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# Chromosome Changes in FA: What are they and what do they mean?

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# Chromosomes are prepared from dividing cells

- Some cells need to be “stimulated” to divide (white blood cells)
  - Some cells divide spontaneously (bone marrow cells)
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The dividing cells that contain the chromosomes are prepared on glass slides, treated and stained to reveal a G-banding pattern

(G = Giemsa – a common stain used for preparing chromosomes)

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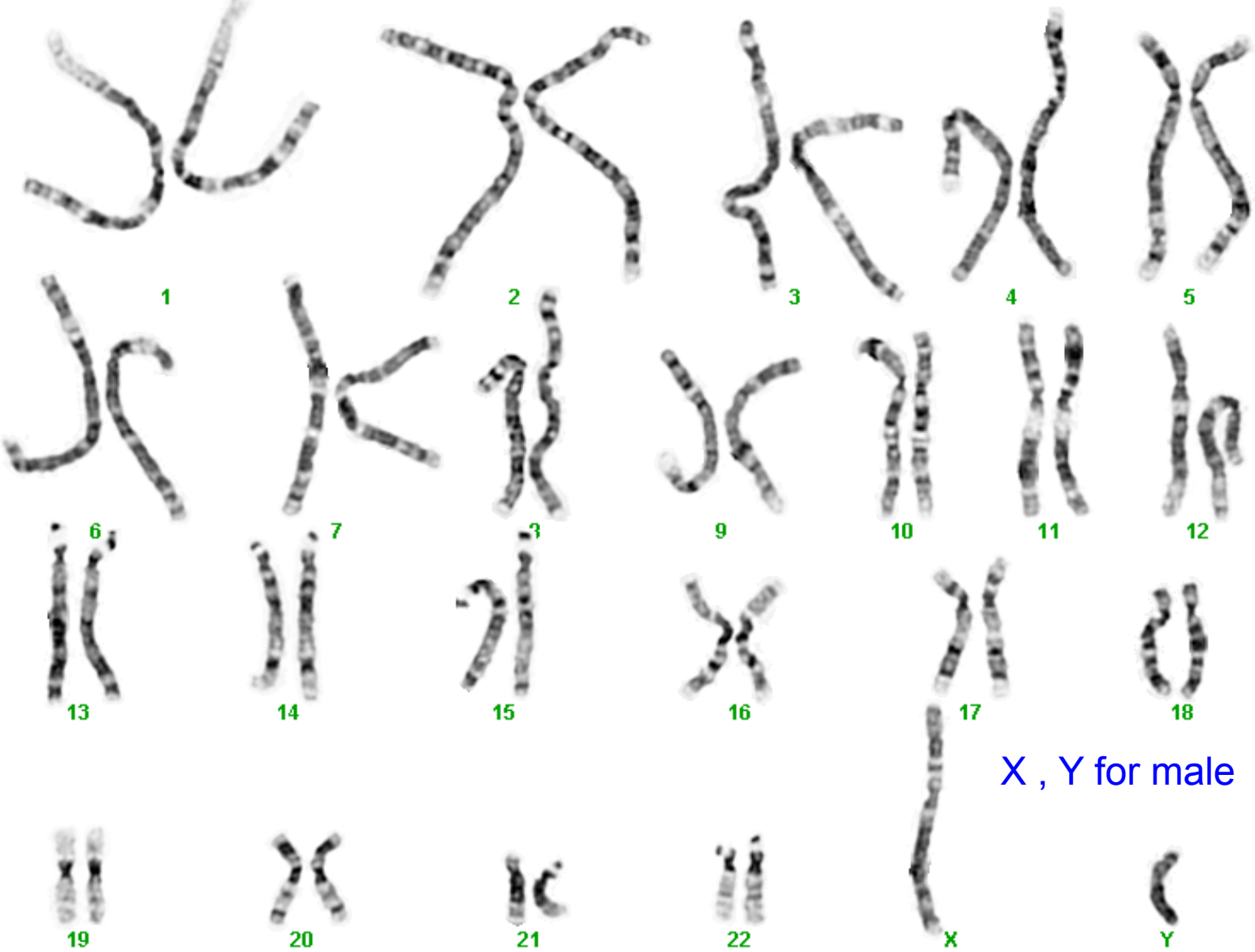
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Each chromosome has a unique  
G-banding pattern

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A normal cell has 46 chromosomes; 23 pairs



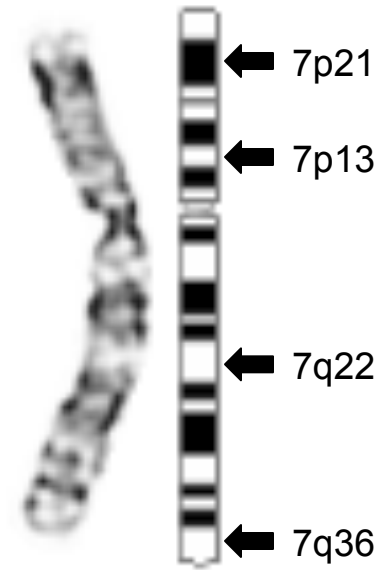
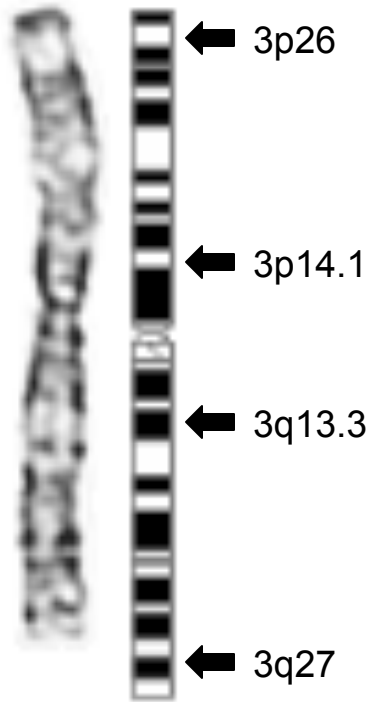
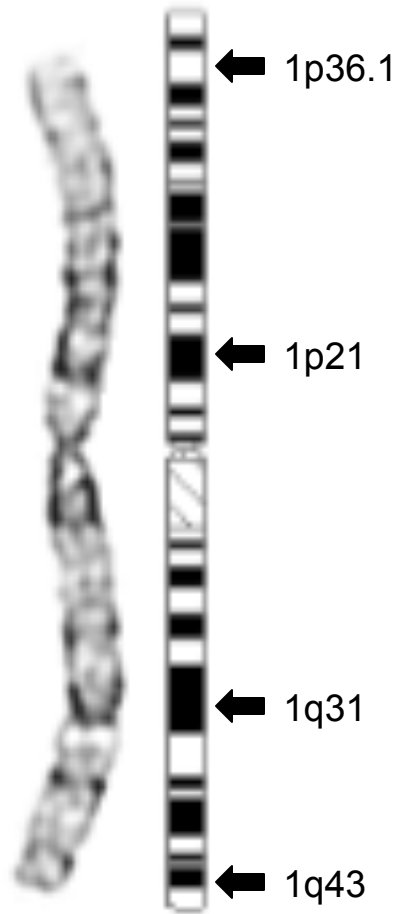
X, Y for male

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Each band in the chromosome is given a unique identifier

- P or Q (short or long arm)
- Numerical assignment



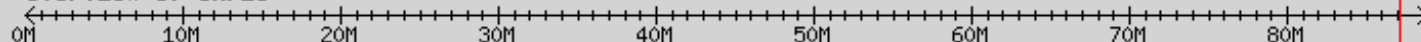


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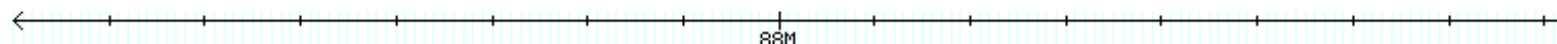
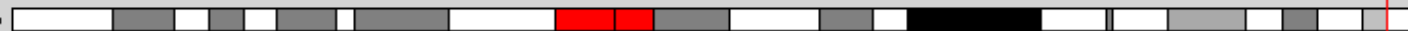
# Each band contains contains multiple genes

- FANCA is in band 16q24.3
- So are 50 other genes

Overview of chr16



Chromosome (overview)



Cytogenetic Bands (Chromosome)

16q24.3

RefSeq Genes (Gene)



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# Chromosome abnormalities can be:

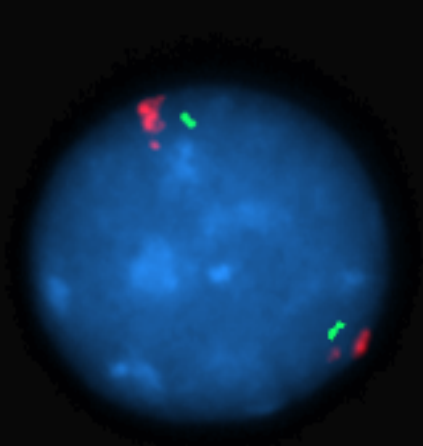
- ❑ Numerical (too few or too many chromosomes)
  - 7 = monosomy 7
  - +8 = trisomy 8
- ❑ Structural (banding pattern is not correct)



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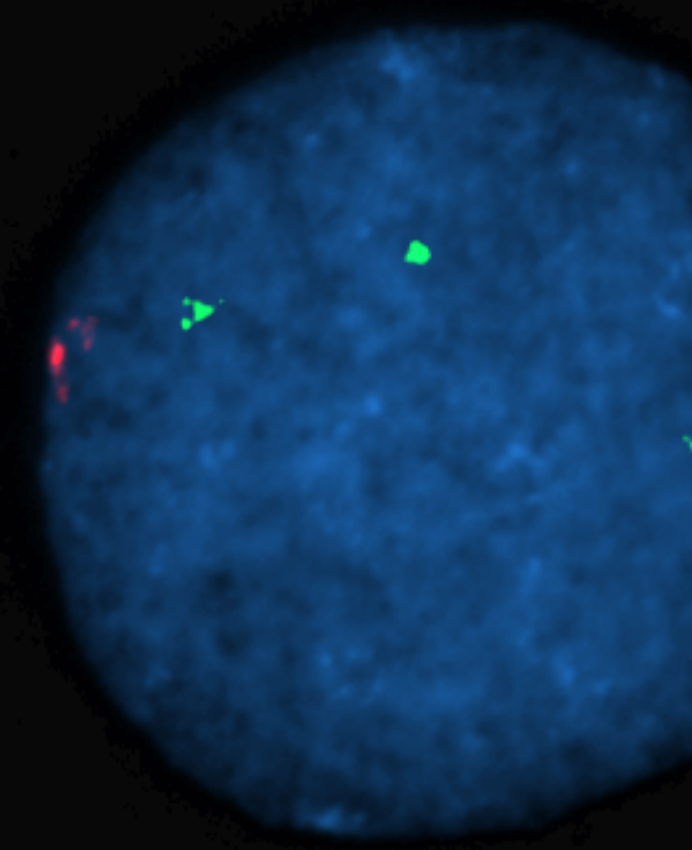
# Many different types of structural abnormalities of chromosomes

- **Deletions** that result in partial monosomy
  - **Duplications** that result in partial trisomy
  - **Translocations** between two or more different chromosomes that result in **derivative chromosomes**
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## FISH for 3q

Three **green** signals  
Consistent with gain of **3q**



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The chromosome abnormalities of concern in Fanconi Anemia are **CLONAL** abnormalities that arise in the bone marrow

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# Clonal abnormalities in bone marrow:

- Are NOT present in all cells of the individual
  - Are acquired (typically not present at birth)
  - Are an indication of an abnormal process in the bone marrow
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# CHROMOSOME ABNORMALITIES AND AGE

	0 - 10 yrs N = 46	11-20 yrs N = 32	> 20 yrs N = 20	p value
CLONAL ABNL	24%	56%	70%	p = .001

Tonnies et al: 47% (median age 11.75 yrs)

~~Cioc et al: 32.4% (median age 9 yrs)~~

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# Clonal Chromosome Abnormality

- ❑ An abnormality that is found in more than one cell

## Clone:

- ❑ group of cells that have the same abnormalities
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# Significance of chromosome abnormalities in non-FA patients

- Associated with the development of malignancy in non-FA patients; used to help in diagnosis
  - Specific abnormalities have been shown to have important prognostic significance; used to plan therapy
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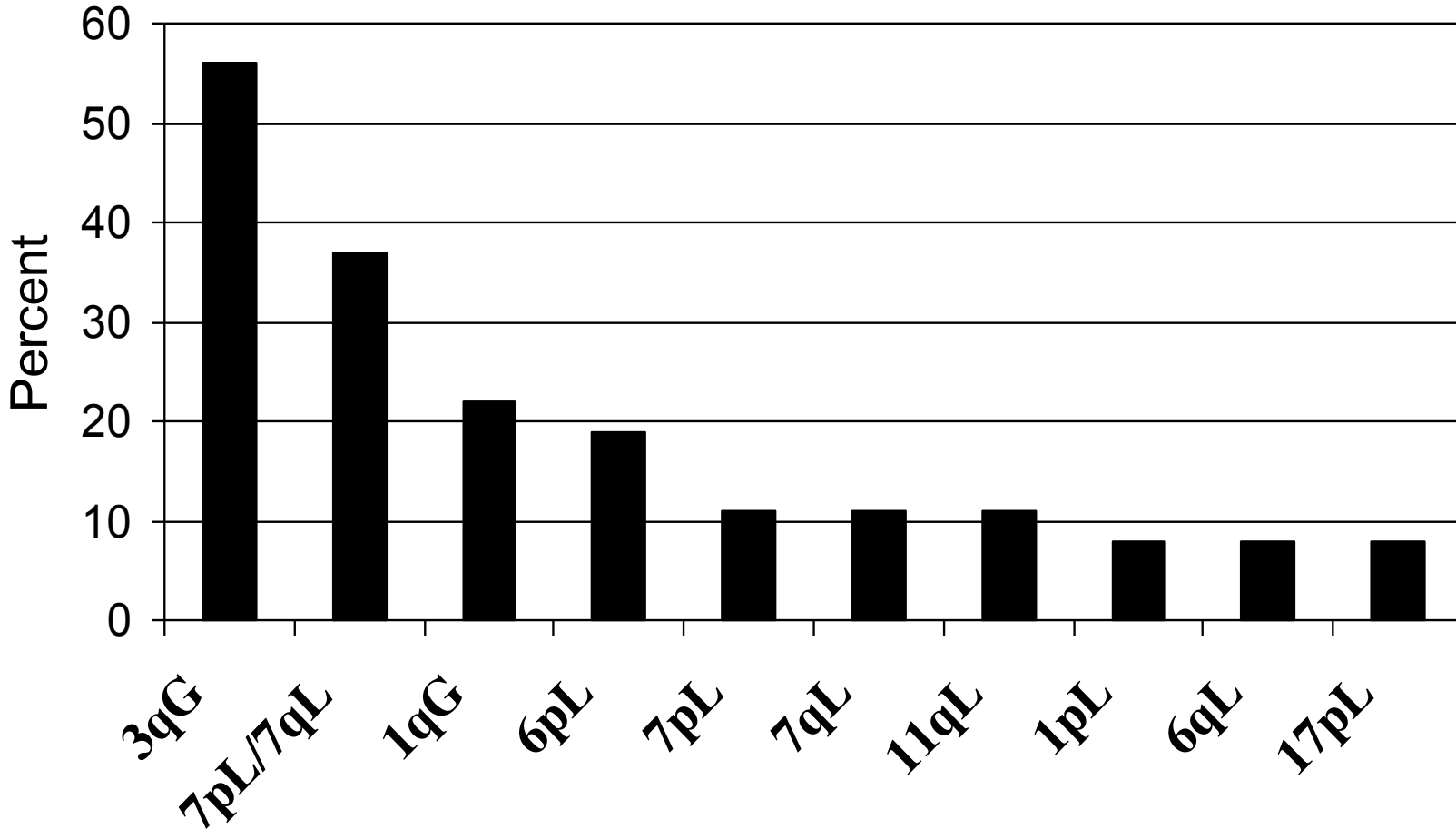
## What are the Clonal Abnormalities that Arise in FA and how do they compare to the Non-FA patients?

- ❑ Abnormalities in FA are MOSTLY unbalanced; leading to gains and losses of portions of chromosomes
  - ❑ There are specific chromosomes that are involved in the majority of abnormalities in FA.
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# Clonal chromosomal abnormalities

G = gain

L = Loss



Data from U of MN

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Gain of 1Q, Gain of 3Q, Monosomy 7 or loss of 7Q account for >75% of the clonal abnormalities seen in FA

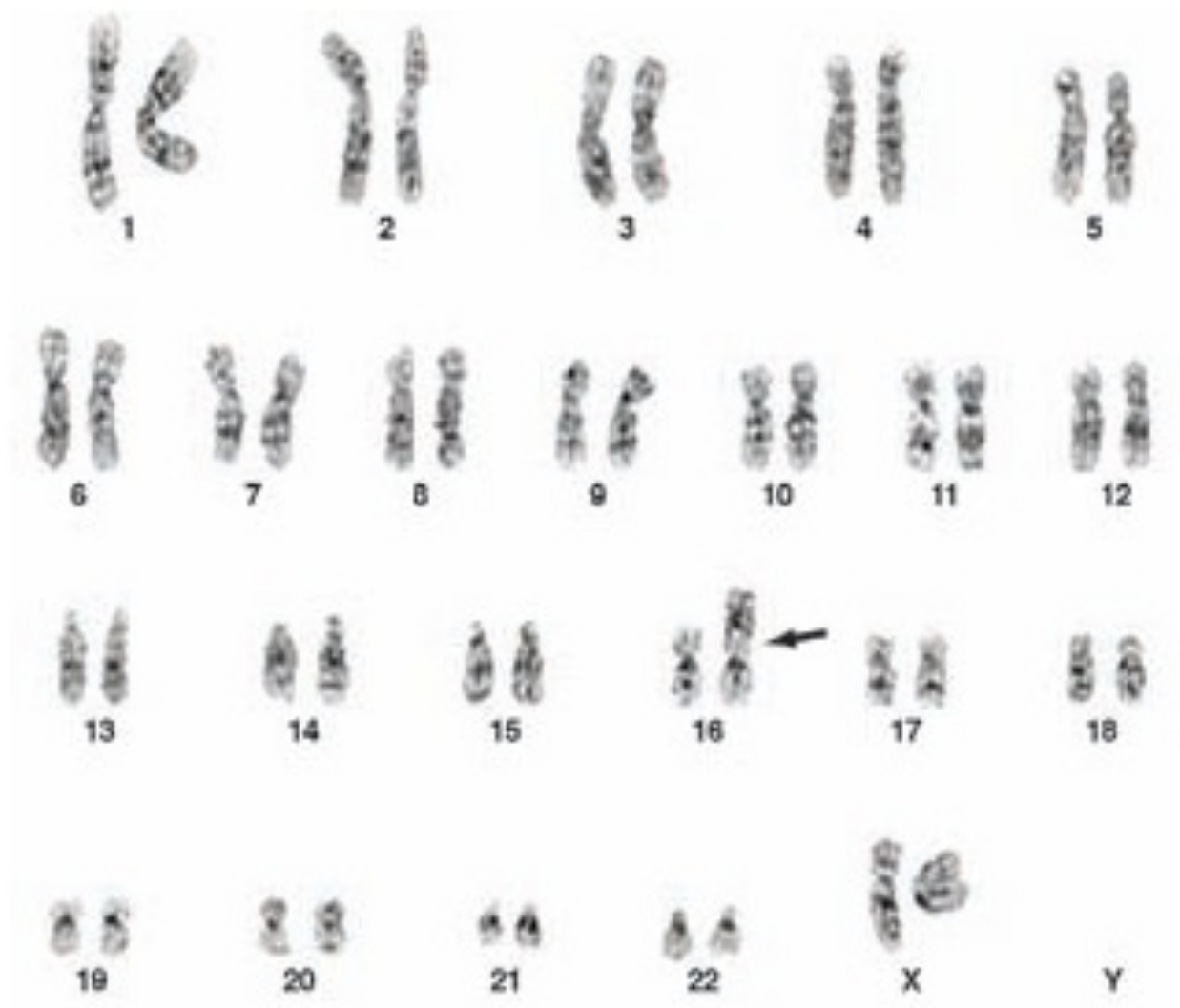
Gain of 3q *RARELY* seen in pediatric AML or MDS in non-Fanconi patient

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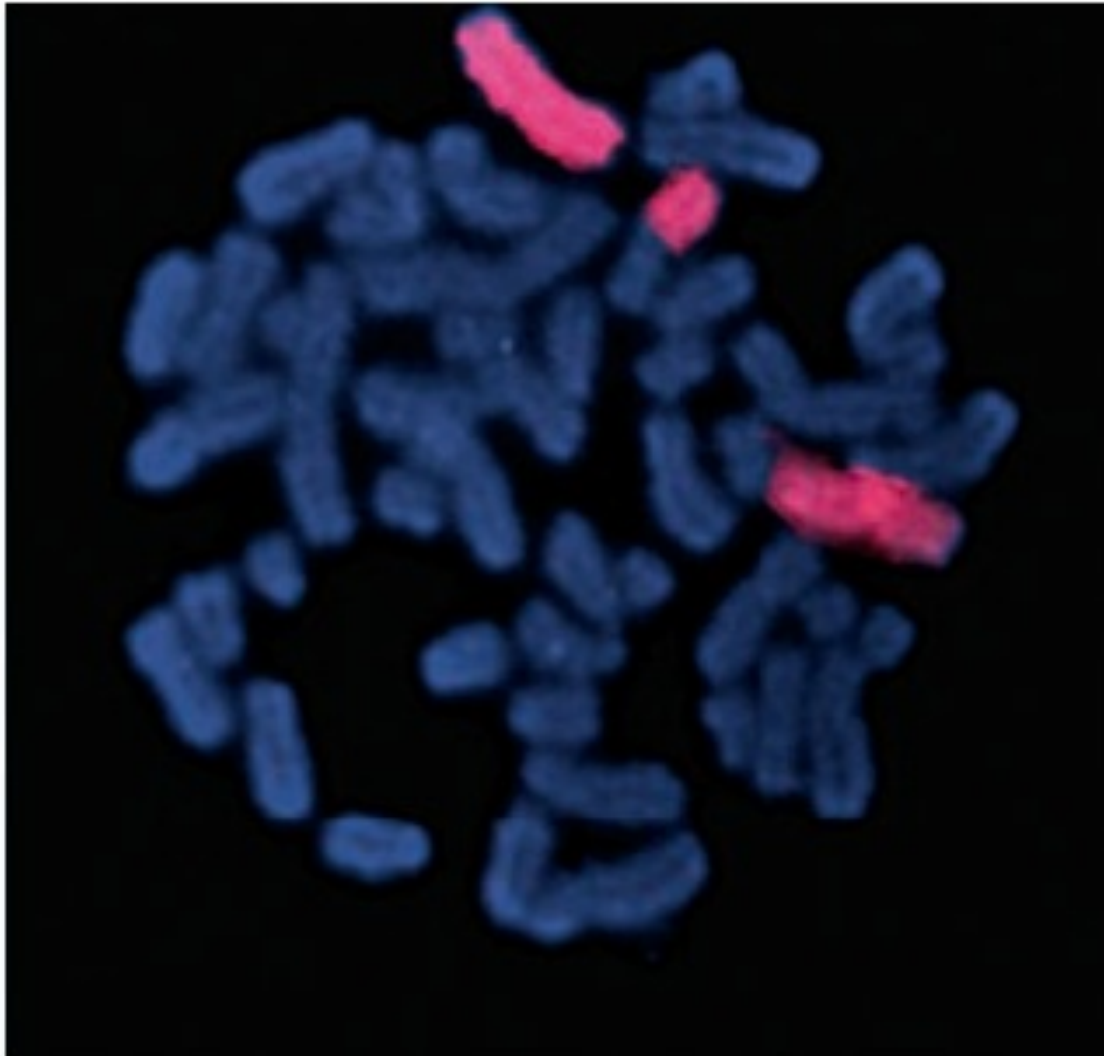
# Earlier studies did not recognize 3Q gain in the karyotypes

- ❑ Frequently disguised as part of a derivative chromosome
  - ❑ Frequently need FISH or array technology to identify
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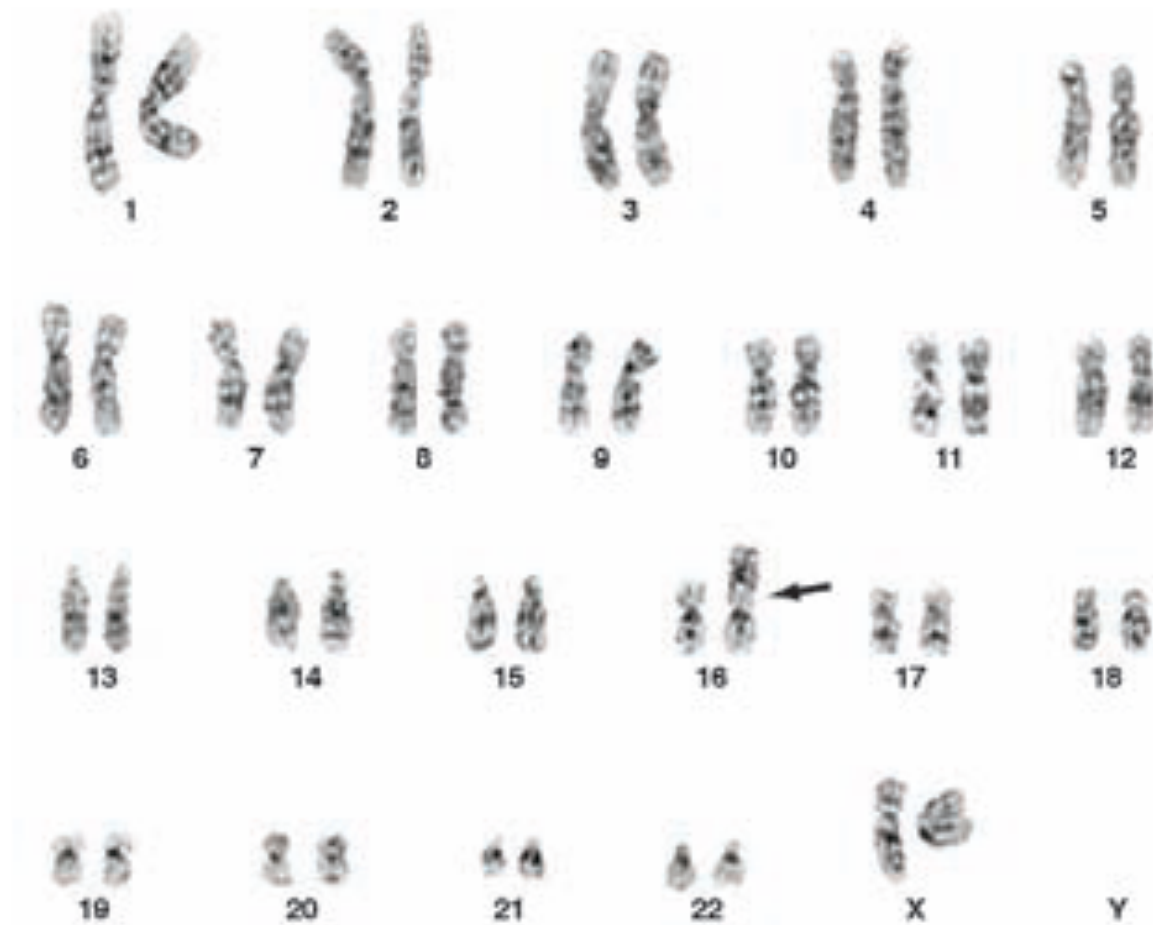
add (16)(p13)  
additional material of unknown origin

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FISH with chromosome 3  
"paint"

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Der (16)t(3;16) = GAIN of 3Q  
The material "Added" to 16p was 3q!

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Labs performing testing must be able to characterize the clonal abnormality

Look for “add” (additional material of unknown origin)

Look for “mar” (marker chromosome of unknown origin)

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There is a **highly significant association** between the presence of clonal chromosomal abnormalities and the development of MDS or AML in FA

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# Minneapolis Study of MDS in FA

N=111

- Presence of a clone associated with a 73 fold increased risk for MDS and 26 fold increased risk for borderline MDS
- 76% patients with MDS had clonal abnormalities vs. 12% of non-MDS

Cioc et al, 2010, Am. J. Clin. Path, 2010

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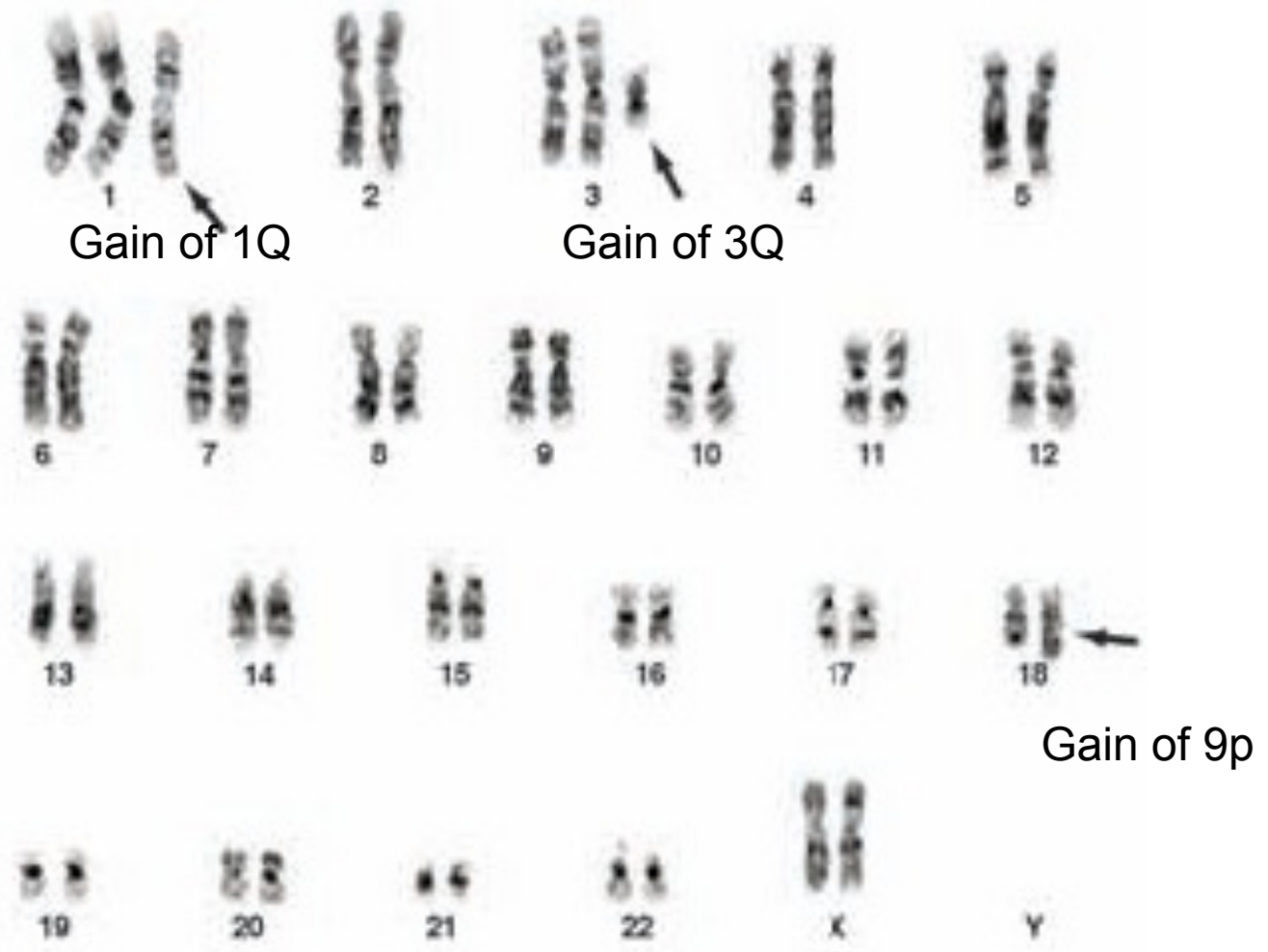
Other studies also show increased risk for MDS/AML with presence of 3qG and/or monosomy 7

Tonnies et al, 2003, Blood 101:3872

Mehta et al, 2010, Cancer Genetics and Cytogenetics 203:180

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Gains of 1q, 3q and loss of 7  
Frequently occur together in the clone



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# Consensus on 3Q gain

- ❑ **Most frequent** recurring clonal abnormality in FA (Tonnes et al : 72%, Cioc et al : 54% of abnormalities found)
  - ❑ **Persistent abnormality** – No evidence of being transient (Berlin, Minneapolis, Cincinnati studies)
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## Identifying a clone in absence of frank MDS or AML calls for close monitoring for:

- **Evolution:** clone acquires **ADDITIONAL** chromosome abnormalities
  - **Expansion:** % of cells with chromosome abnormality **INCREASES** over time
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## Clones with 3q Gain:

- Frequently expand over time
  - Frequently evolve and acquire monosomy 7
  - Can remain as a sole abnormality for two or more years without evidence of MDS or AML
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# What is the time course for evolution?

- We don't know

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Ultimate goal :understand HOW the clonal abnormality is involved in the disease process; to facilitate development of targeted therapies.

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# Information that should be provided from the laboratory:

- ❑ The number of cells studied: At least 20 cells should have been analyzed
- ❑ Was a clonal chromosomal abnormality detected?
- ❑ A complete description of the abnormality

Loss of chromosome 5 or 7?

Gain of part of chromosome 1 or 3?

**Beware of “add” and “mar”.** These indicate that the abnormality has NOT been completely described. The laboratory may need to use additional techniques (FISH, microarrays) to determine if the material in the add or mar is part of chromosome 1 or 3

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