletion and CN loss in RC

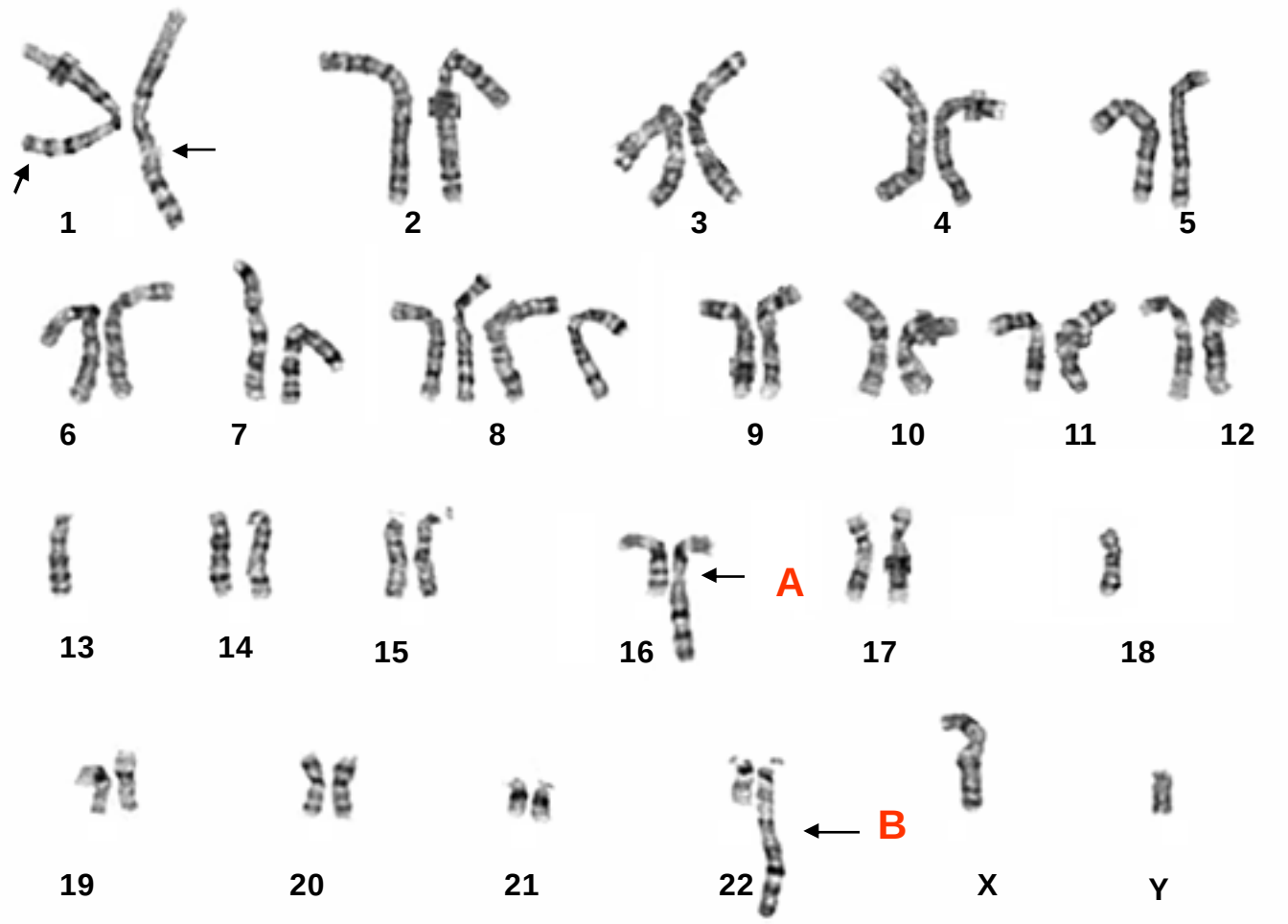
- By interphase FISH the frequency of JT1q21 increases from 43% in overt myeloma to 72% at relapse

- New type of JT1q12 which can apparently duplicate and translocate the distal segment of a RC, thus increasing CN of a segment of the receptor chromosome

Patients and Methods

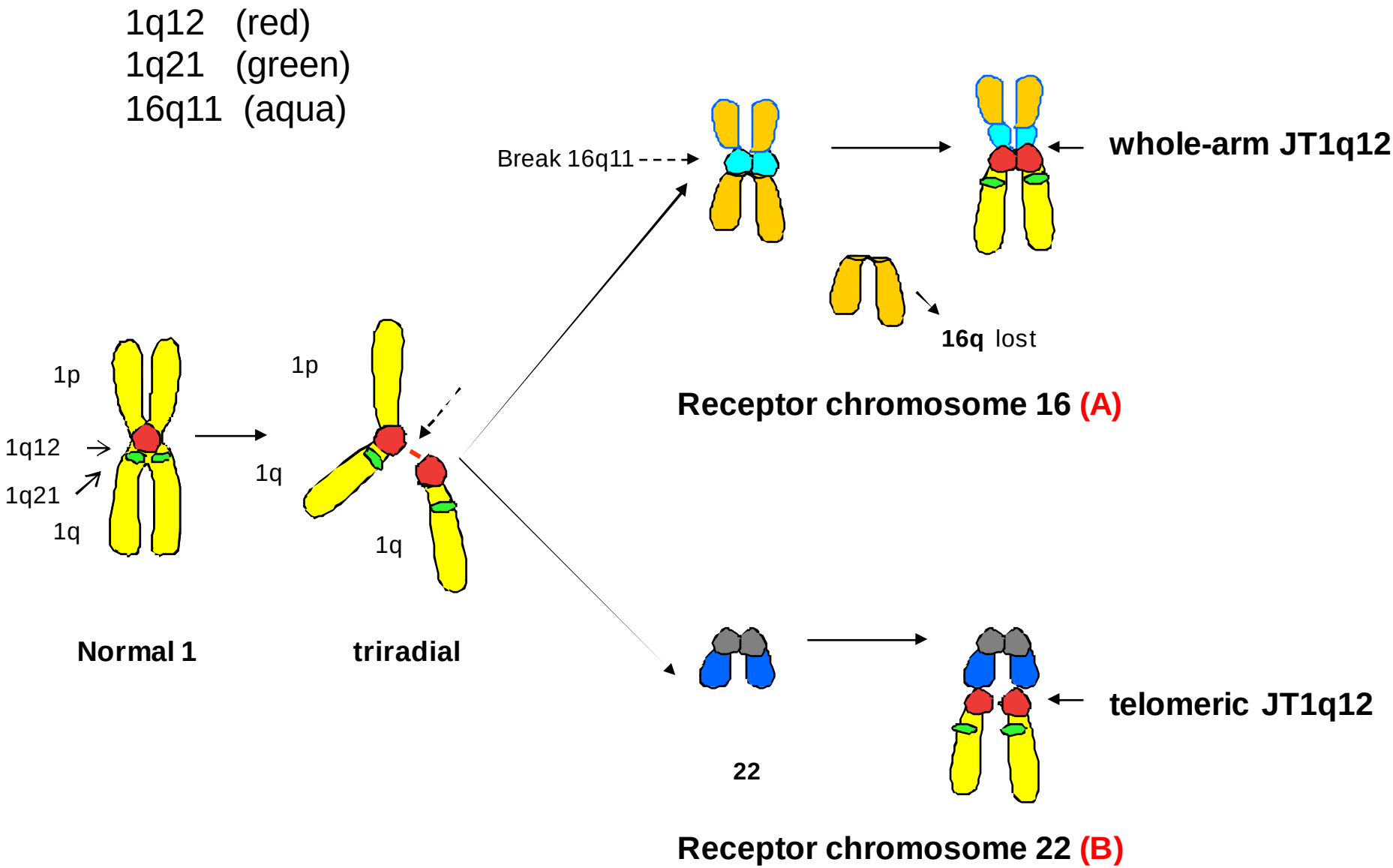
- 60 patients showing gain of 1q by G-bands were studied by FISH and SKY
    - 35 cases showed deletions in RC caused by JT1q12
        - 11 cases with 16q-
        - 6 cases with 19q-
        - 3 cases with 6q-
        - 2 cases each with 5q- and 8p-
- 4 cases showed unexpected duplications and translocations in RC and associated CN gains
    - Gain of 18q BCL2 (Case # 1)
    - Gain of 8q cMYC (Case # 2)
    - Gain of 16q11 (Case # 3)

Jumping translocations (JT1q12)



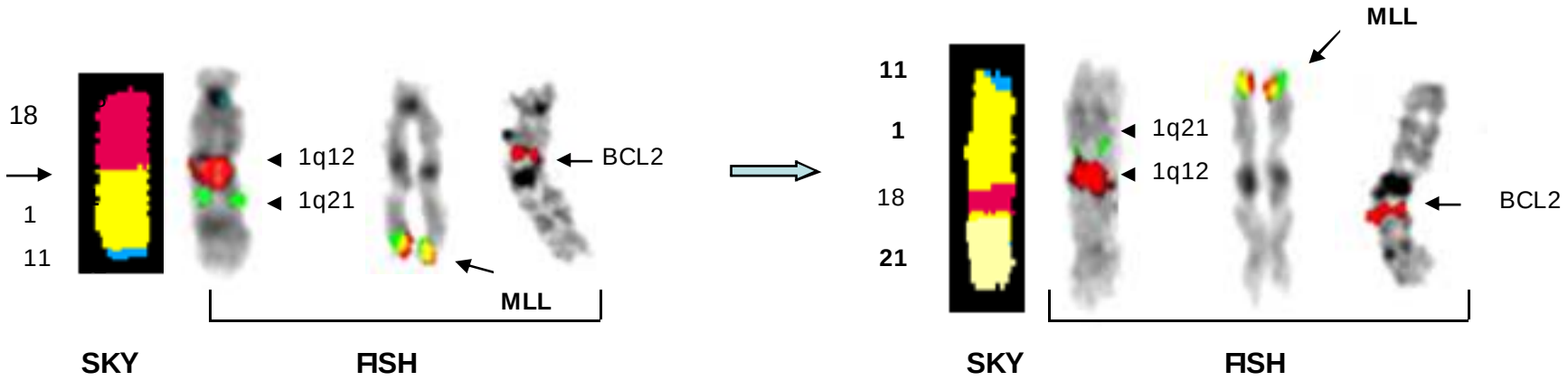
Two types of JT1q12: (A) whole-arm JT1q12 to the centromere of 16 (CN loss), and (B) telomeric JT1q12 to the distal end of chromosome 22

Two Types of JT1q12



Telomeric JT1q12 to 18q

Case # 1



JT1q12 to 18q → **JT 1q12 to 21p**

First jump

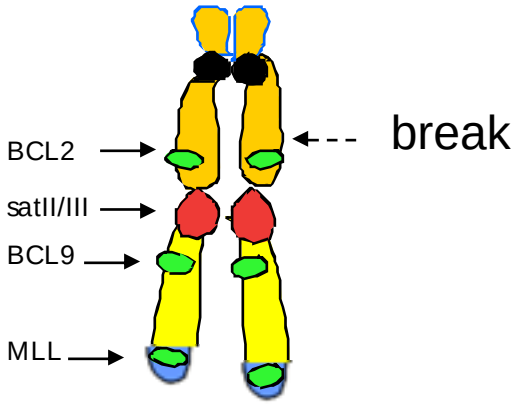
CN 1q21 = 4
CN BCL2 = 2
CN MLL = 4

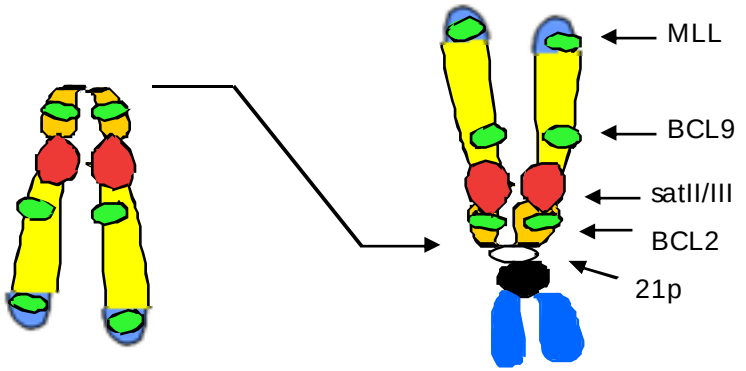
Second jump

CN 1q21 = 5
CN BCL2 = 3
CN MLL = 5

Telomeric JT1q12 to 18q

Duplication and translocation of BCL2





telomeric JT1q12 to 18q

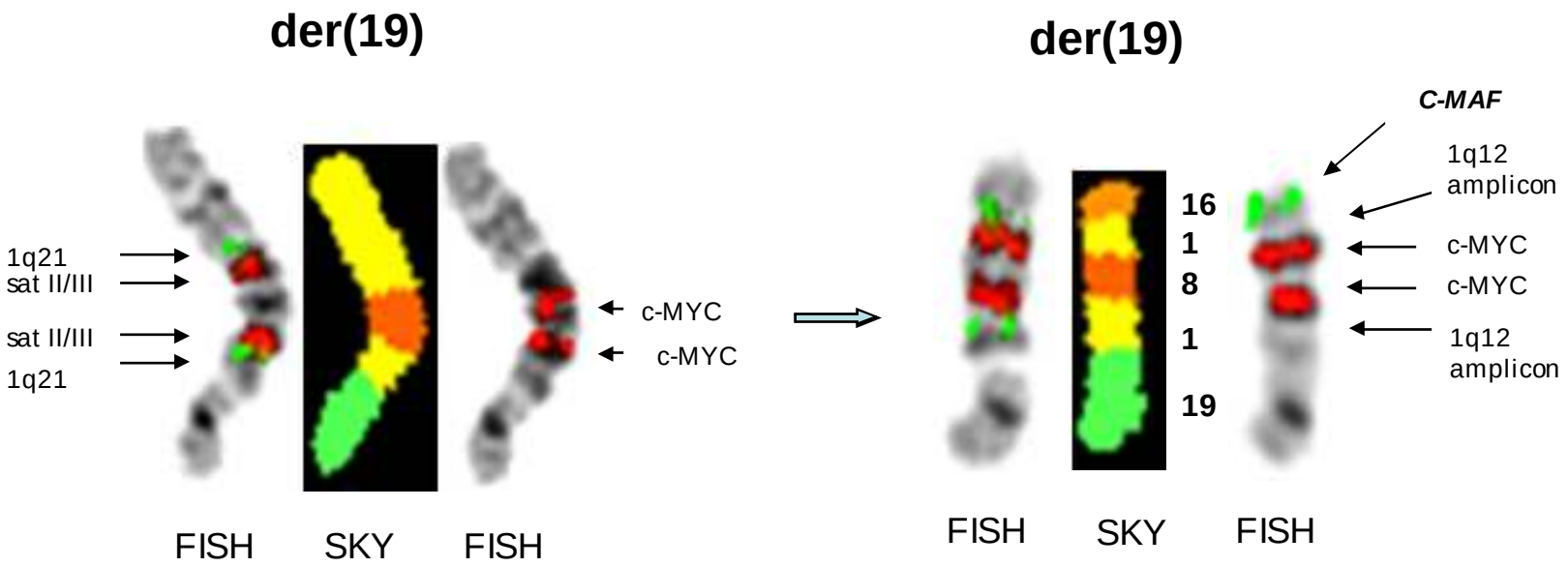
Second JT1q12 to 21p

CN 1q21 = 4
CN BCL2 = 2
CN MLL = 4

CN 1q21 = 5
CN BCL2 = 3
CN MLL = 5

Telomeric JT1q12 to 8q

Case # 2

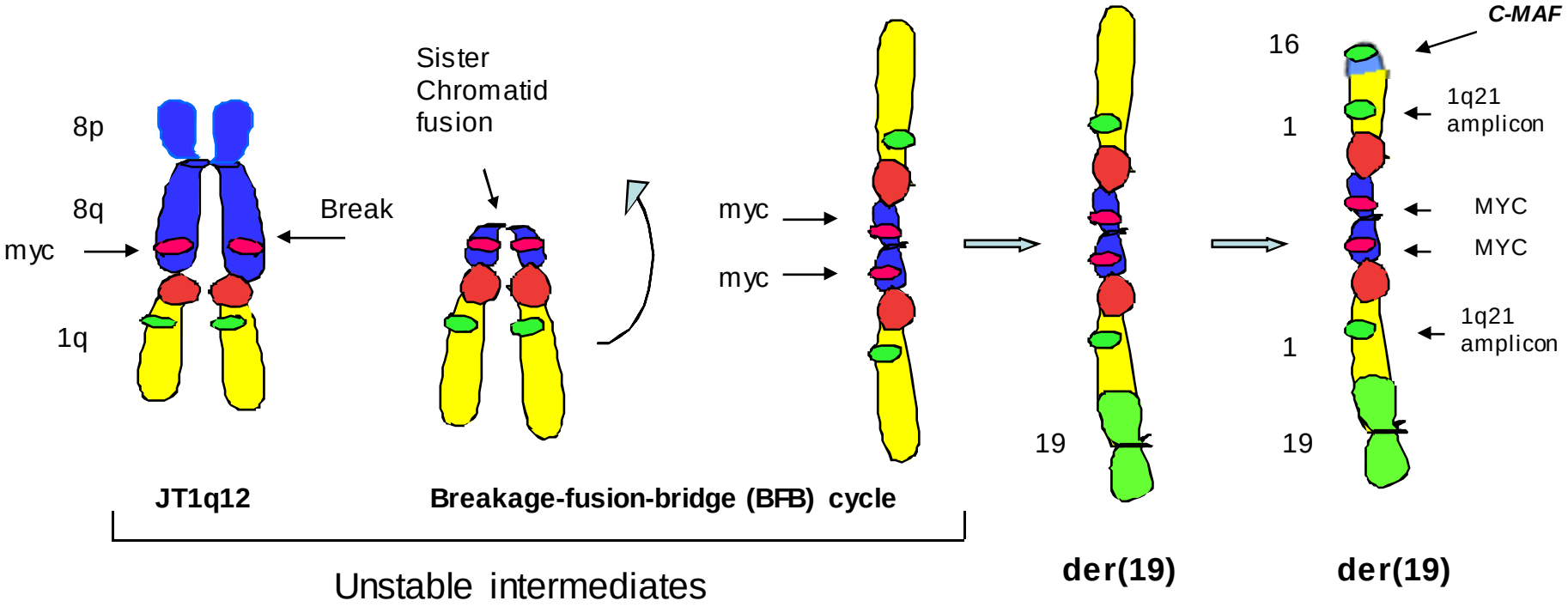


CN 1q21 = 13
CN cMYC = 12

CN 1q21 = 13
CN cMYC = 12

Telomeric JT1q12 to 8q

Proposed events in duplication and translocation of *cMYC*



Whole-arm unbalanced JT1q12 to 16q11

(Case # 3)

Subclone A

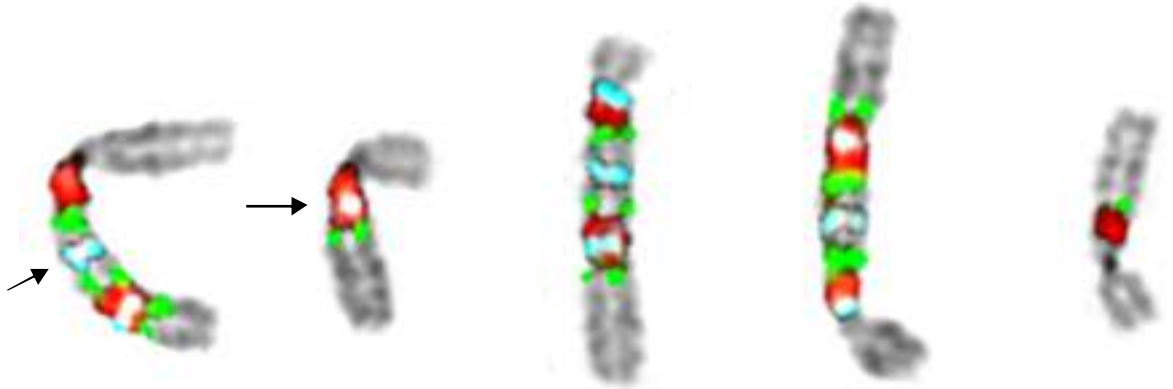
February 2009

1 **del 1p** **der(1;16)** **der(11)** **der(18)**

CN 1q21 = 9
CN 16q11 = 6
CN 16q- = 1
CN 11p- = 1
CN 18p- = 1

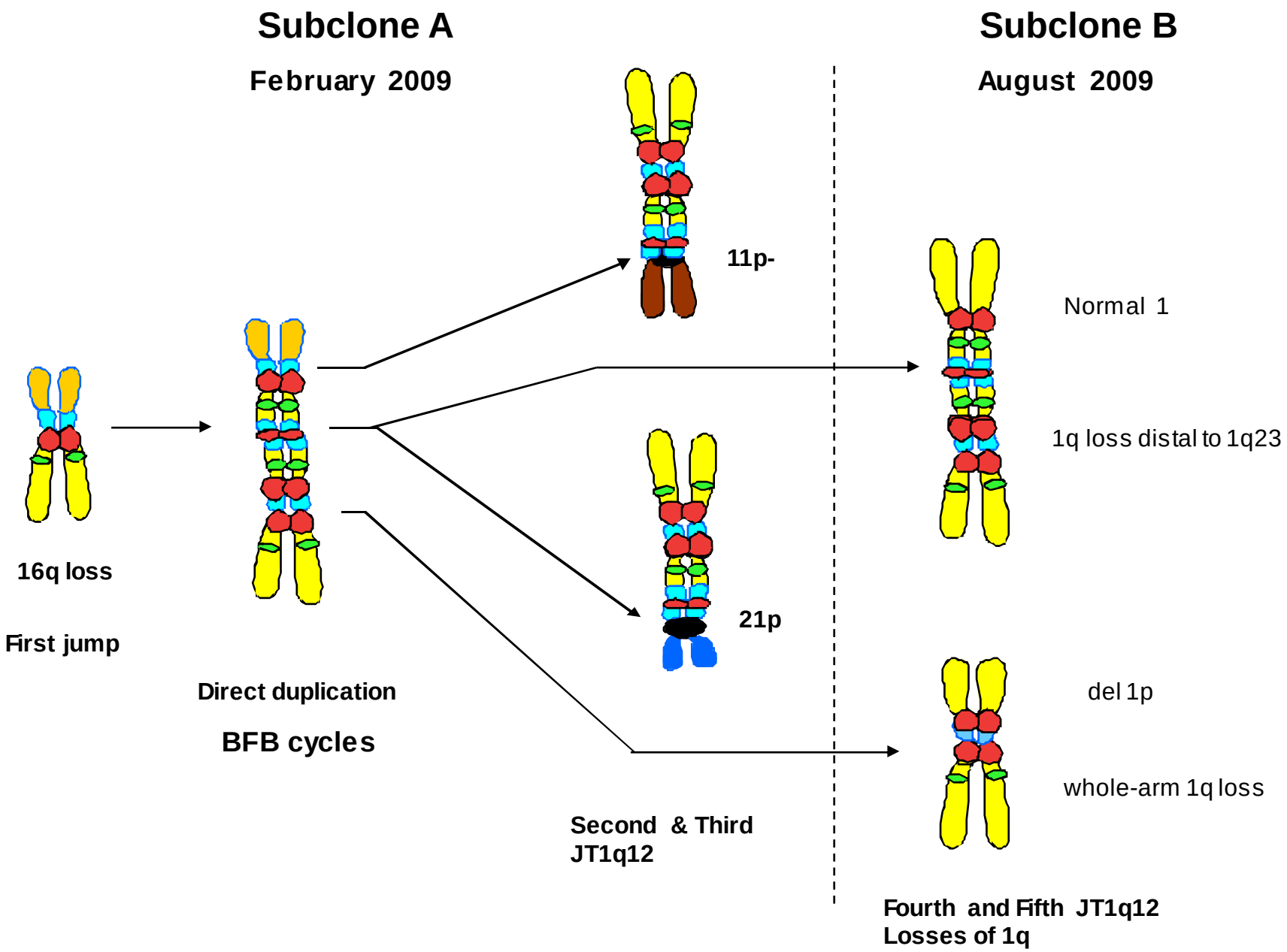
Subclone B

August 2009



1 **del 1p** **der(1;16)** **der(11)** **der(18)**

CN 1q21 = 11
CN 16q11 = 9
CN 16q- = 1
CN 11p- = 1
CN 18p- = 1


Subclone A
February 2009
Subclone B
August 2009
11p-
Normal 1
1q loss distal to 1q23
16q loss
First jump
Direct duplication
BFB cycles
21p
del 1p
whole-arm 1q loss
Second & Third
JT1q12
Fourth and Fifth JT1q12
Losses of 1q

Multiple mechanisms contribute to CN variations relating to JT1q12

- JT1q12 pericentromeric heterochromatin duplicates segments both proximal and distal (Cases # 1, 2 & 3)
- JT1q12 translocations and BFB cycles interact to amplify chromosome segments into ladder-like structures composed of equally spaced inverted duplications (Cases # 2 & 3)
- The same JT1q12 can cause deletions in multiple RC, and help explain uniparental disomy of 1q (Case # 3)
- JT1q12 aberrations are inherently unstable and may be lost as micronuclei in subclones (Case # 3)

Summary

- JT1q12 and amplification of 1q21 are mediated by unstable pericentromeric heterochromatin
- Telomeric JT1q12 are usually associated only with CN gain of the 1q21 amplicon
- Whole-arm JT1q12 are associated with CN gain of 1q21 amplicon but also cause deletions in RC
- JT1q12 aberrations can duplicate and translocate non-homologous chromosome segments resulting in multiple CN variations in RC