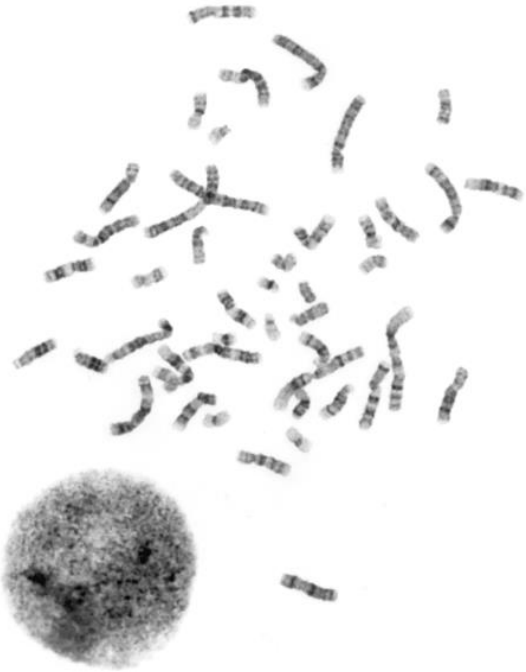


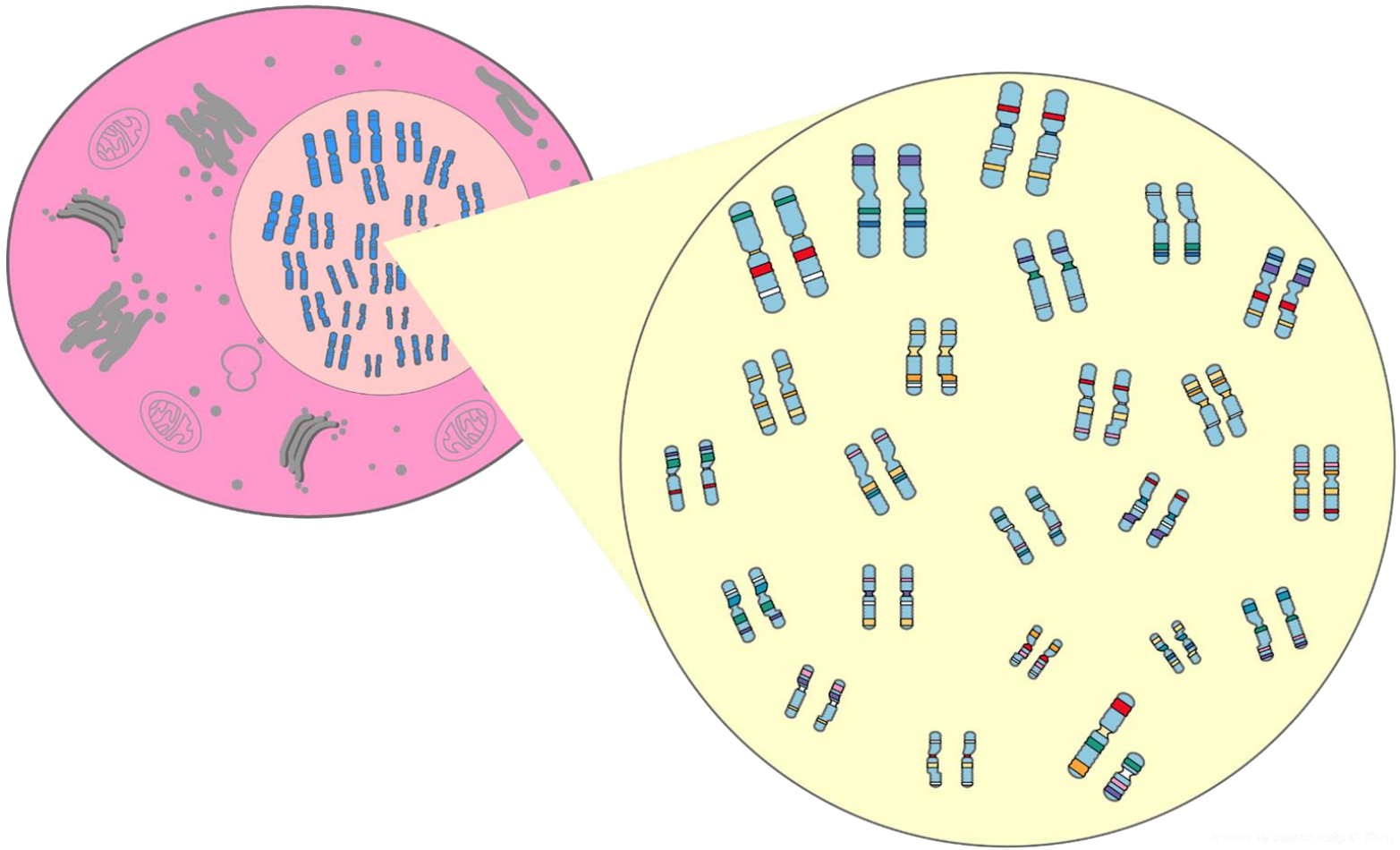
Citogenética Clínica

Prof. Dr. Israel Gomy

Departamento de Genética

Faculdade de Medicina de Ribeirão Preto

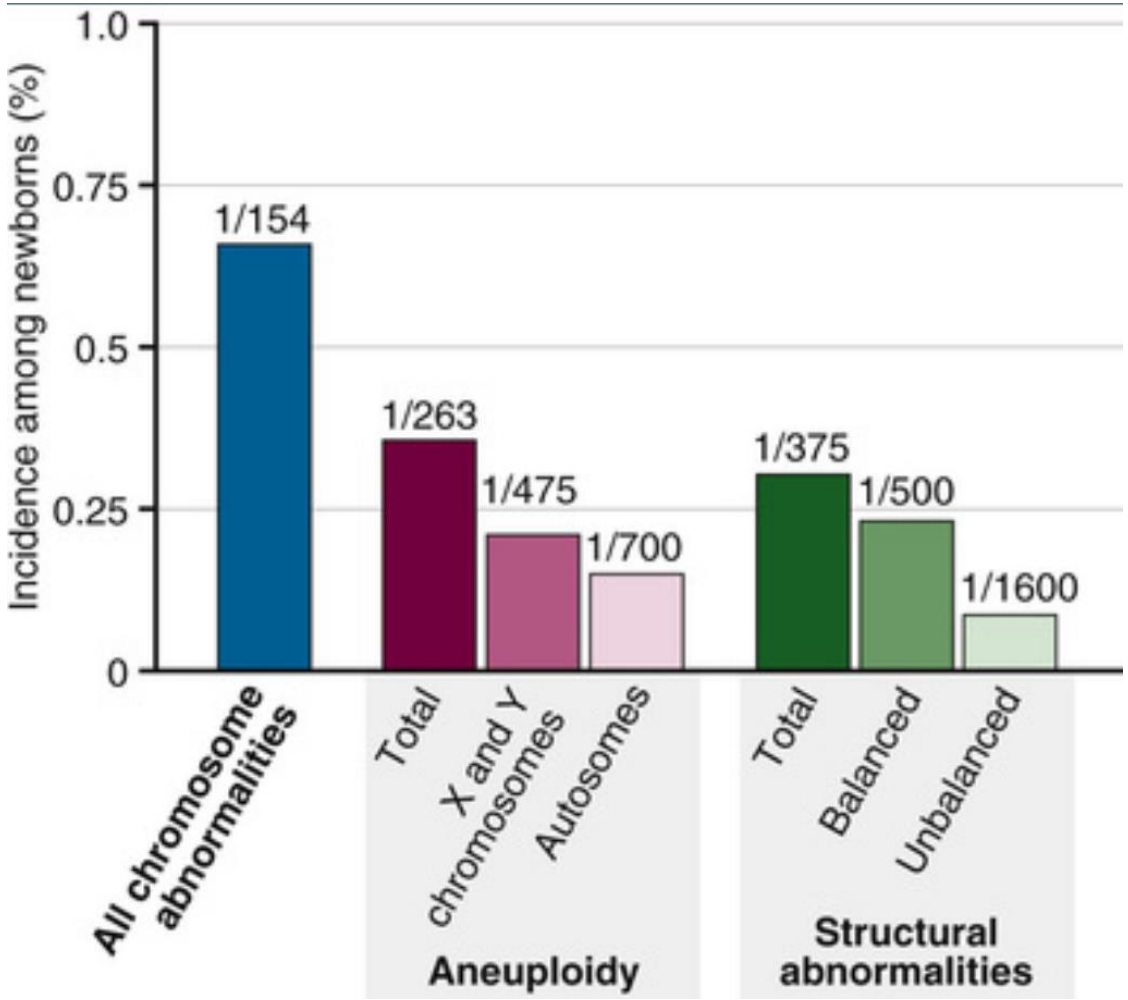
Universidade de São Paulo



Citogenética clínica

- Estudo dos cromossomos, sua estrutura e herança aplicado na prática clínica
- 1956 (Tjio&Levan) → cariótipo humano diplóide = 46 cromossomos
- Importante ferramenta clínica para o diagnóstico de doenças cromossômicas
  - anomalias congênitas múltiplas
  - atraso de desenvolvimento
  - atraso de crescimento
  - anomalias de diferenciação sexual
  - câncer
  - 0.7% recém-nascidos
  - 2% fetos de gestantes > 35 anos
  - 10% natimortos e óbitos neonatais
  - 40-50% abortos espontâneos no 1º trimestre
  - 3-6% infertilidade

Epidemiologia das anormalidades cromossômicas

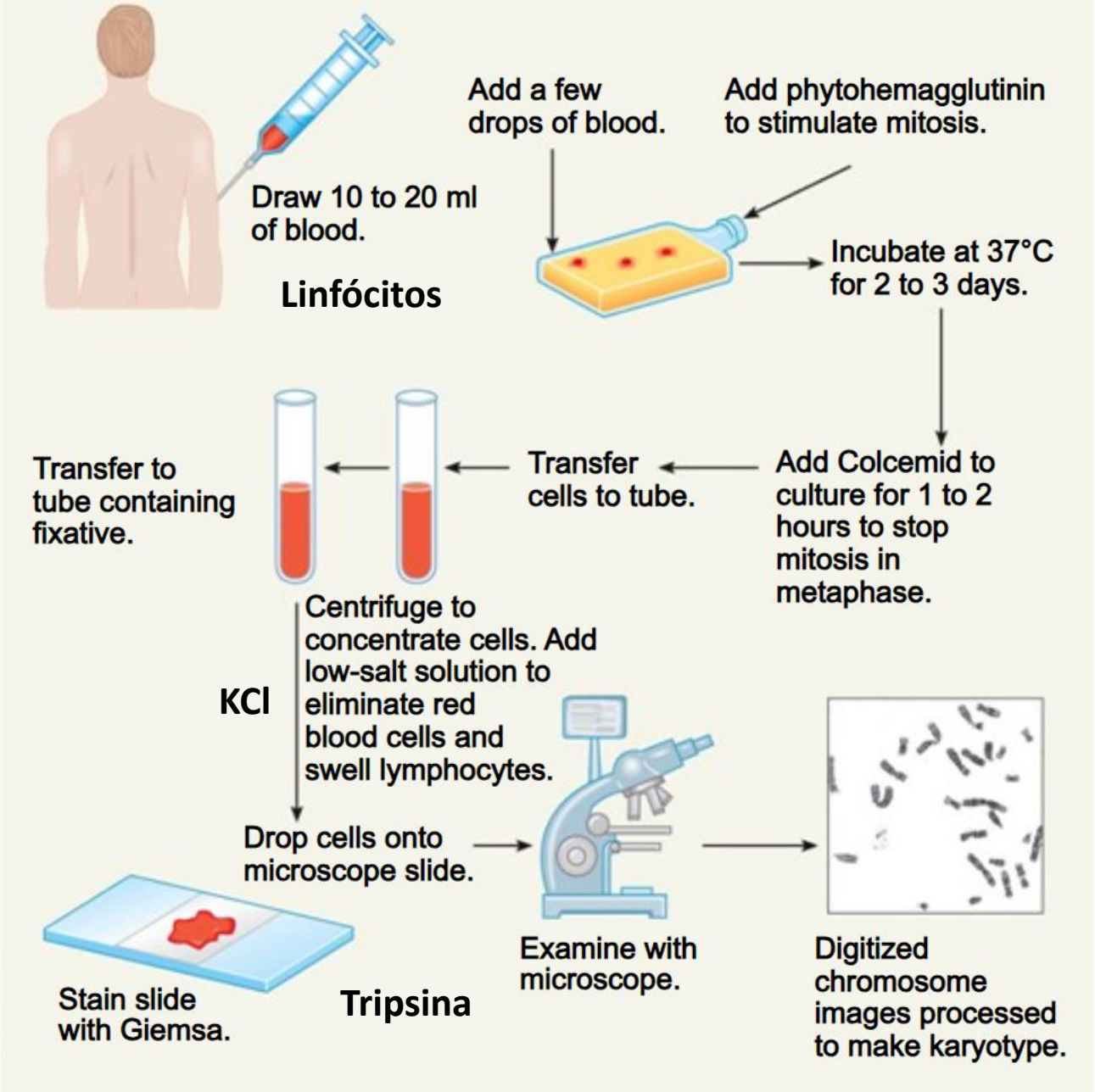


THOMPSON&THOMPSON, 2016

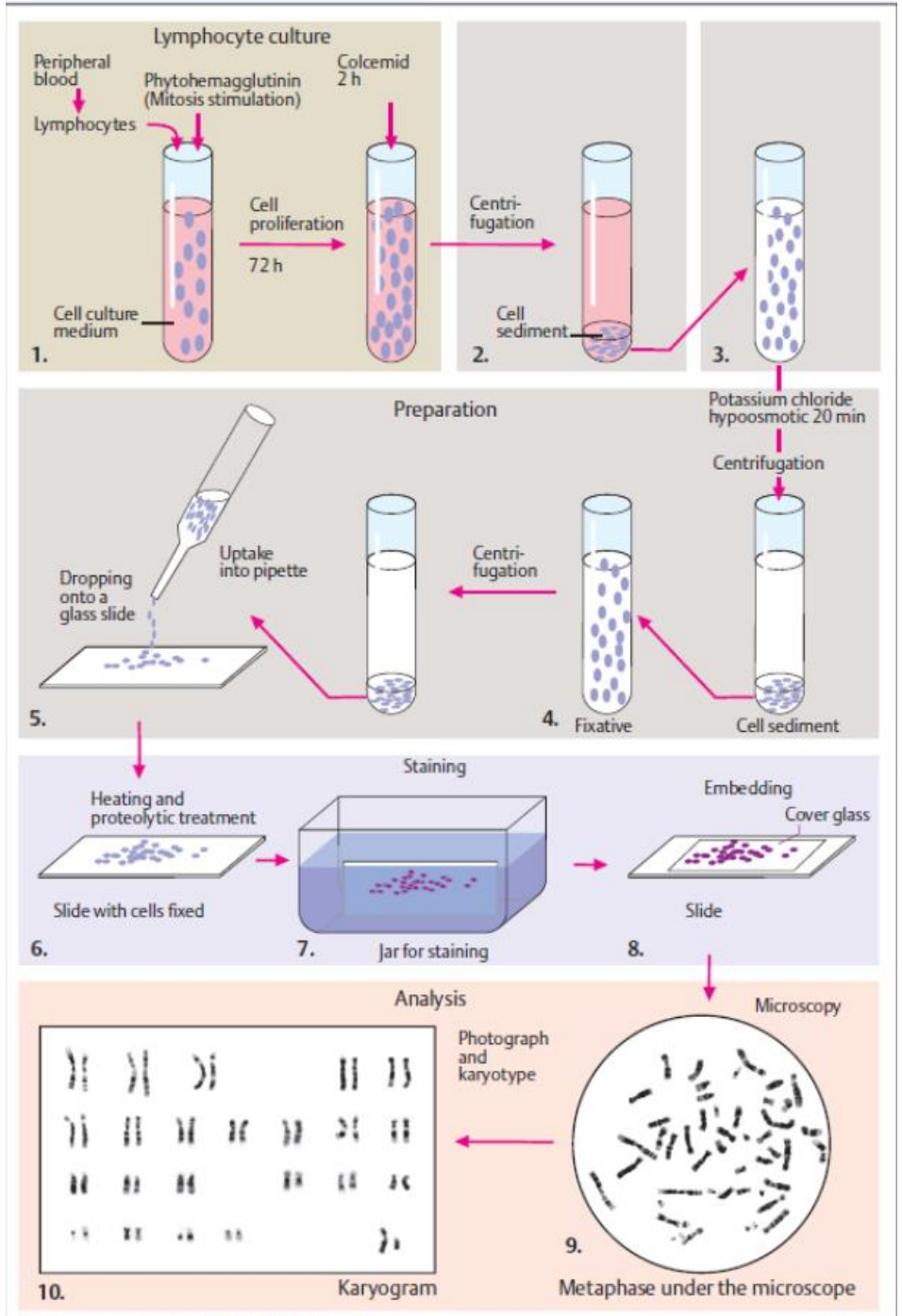
Mecanismos das anormalidades cromossômicas e desequilíbrio genômico

CATEGORIA	MECANISMO	CONSEQUÊNCIA (EXEMPLOS)
Segregação anormal dos cromossomos	Não-disjunção	Aneuploidia (Down, Edwards, Turner) Dissomia uniparental (Prader-Willi)
Síndromes cromossômicas recorrentes	Recombinação meiótica de segmentos cromossômicos	Síndromes de microdeleção ou microdup (Williams, velocardiofacial)
Anomalias cromossômicas idiopáticas	Esporádico por vários pontos de quebra Translocações balanceadas	Deleção (cri-du-chat, 1p36)
Anomalias cromossômicas não balanceadas	Segregação meiótica não balanceada	Prole de translocações balanceadas Prole de inversões pericêntricas

- Medula óssea
- Vilosidade coriônica
- Líquido amniótico
- Fibroblastos (pele)
- Biópsia gonadal

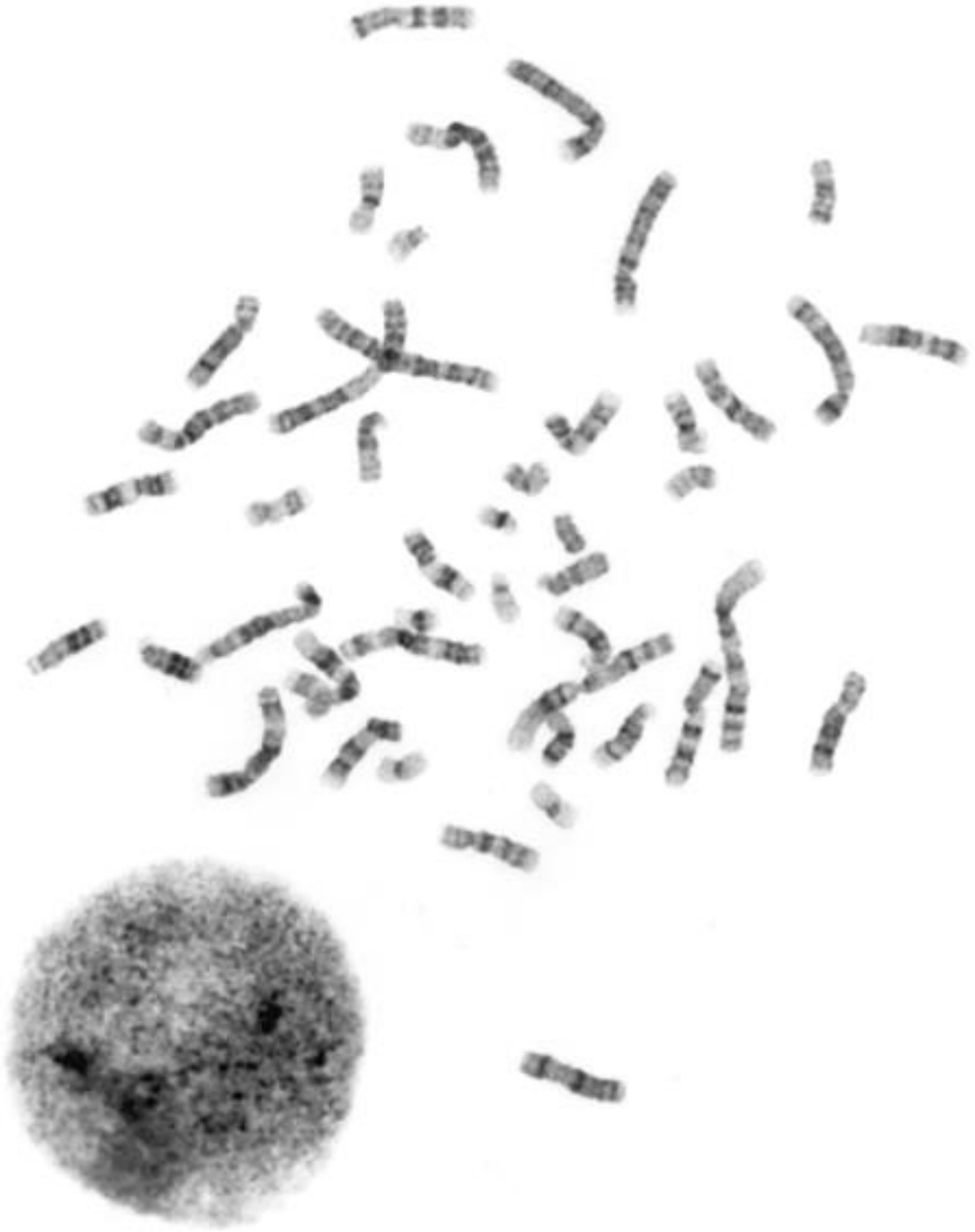


https://slideplayer.com/slide/6204997/



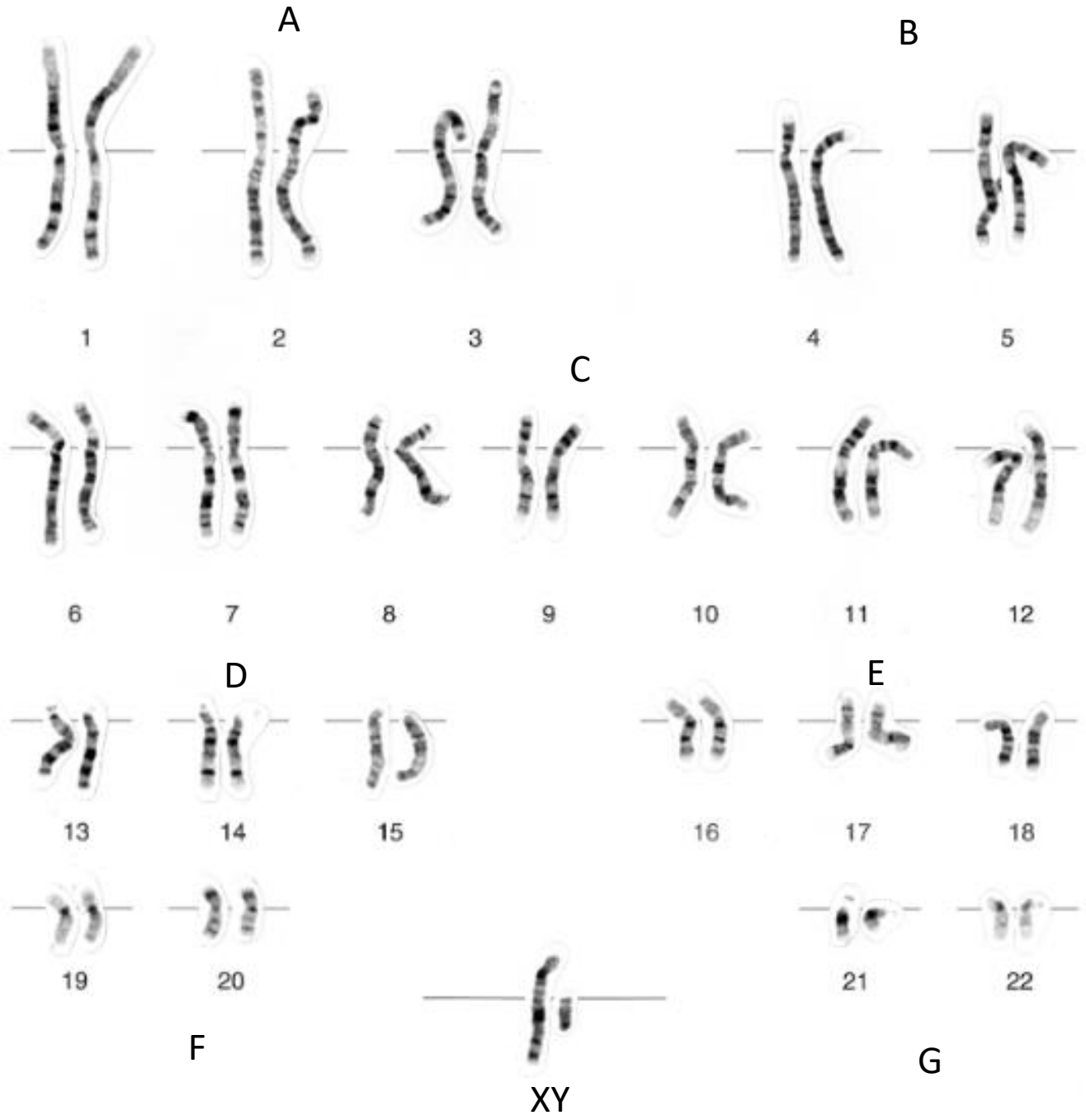
A. Chromosomal analysis from blood

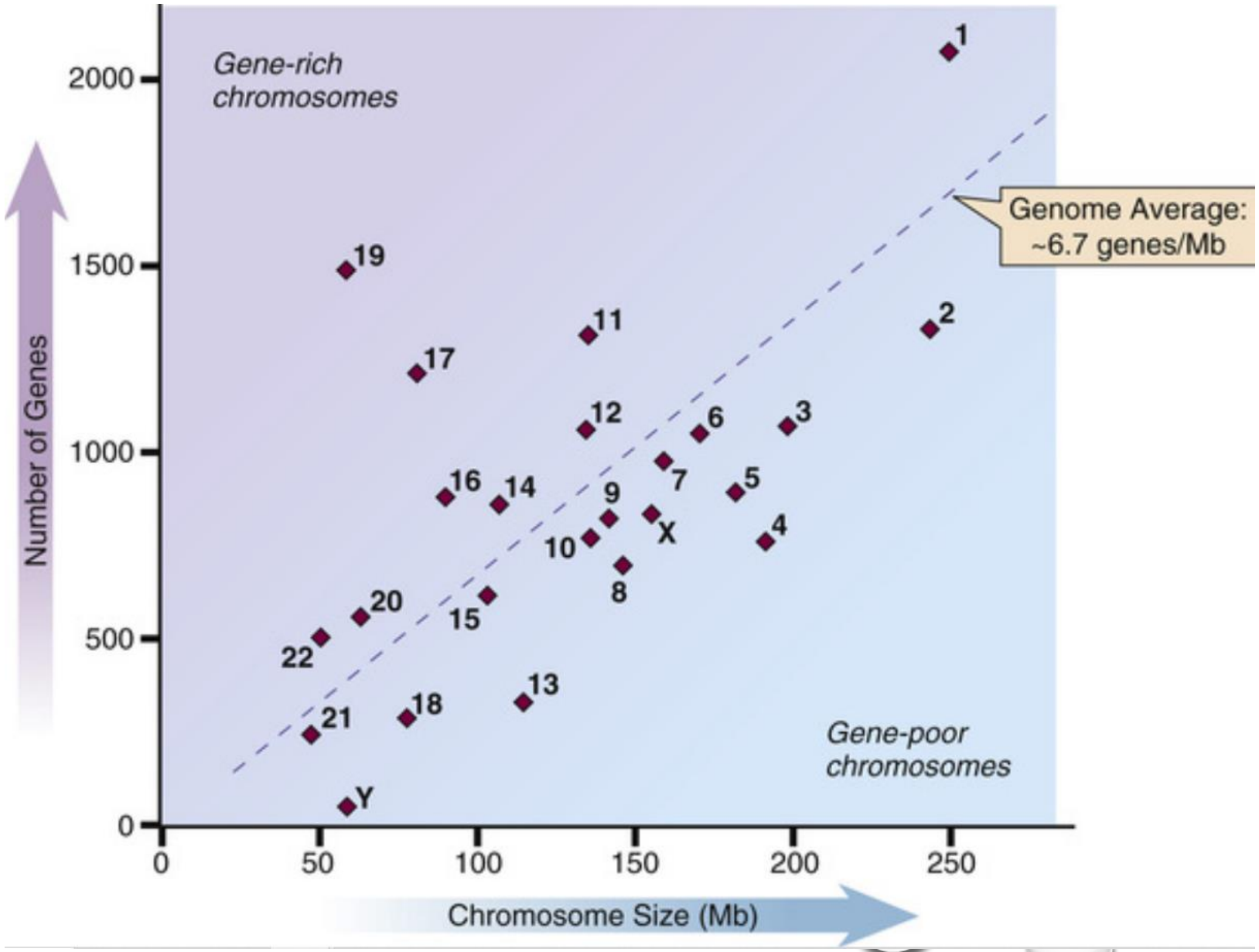
- Bandeamento G
  - tripsina → digere proteínas (histonas)
  - Giemsa (corante)
  - bandas claras (GC) e escuras (AT)
  - AT = menos genes ativos (heterocromatina)
  - GC = mais genes ativos (eucromatina)



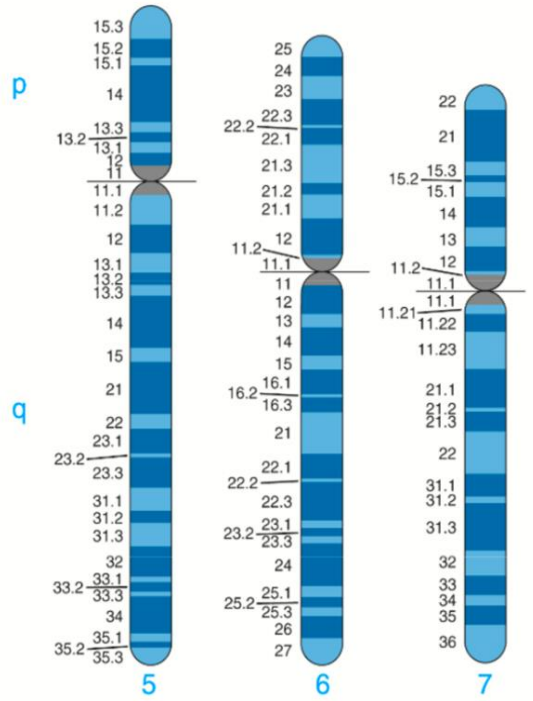
Cariótipo (cariograma)

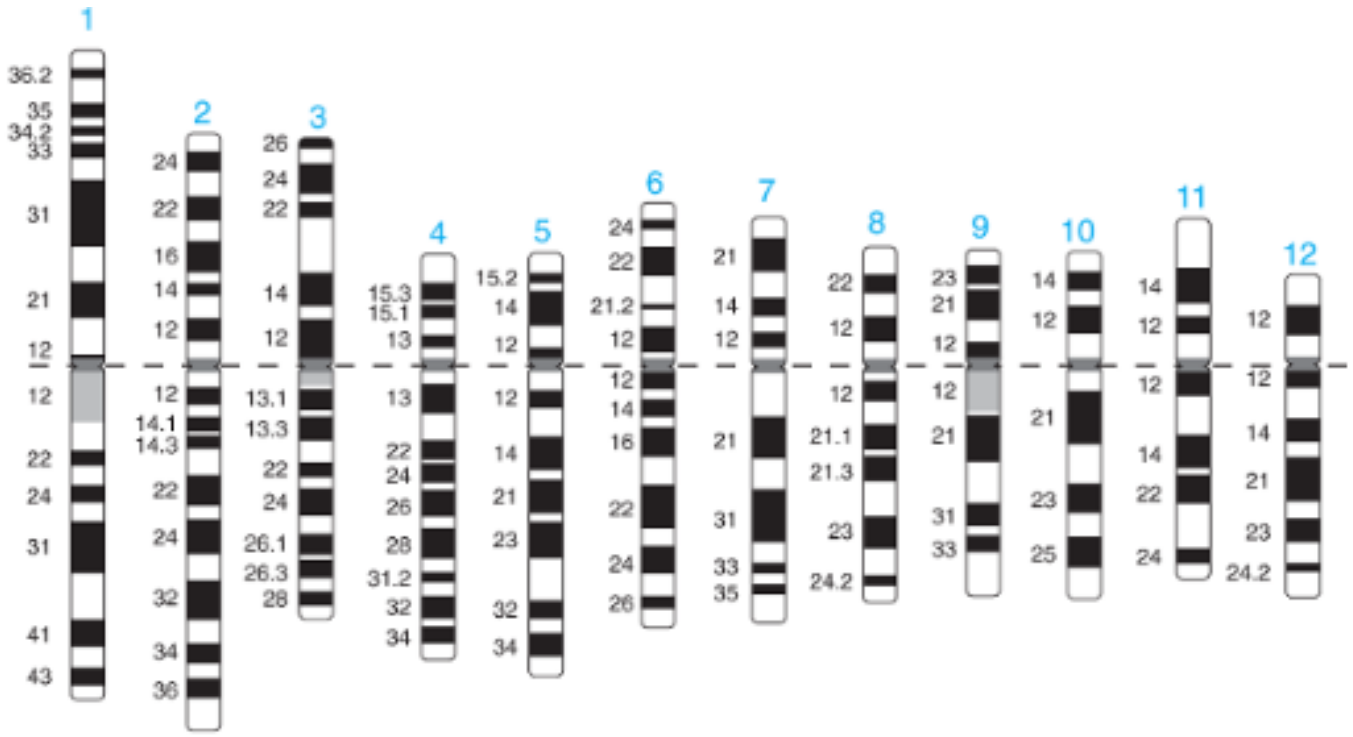
- constrição 1ª = centrômero
- braço curto = p
- braço longo = q
- metacêntricos (1,3,16,19,20)
- acrocêntricos (13,14,15,21,22)
- submetacêntricos
- constrição 2ª (p)
- satélites



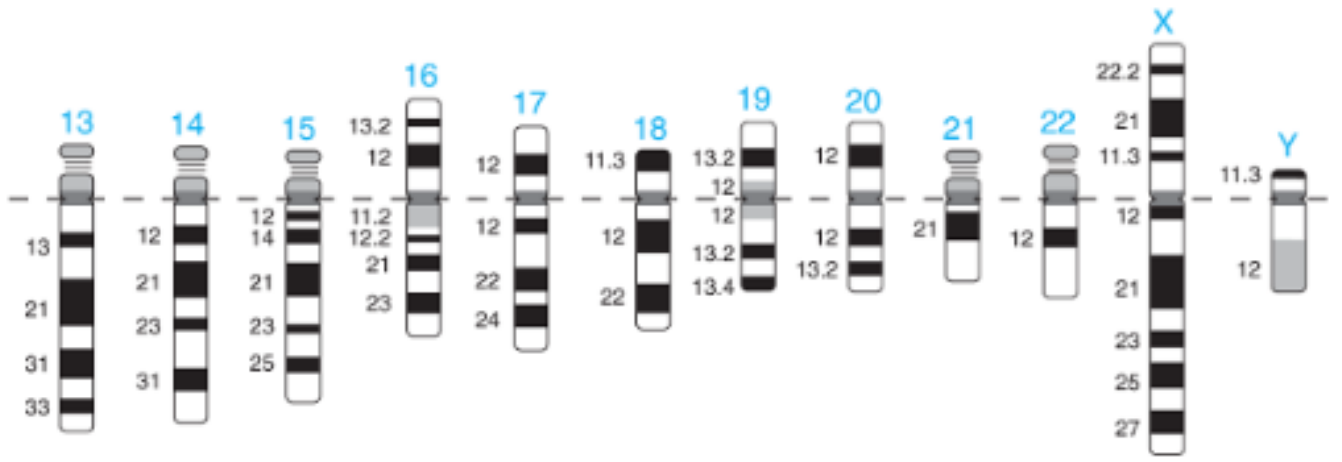

Gene-rich chromosomes
Gene-poor chromosomes
Genome Average: ~6.7 genes/Mb
Number of Genes
Chromosome Size (Mb)
2000
1500
1000
500
0
0
50
100
150
200
250
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

- ideogramas
- resolução = n bandas
- 550 bandas (convencional)



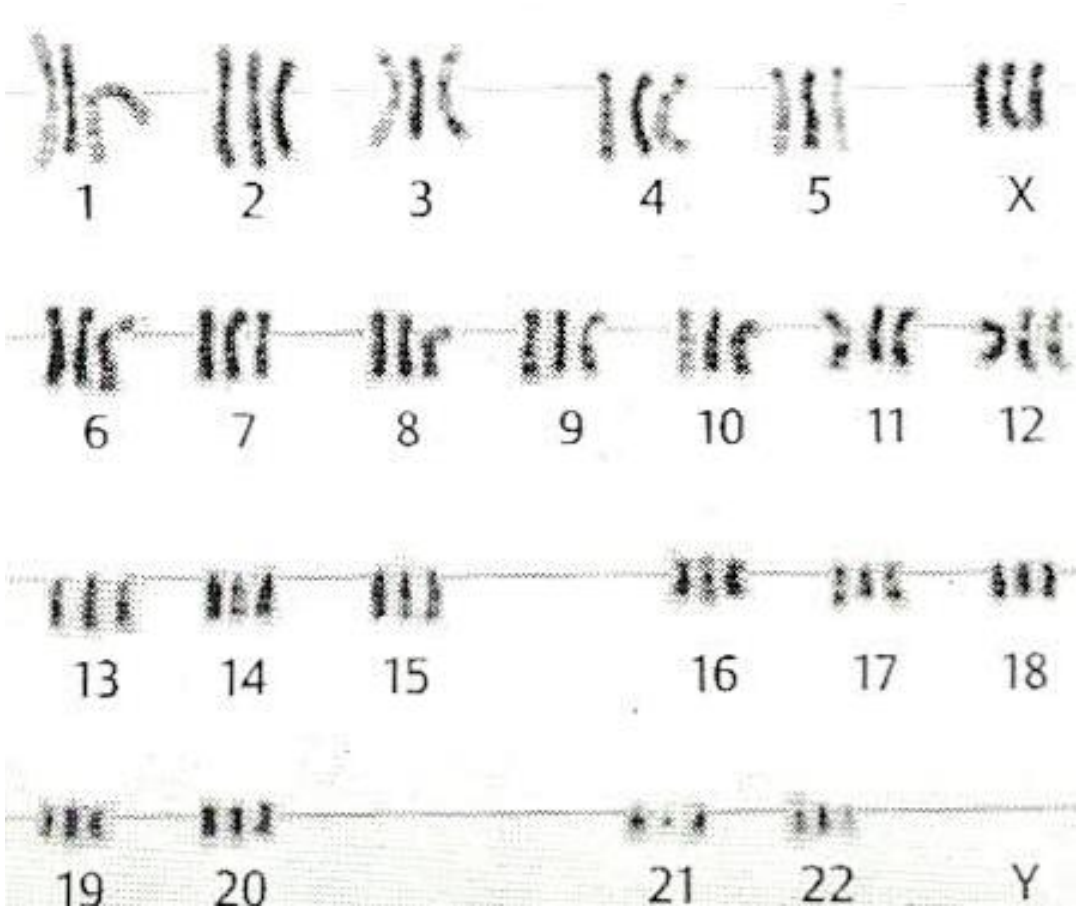


400 bandas

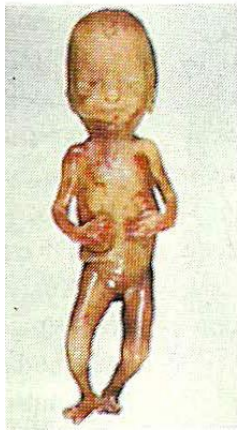


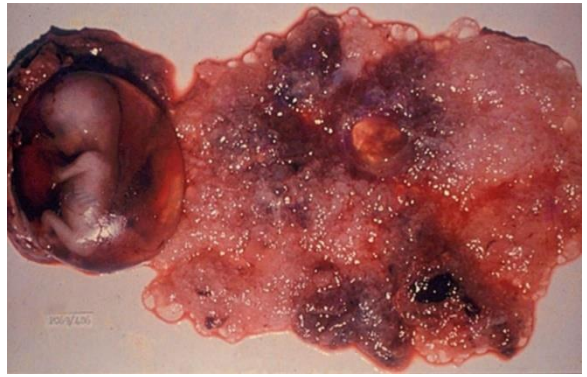
Anomalias cromossômicas

- Numéricas
  - euplóides



TRIPLOIDIA = 69, XXX





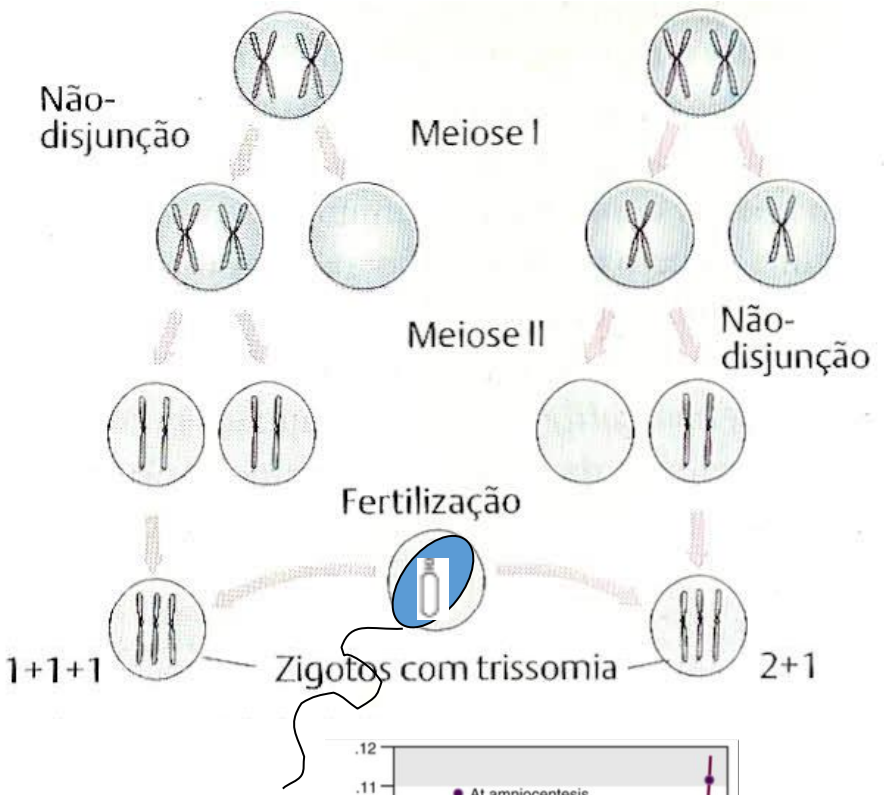
DISPERMIA = MOLA PARCIAL

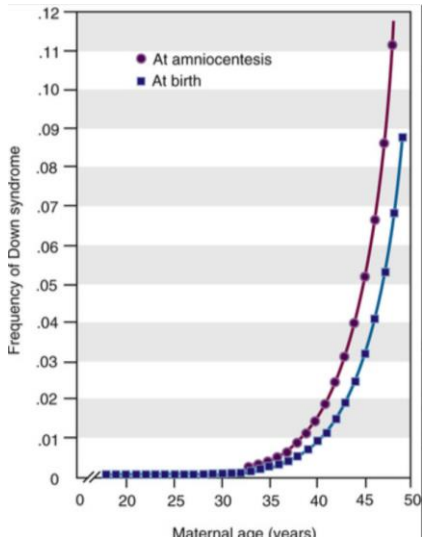
Anomalias cromossômicas

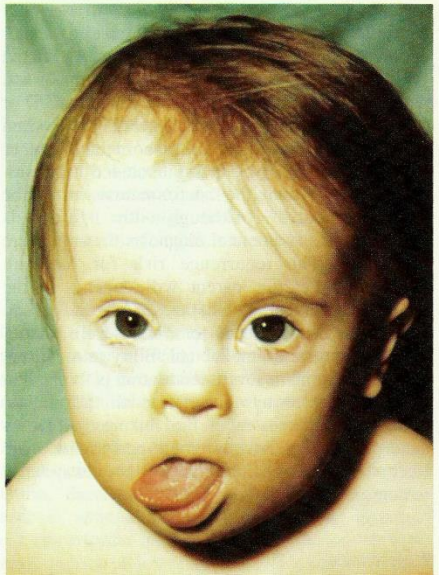
- Numéricas aneuplóides

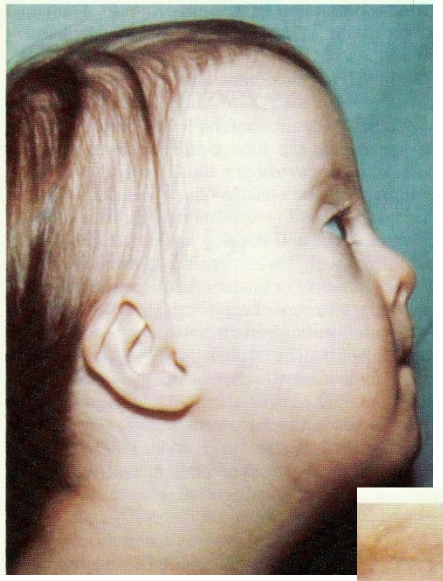
TRISSOMIA = 47, XX+21

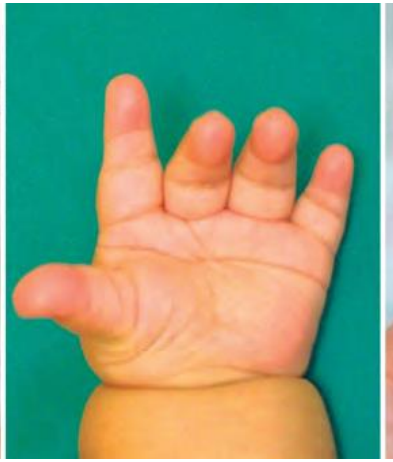
90% (meiose I materna)

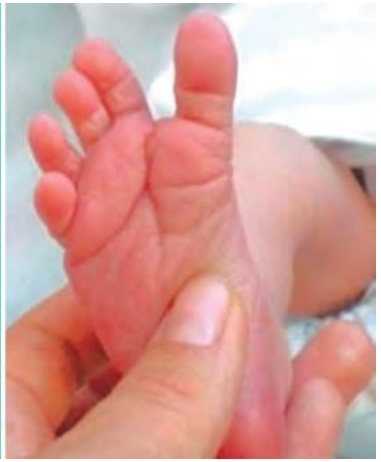








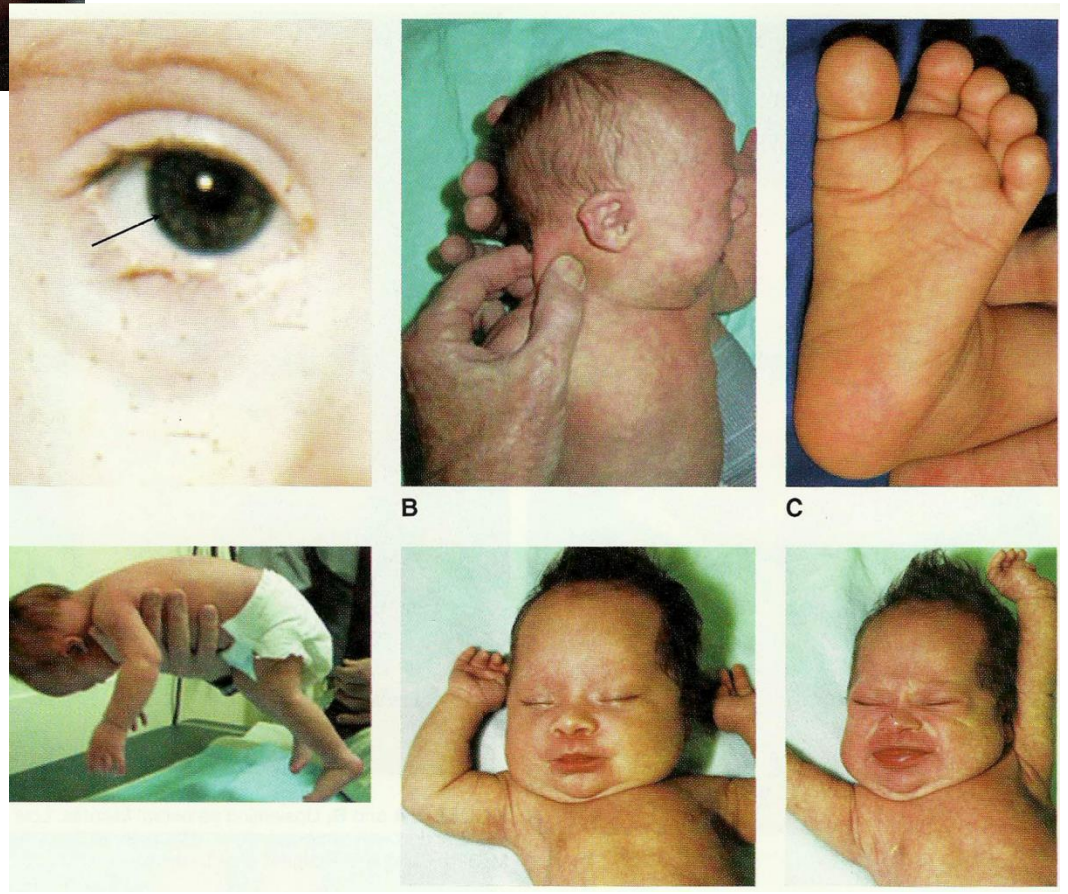




CRITÉRIOS DE HALL (1966)

1. hipotonia
2. reflexo de Moro diminuído
3. perfil facial achatado
4. fendas obliquas superior
5. orelhas displásicas
6. prega palmar única
7. hiperextensib.articular
8. clinodactilia 5º dedo
9. excesso prega nucal
10. displasia da pélvis

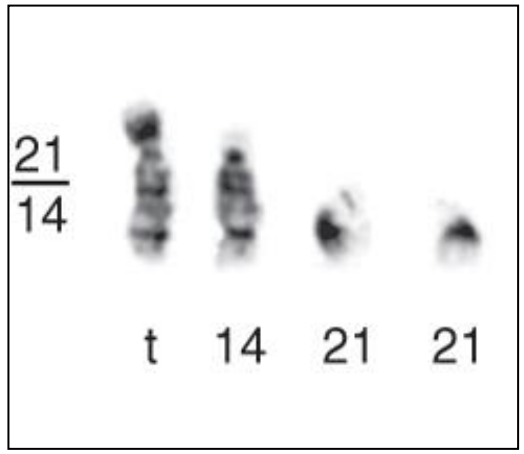
RN: 4 ou mais: 100%; 6 ou mais: 89%



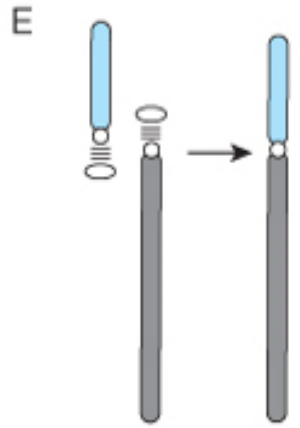
Anomalias cromossômicas

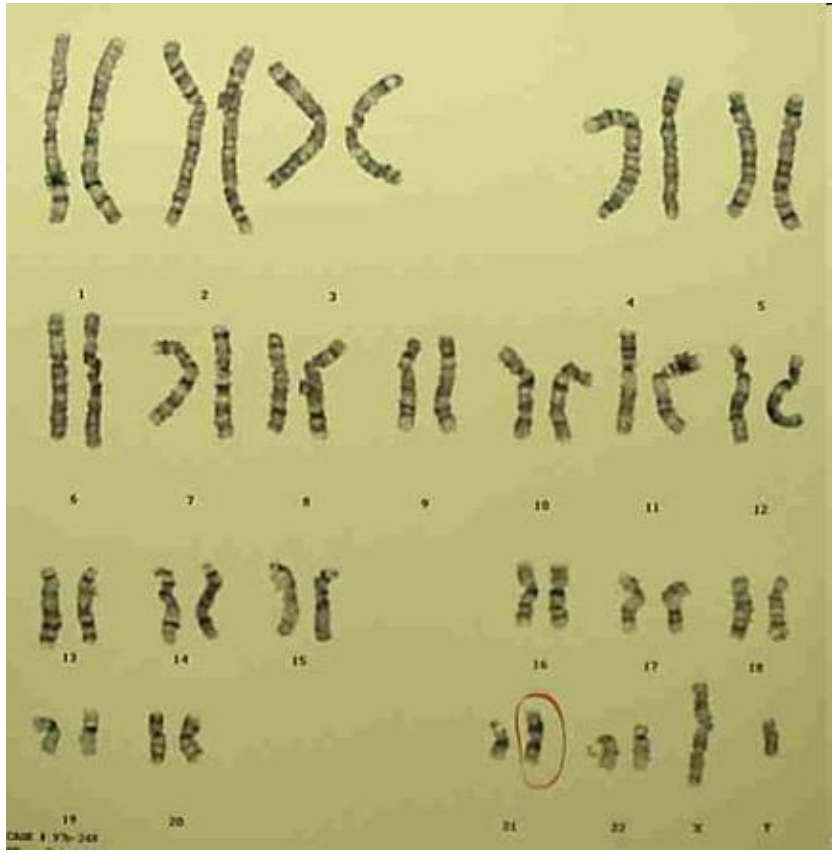
- Estruturais

~5% casos SD = translocação robertsoniana

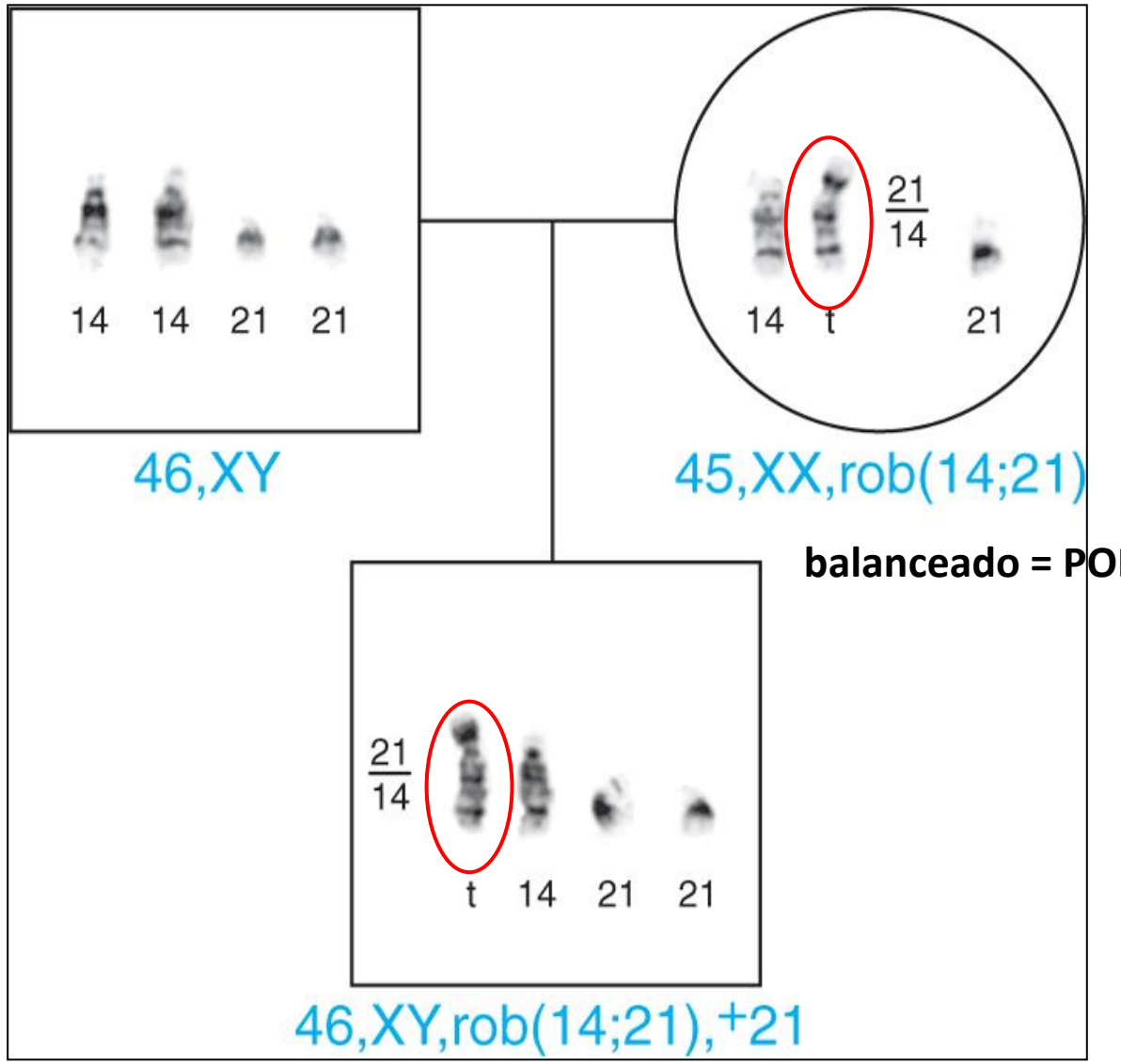


46, XX ou XY, t(14;21),+ 21



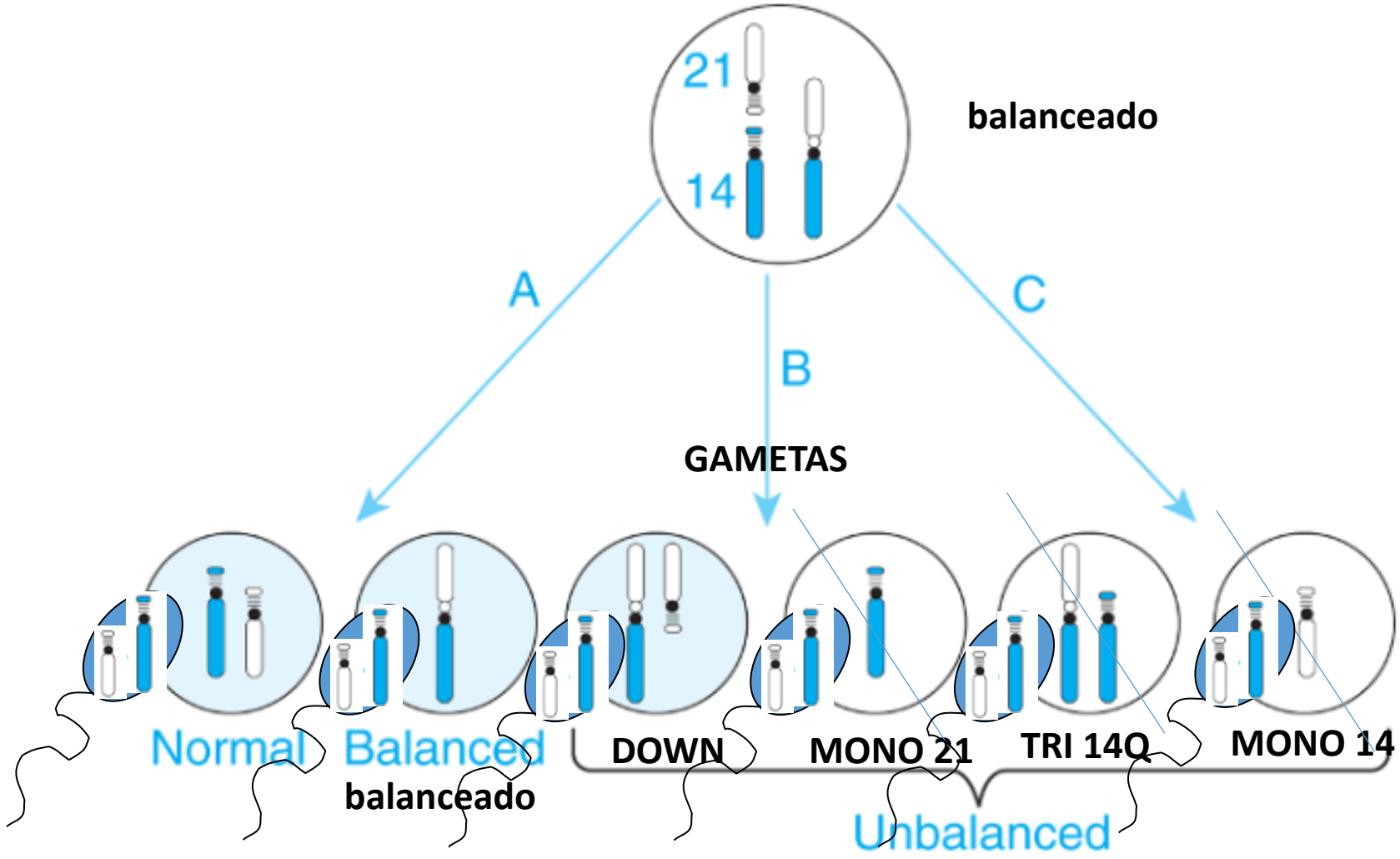


46,XY,t(21q;21q)



balanceado = PORTADOR

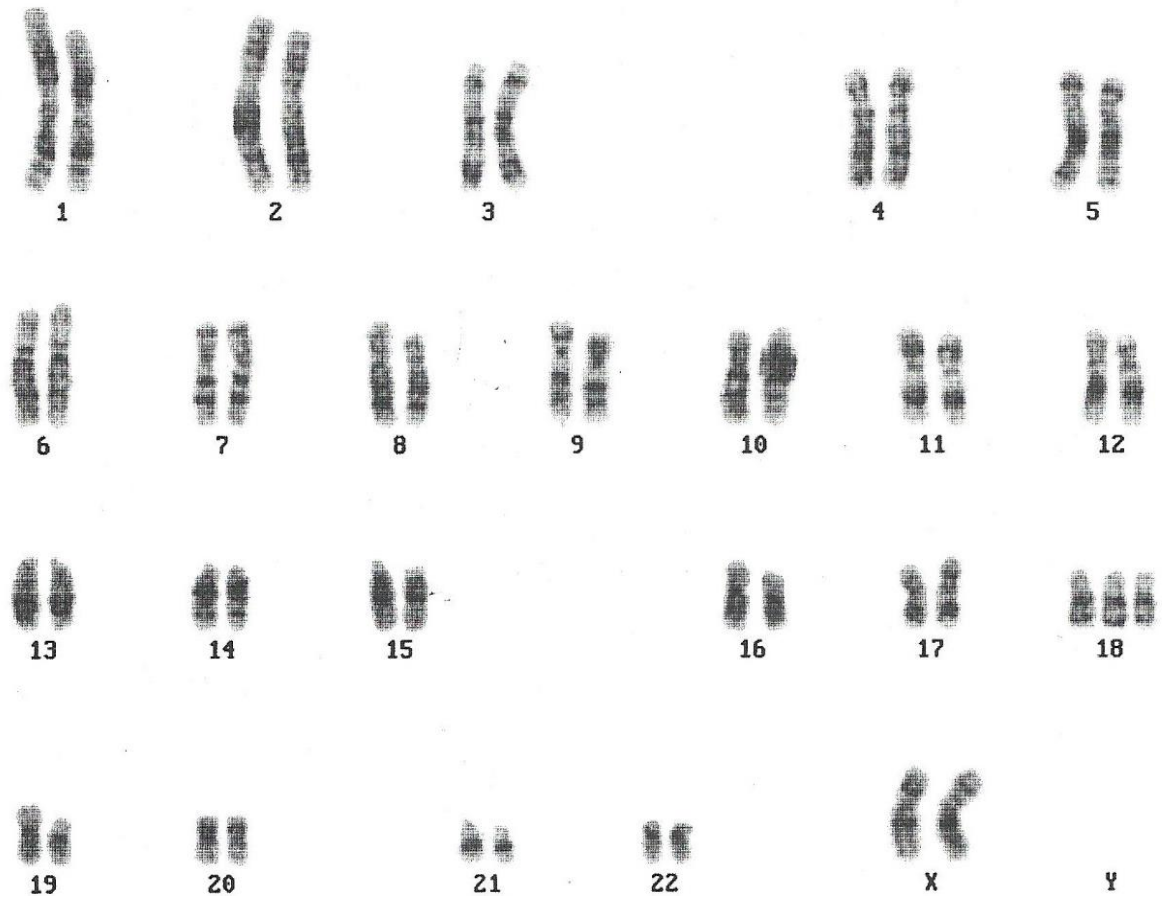
não-balanceado = afetado (DOWN)



DOWN = 1/3 = 30%

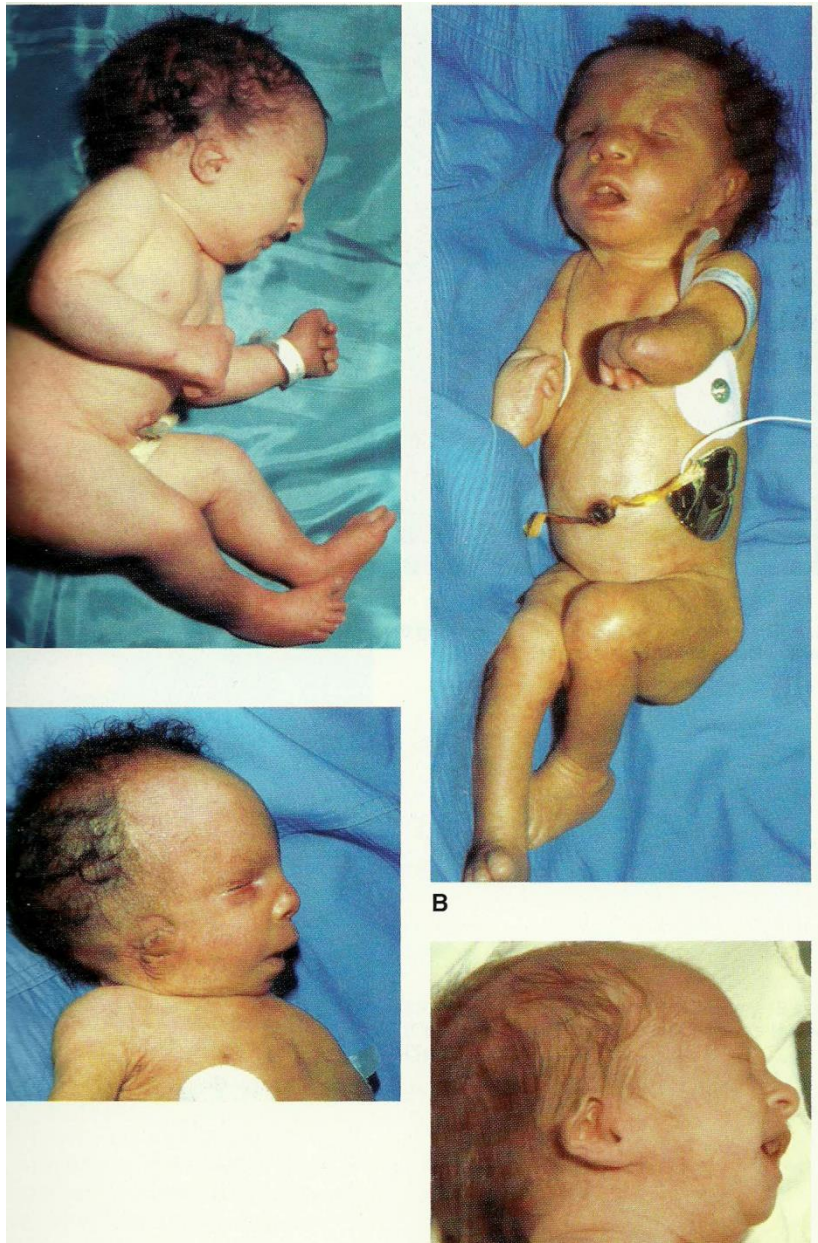
Mãe balanceada = 10-15%

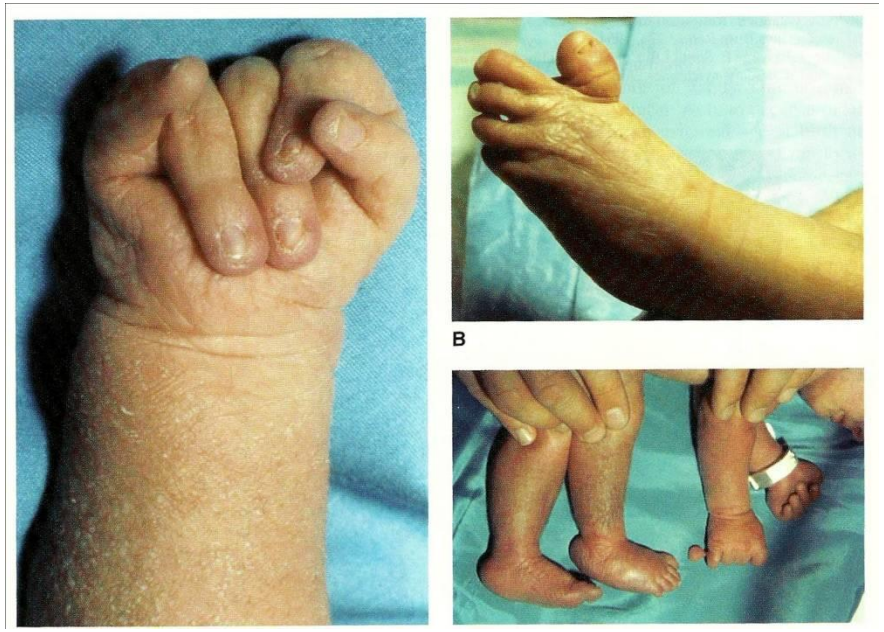
Pai balanceado = 2-3% (espermatozoides?)



TRISSOMIA (47, XX+18)

S. Edwards

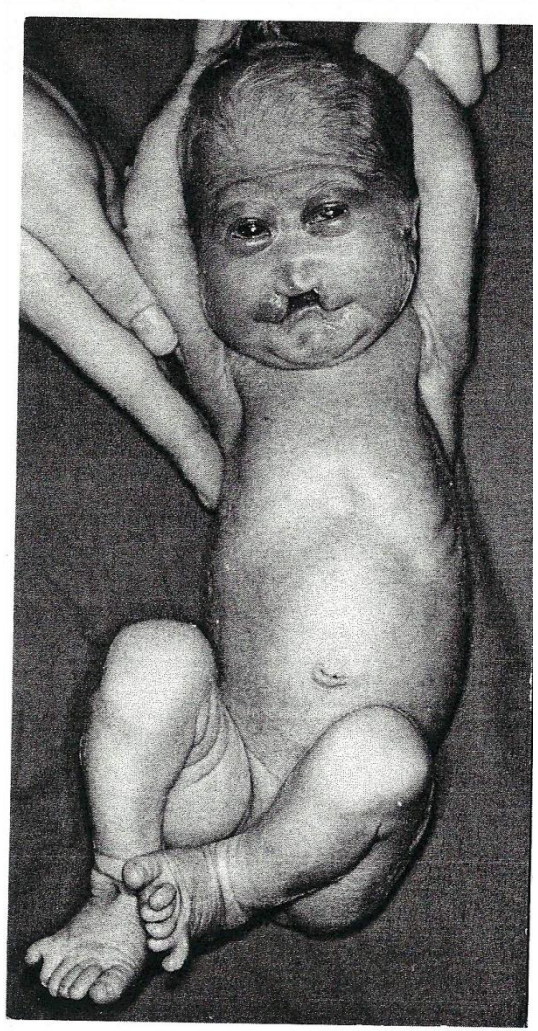




>150 malformações

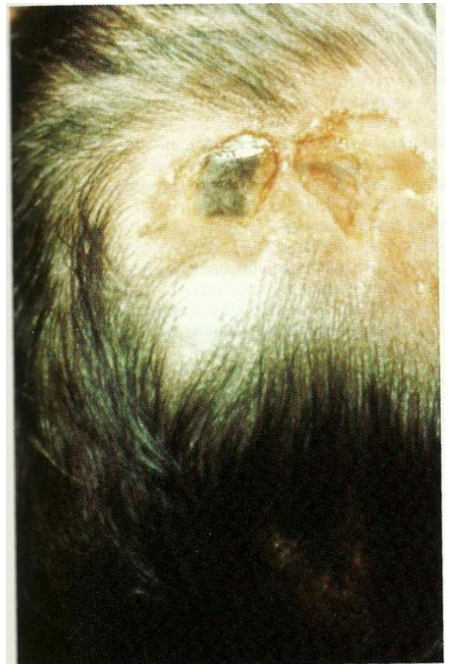
occipital proeminente
fendas palp.pequenas
orelhas baixo-implantadas displásicas
microstomia, micrognatia
pálato alto
esterno curto, mamilos hipoplásicos
sobreposição dedos
hálux curto (“em martelo”)
calcâneo proeminente (pé “cadeira-de-balanço”)

S.Patau → trissomia 13

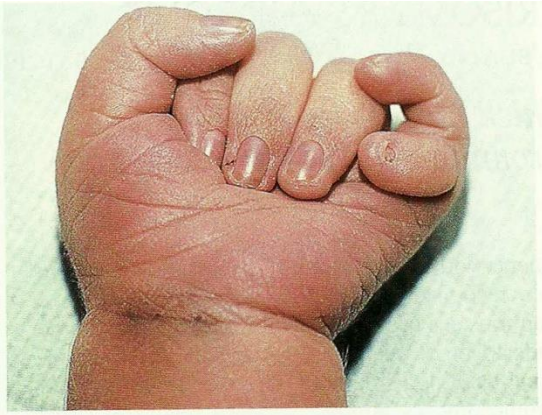


holoprosencefalia
polidactilia

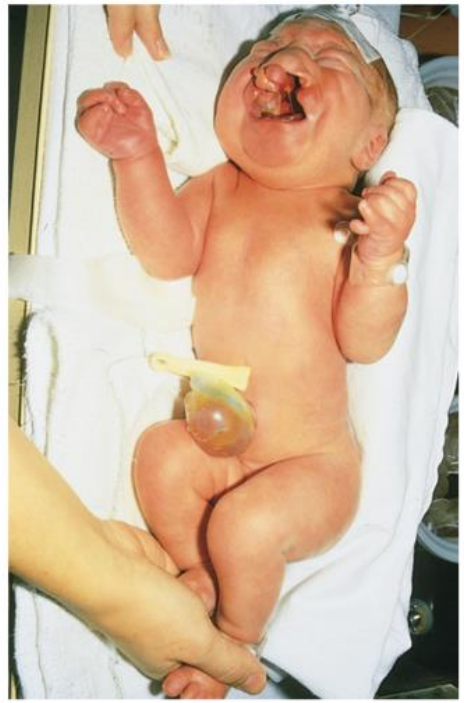
>180 malformações



aplasia cutis



polidactilia pós-axial



onfalocele

TABLE 6-2

Features of Autosomal Trisomies Compatible with Postnatal Survival

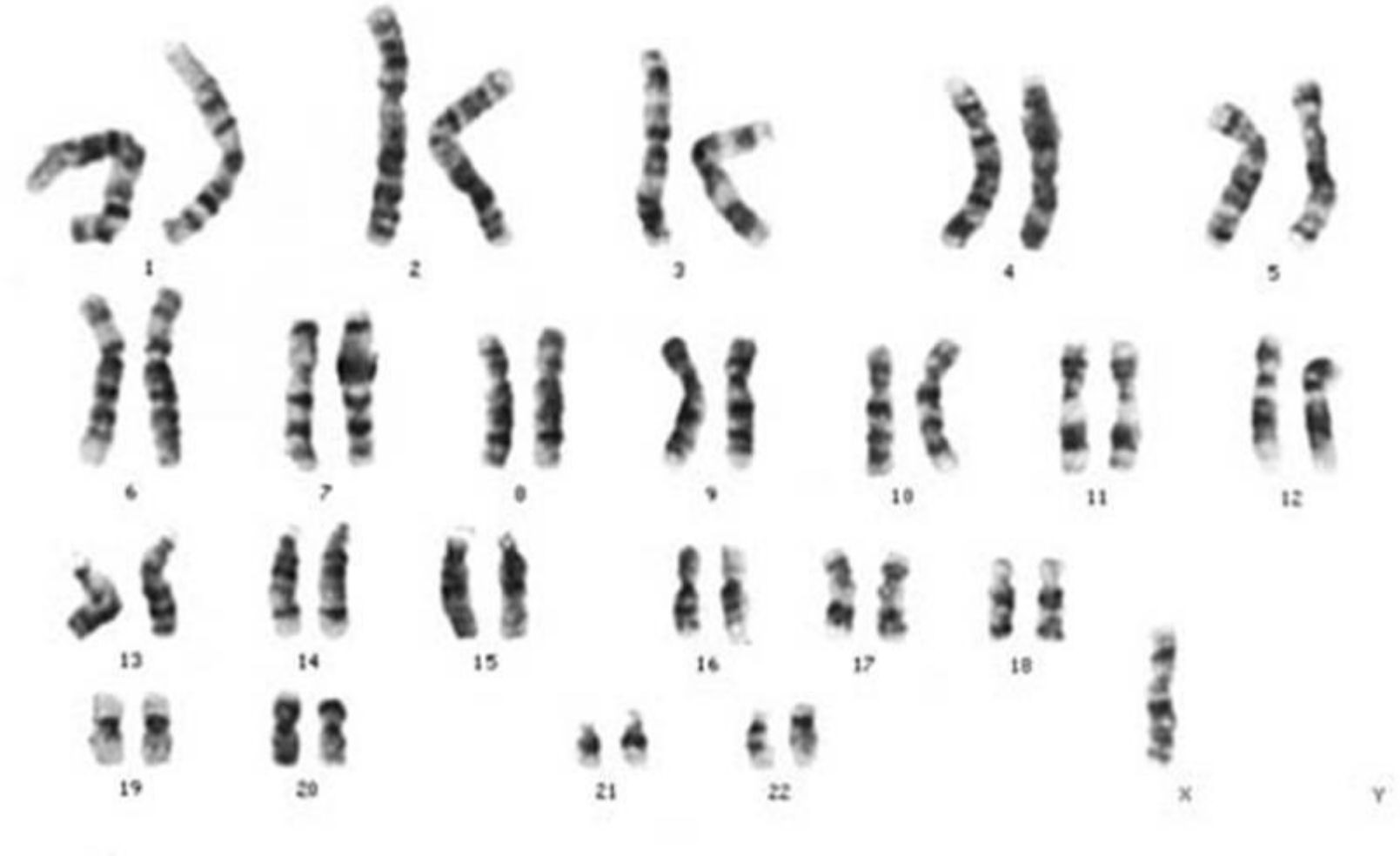
Feature	Trisomy 21	Trisomy 18	Trisomy 13
Incidence (live births)	1 in 850	1 in 6,000-8,000	1 in 12,000-20,000
Clinical presentation	Hypotonia, short stature, loose skin on nape, palmar crease, clinodactyly	Hypertonia, prenatal growth deficiency, characteristic fist clench, rocker-bottom feet	Microcephaly, sloping forehead, characteristic fist clench, rocker-bottom feet, polydactyly
Dysmorphic facial features	Flat occiput, epicanthal folds, Brushfield spots	Receding jaw, low-set ears	Ocular abnormalities, cleft lip and palate
Intellectual disability	Moderate to mild	Severe	Severe
Other common features	Congenital heart disease	Severe heart malformations	Severe CNS malformations
	Duodenal atresia	Feeding difficulties	Congenital heart defects
	Risk for leukemia		
	Risk for premature dementia		
Life expectancy	55 yr	Typically less than a few months; almost all <1 yr	50% die within first month, >90% within first year

CNS, Central nervous system.

THOMPSON&THOMPSON, 2016

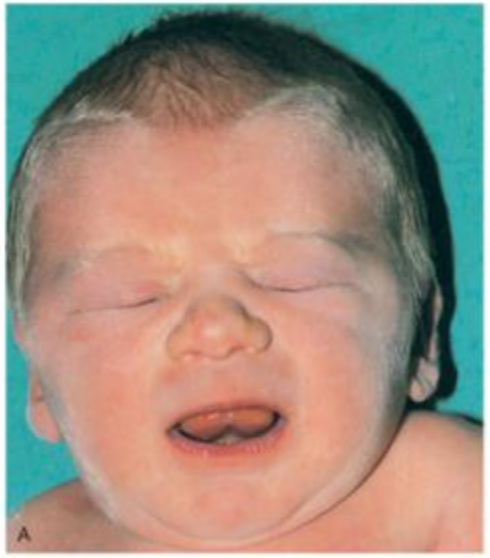
Anomalias cromossômicas sexuais

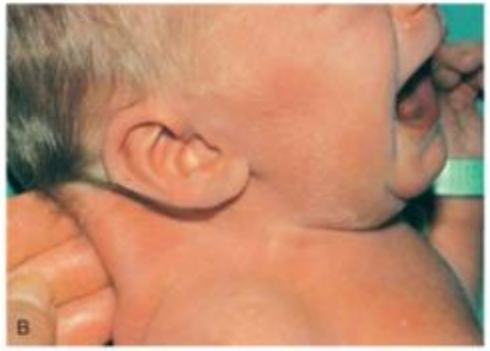
- Numéricas

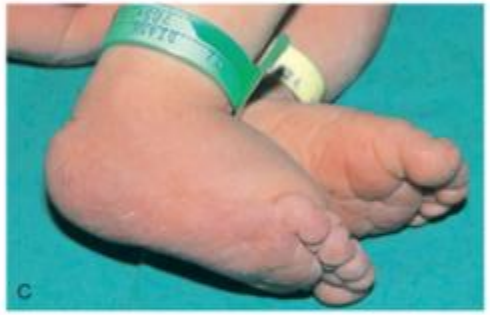


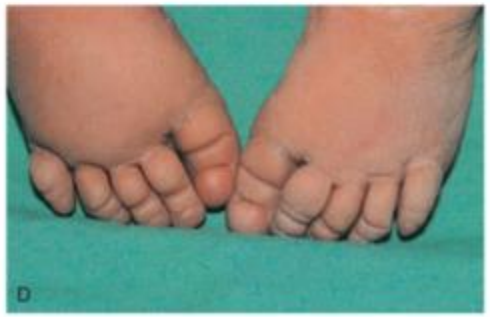
MONOSSOMIA = 45,X

síndrome de Turner = 45, X

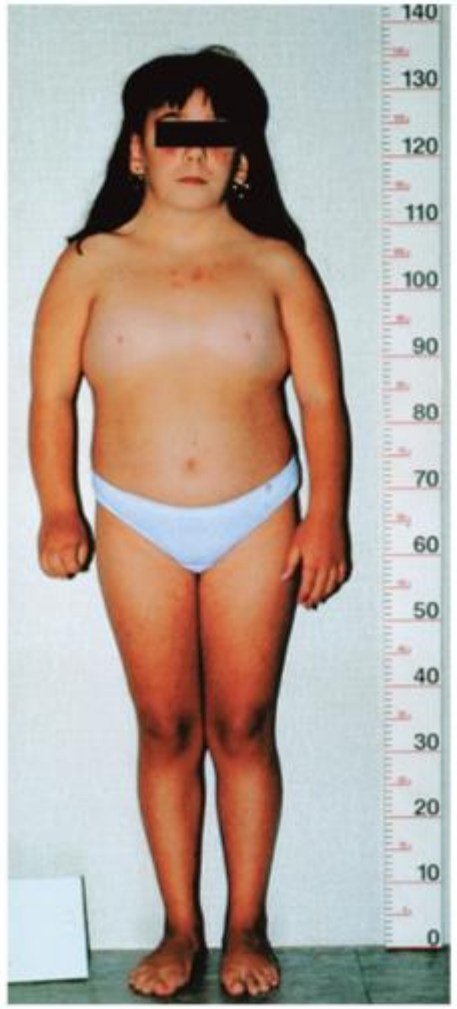




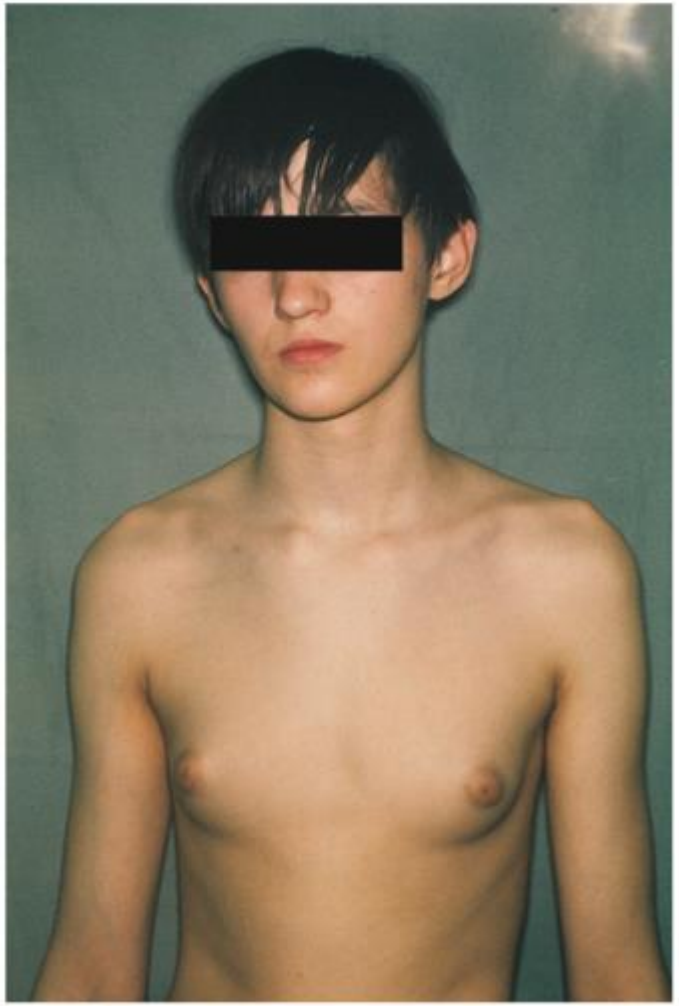




baixa estatura, pescoço curto e alado
linfedema nas mãos e pés
sobra de pele na nuca
hipertelorismo mamilar
valgismo cubital



síndrome de Klinefelter = 47, XXY



Ginecomastia

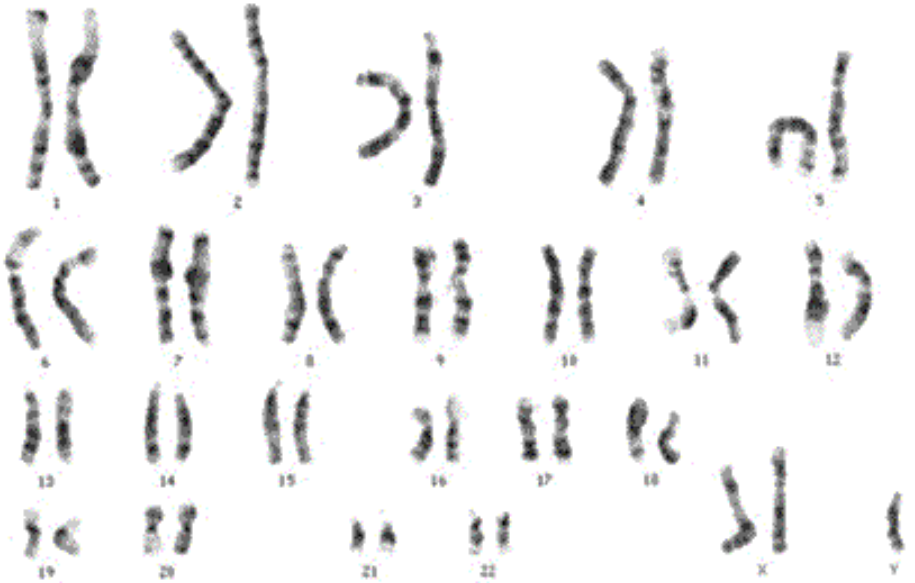


TABLE 6-6

Incidence of Sex Chromosome Abnormalities

Sex	Disorder	Karyotype	Approximate Incidence
Male	Klinefelter syndrome	47,XXY	1/600 males
		48,XXXY	1/25,000 males
		Others (48,XXYY; 49,XXXYY; mosaics)	1/10,000 males
	47,XYY syndrome	47,XYY	1/1000 males
	Other X or Y chromosome abnormalities		1/1500 males
	XX testicular DSD	46,XX	1/20,000 males
		Overall incidence: 1/300 males	
Female	Turner syndrome	45,X	1/4000 females
		46,X,i(Xq)	1/50,000 females
		Others (deletions, mosaics)	1/15,000 females
	Trisomy X	47,XXX	1/1000 females
	Other X chromosome abnormalities		1/3000 females
	XY gonadal dysgenesis	46,XY	1/20,000 females
	Androgen insensitivity syndrome	46,XY	1/20,000 females
		Overall incidence: 1/650 females	

DSD, Disorder of sex development.

Data updated from Robinson A, Linden MG, Bender BG: Prenatal diagnosis of sex chromosome abnormalities. In Milunsky A, edit
Johns Hopkins University Press, pp 249-285.

THOMPSON&THOMPSON, 2016

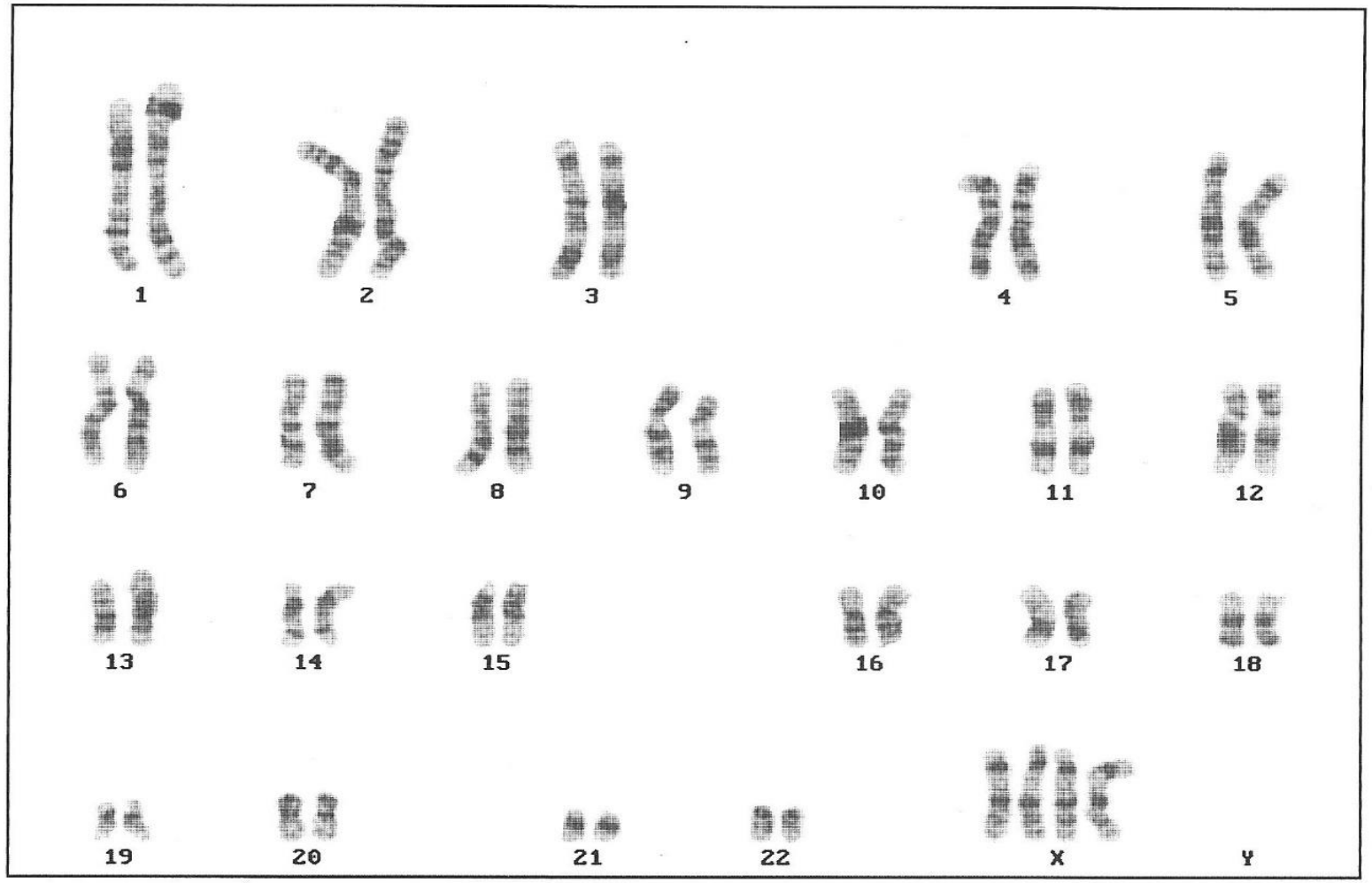
TABLE 6-7

Features of Sex Chromosome Aneuploidy Conditions

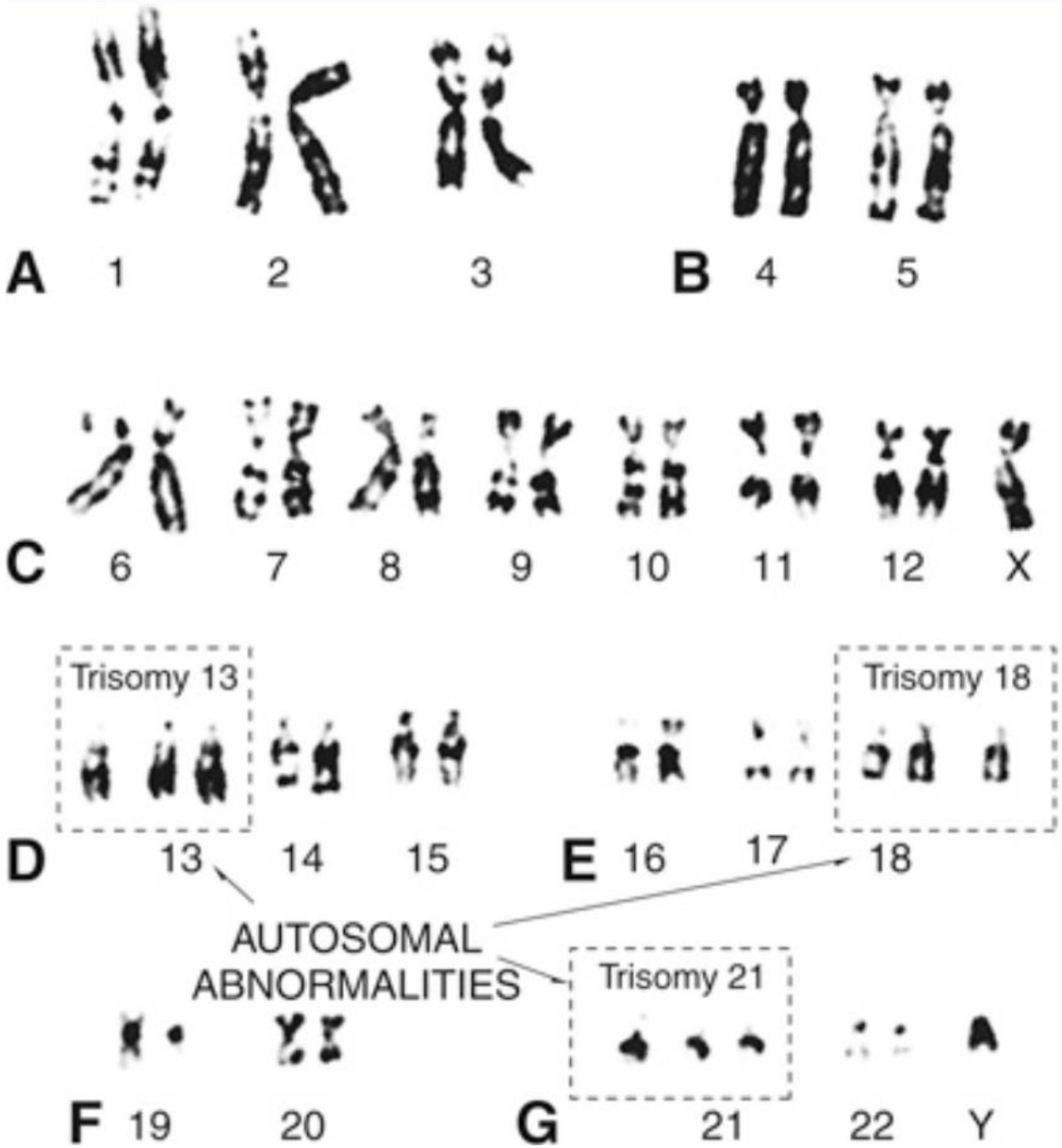
Feature	47,XXY Klinefelter Syndrome	47,XYY	47,XXX Trisomy X	45,X Turner Syndrome
Prevalence	1 in 600 male births	1 in 1000 male births	1 in 1000 female births	1 in 2500 to 4000 female births
Clinical phenotype	Tall male; see Figure 6-15 and text	Tall, but otherwise typical male appearance	Hypotonia, delayed milestones; language and learning difficulties; tend to be taller than average	Short stature, webbed neck, lymphedema; risk for cardiac abnormalities
Cognition/intelligence	Verbal IQ reduced to low-normal range; educational difficulties	Verbal IQ reduced to low-normal range; language delay; reading difficulties	Normal to low-normal range (both verbal and performance IQ decreased)	Typically normal, but performance IQ lower than verbal IQ
Behavioral phenotype	No major disorders; tendency to poor social adjustments, but normal adult relationships	Subset with specific behavioral problems likely associated with lower IQ	Typically, no behavioral problems; some anxiety and low self-esteem; reduced social skills	Typically normal, but impaired social adjustment
Sex development/fertility	Hypogonadism, azoospermia, infertility	Normal	?Reduced fertility in some ?Premature ovarian failure	Gonadal dysgenesis, delayed maturation, infertility
Variant karyotypes	See Table 6-6		48,XXXX; 49,XXXXX Increased severity with additional X's	46,Xi(Xq); 45,X/46,XX mosaics; other mosaics

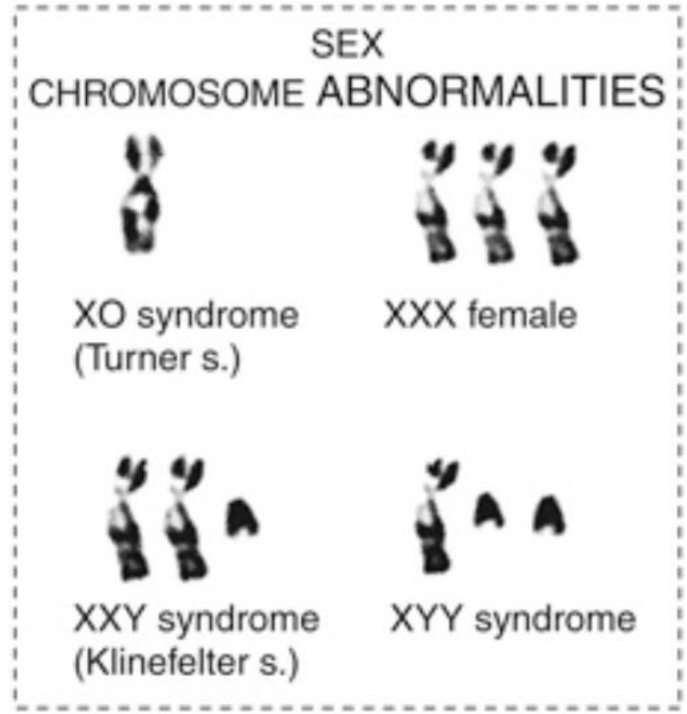
Summarized from Ross JL, Roeltgen DP, Kushner H, et al: Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. *Pediatrics* 129:769-778, 2012; Pinsker JE: Turner syndrome: updating the paradigm of clinical care. *J Clin Endocrinol Metab* 97:E994-E1003, 2012; and AXYS, http: www.genetic.org.

THOMPSON&THOMPSON, 2016



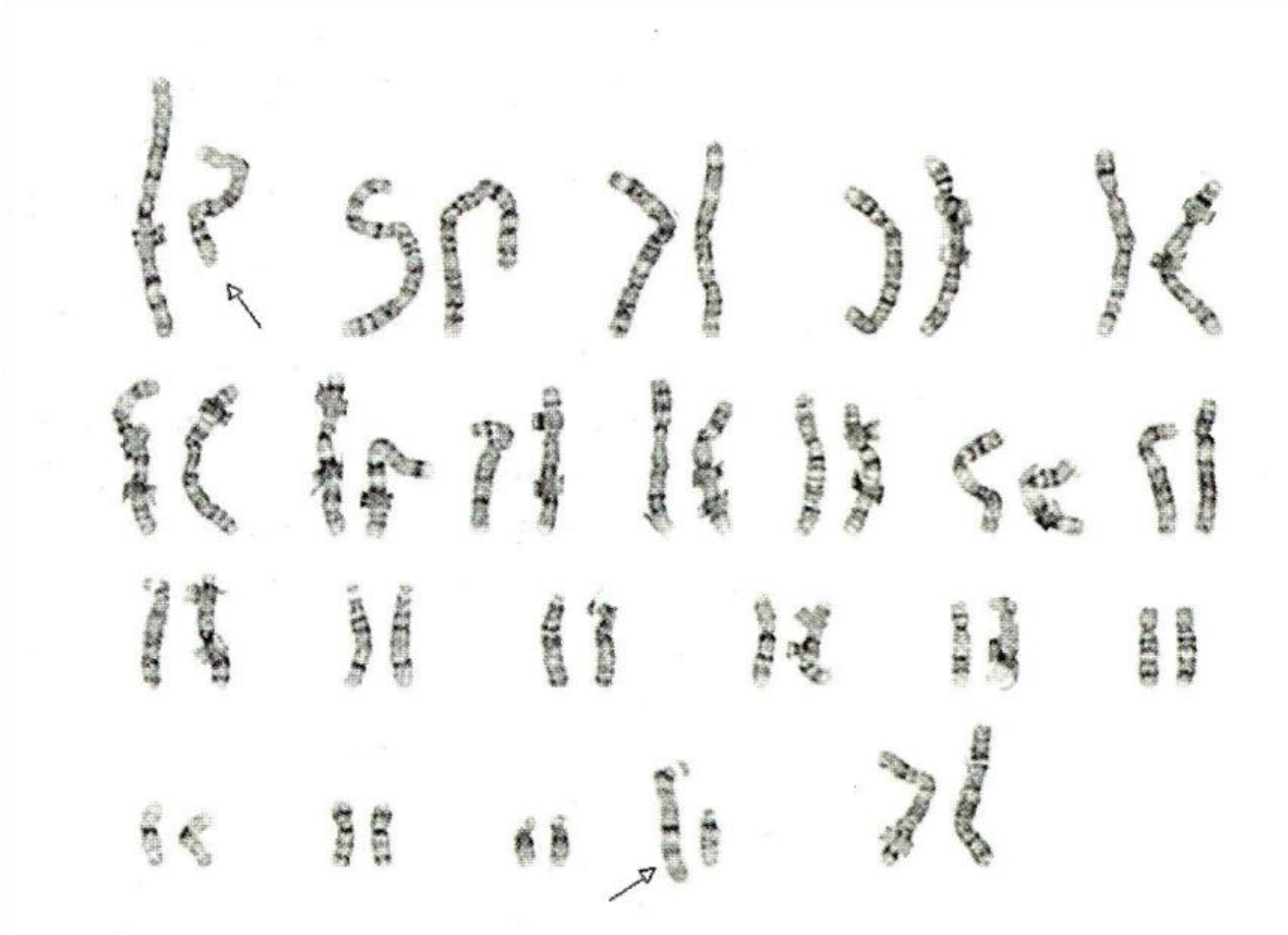
esultado : 45,X,[90]/48,XXXX,[10]


A 1 2 3
B 4 5
C 6 7 8 9 10 11 12 X
Trisomy 13
Trisomy 18
D 13 14 15
E 16 17 18
AUTOSOMAL ABNORMALITIES
Trisomy 21
F 19 20
G 21 22 Y


SEX CHROMOSOME ABNORMALITIES
XO syndrome (Turner s.)
XXX female
XXY syndrome (Klinefelter s.)
XYY syndrome

Anomalias cromossômicas

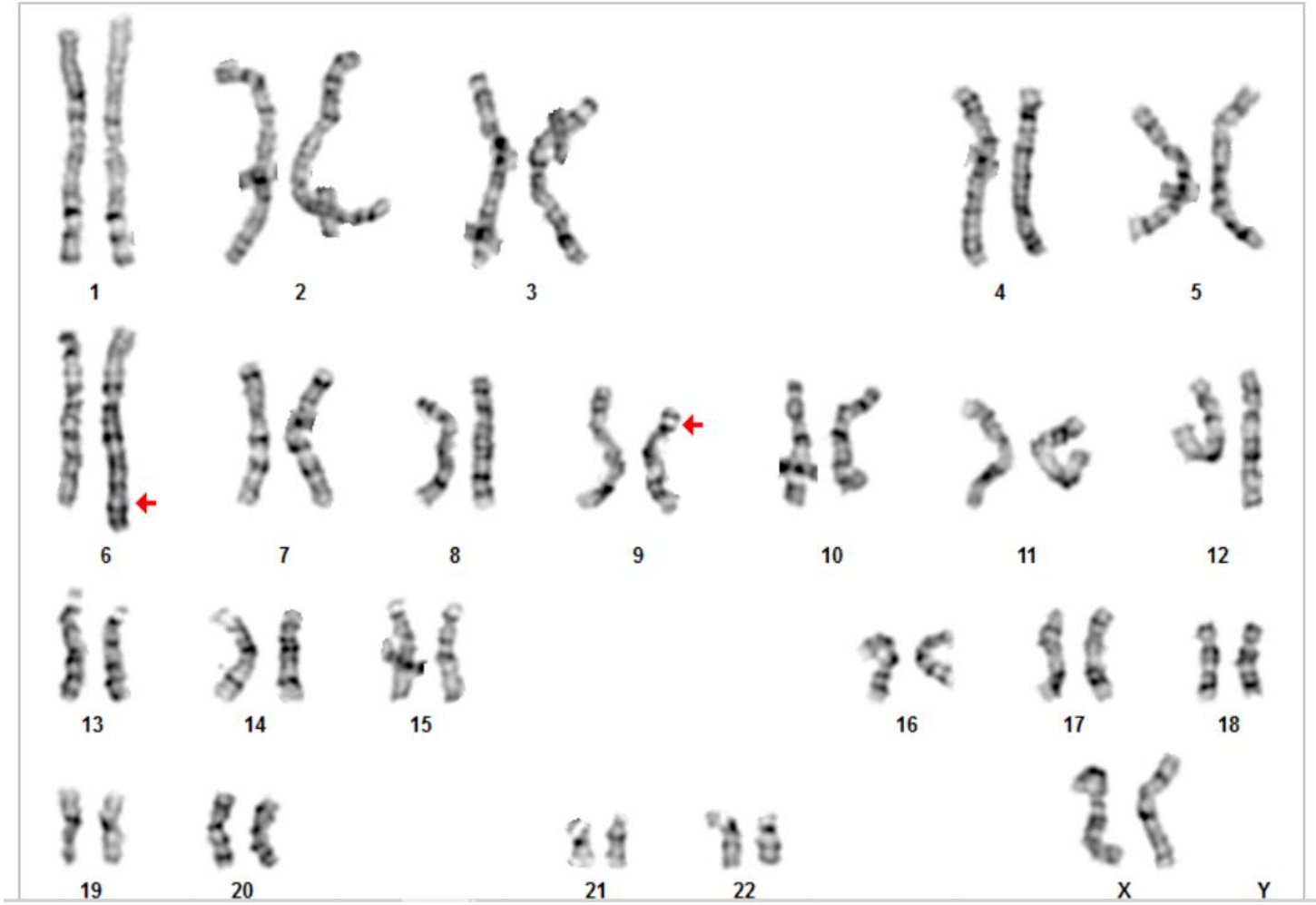
- Estruturais



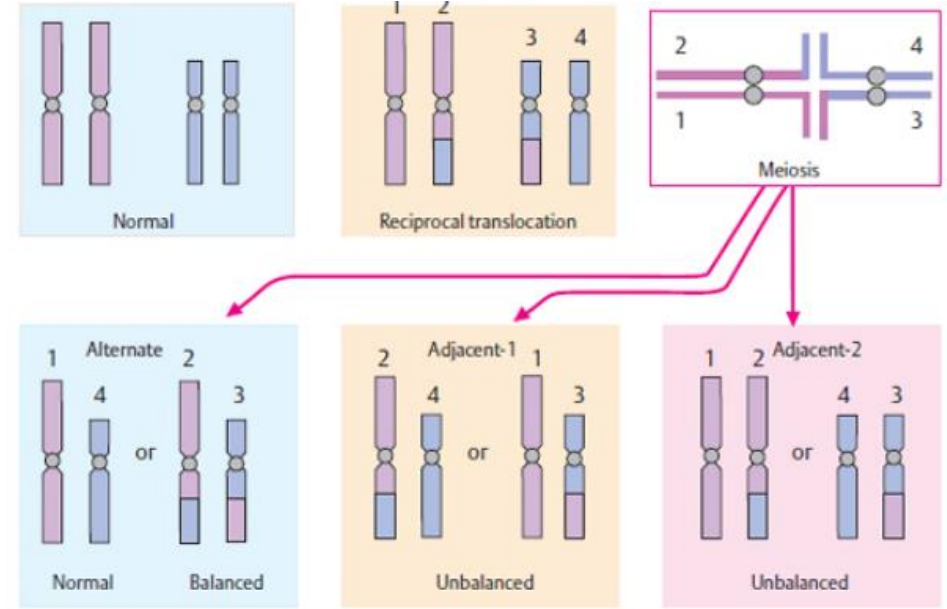
46,XX,t(1q;22q) = translocação recíproca BALANCEADA

Resultado: 46,XX,t(6;9)(q27;p21)

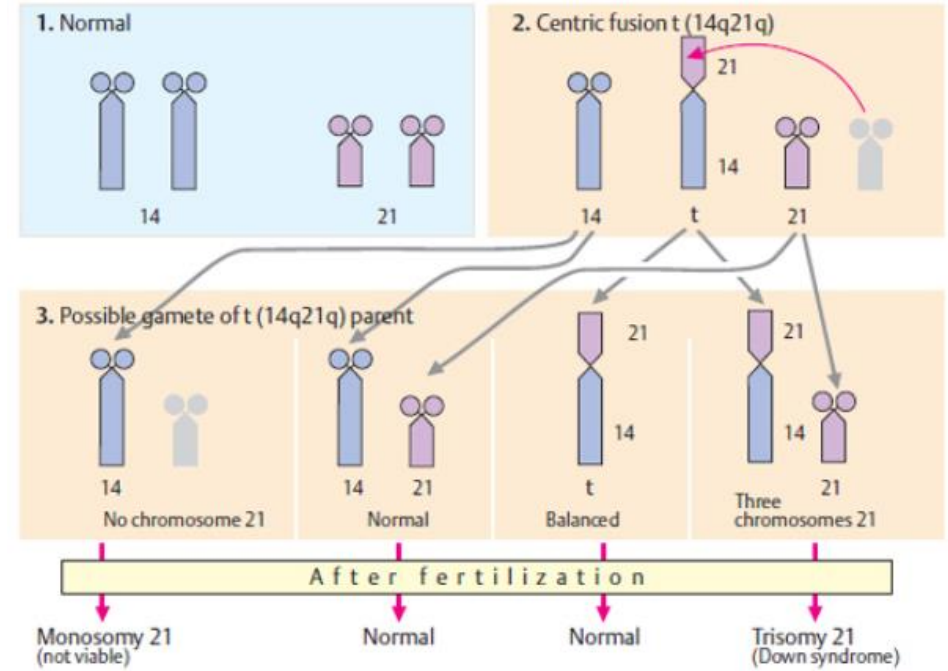
CARIOTIPO ALTERADO



translocação recíproca BALANCEADA



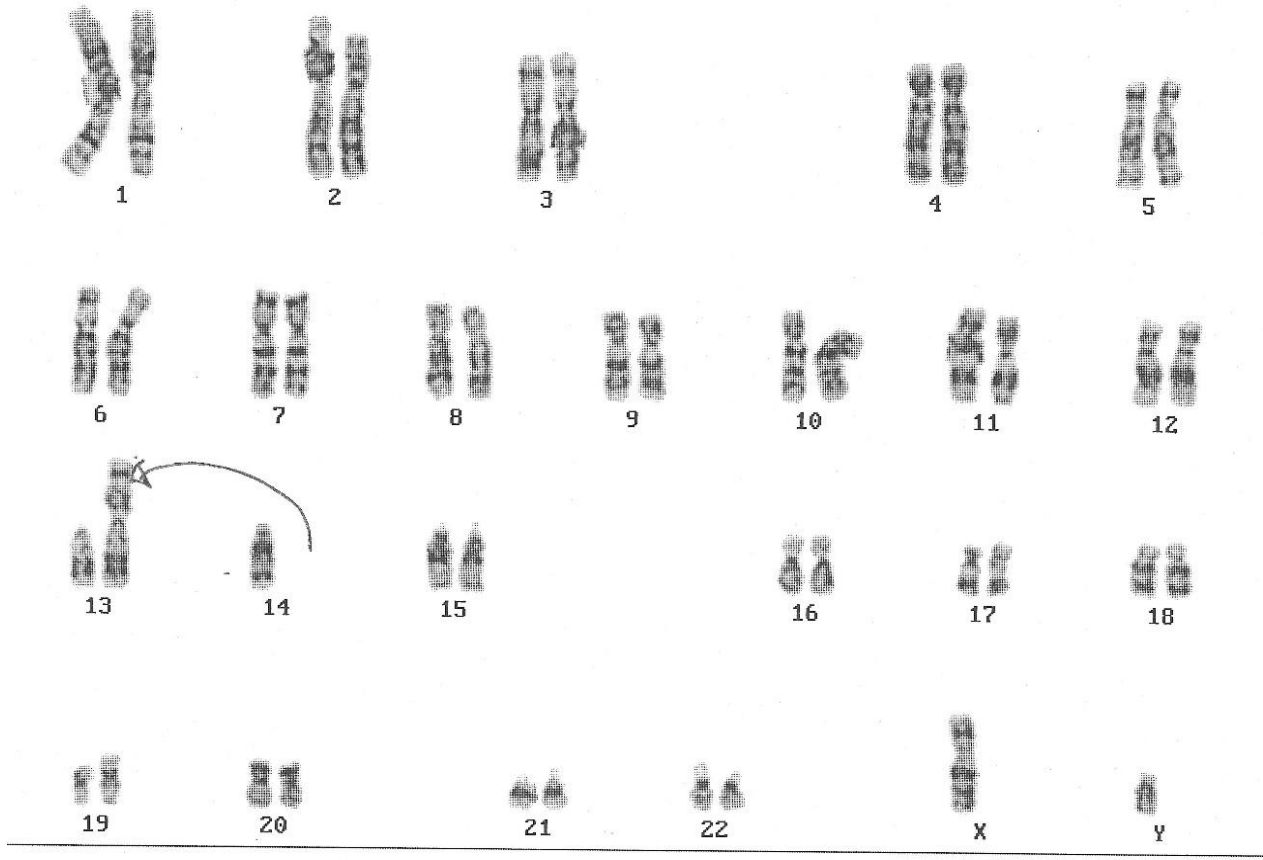
A. Reciprocal translocation



B. Centric fusion of acrocentric chromosomes

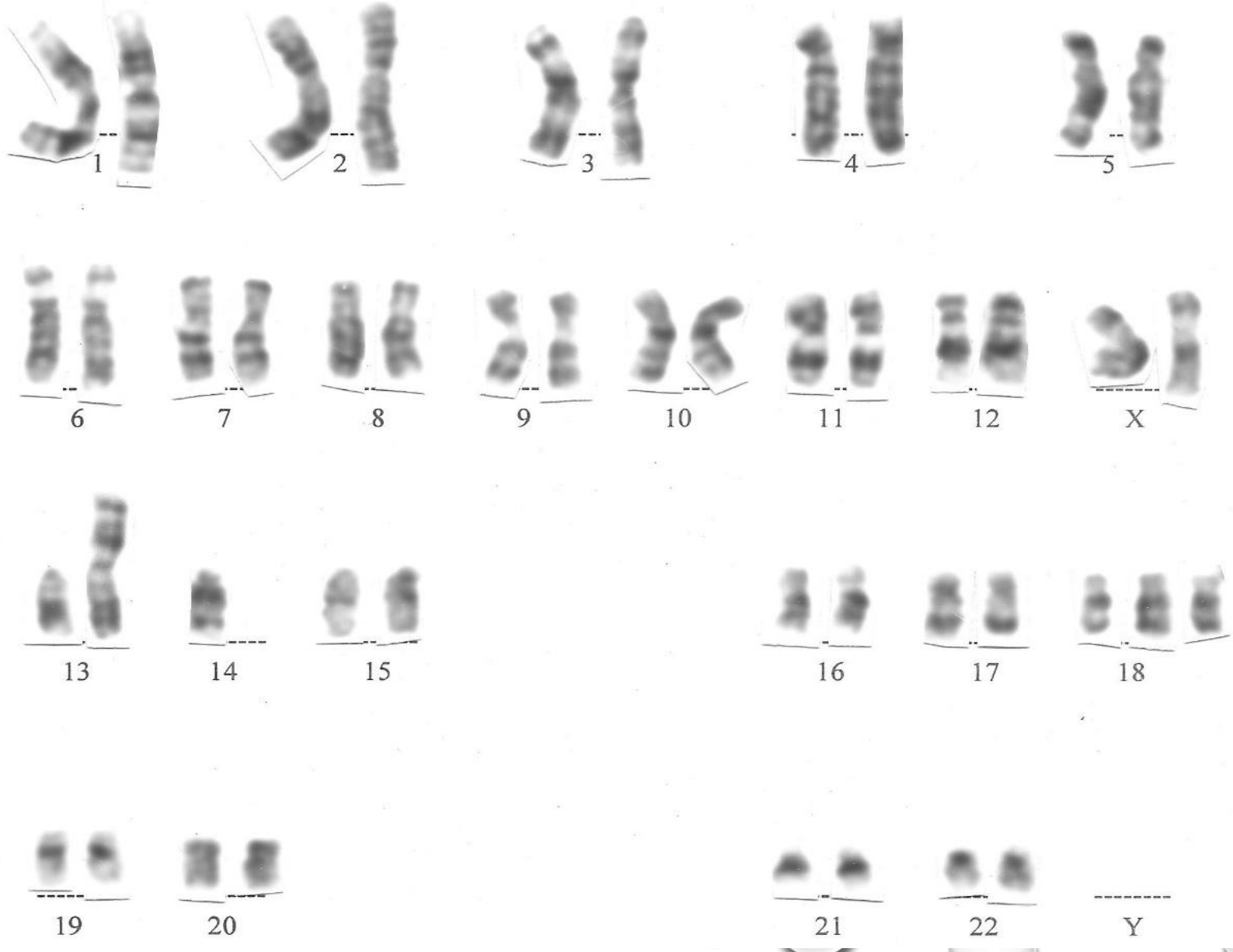
Anomalias cromossômicas

- **Estruturais equilibradas**
  - sem perdas ou ganhos
  - sem alteração do fenótipo
  - risco de prole não equilibrada
  - 1-20%
  - rob(13;14)(q10;q10) = mais comum (1: 1.300)



Resultado : 45,XY,t(13;14)(q10;q10)

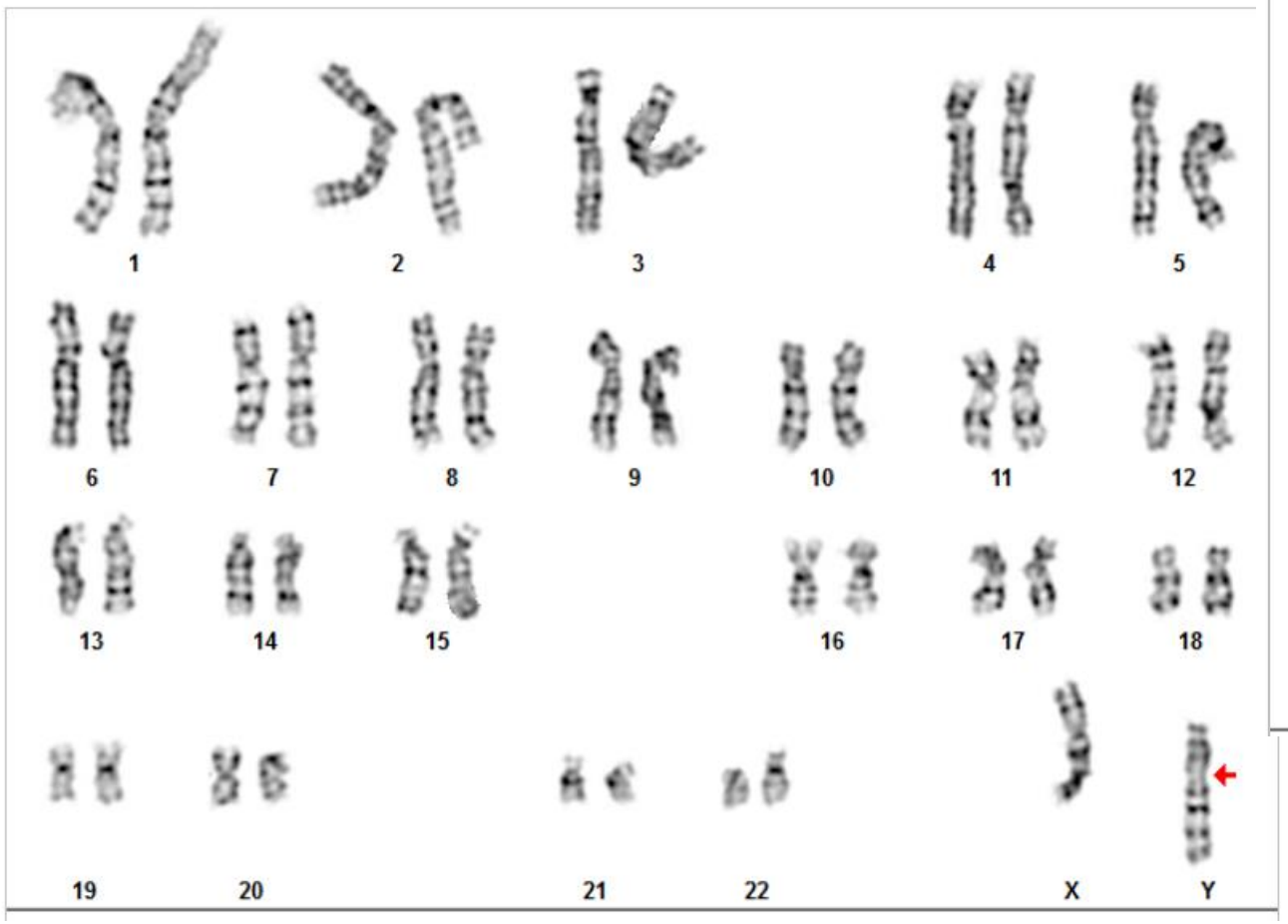
Diagnóstico Citogenético: 46,XX,t(13;14),+18

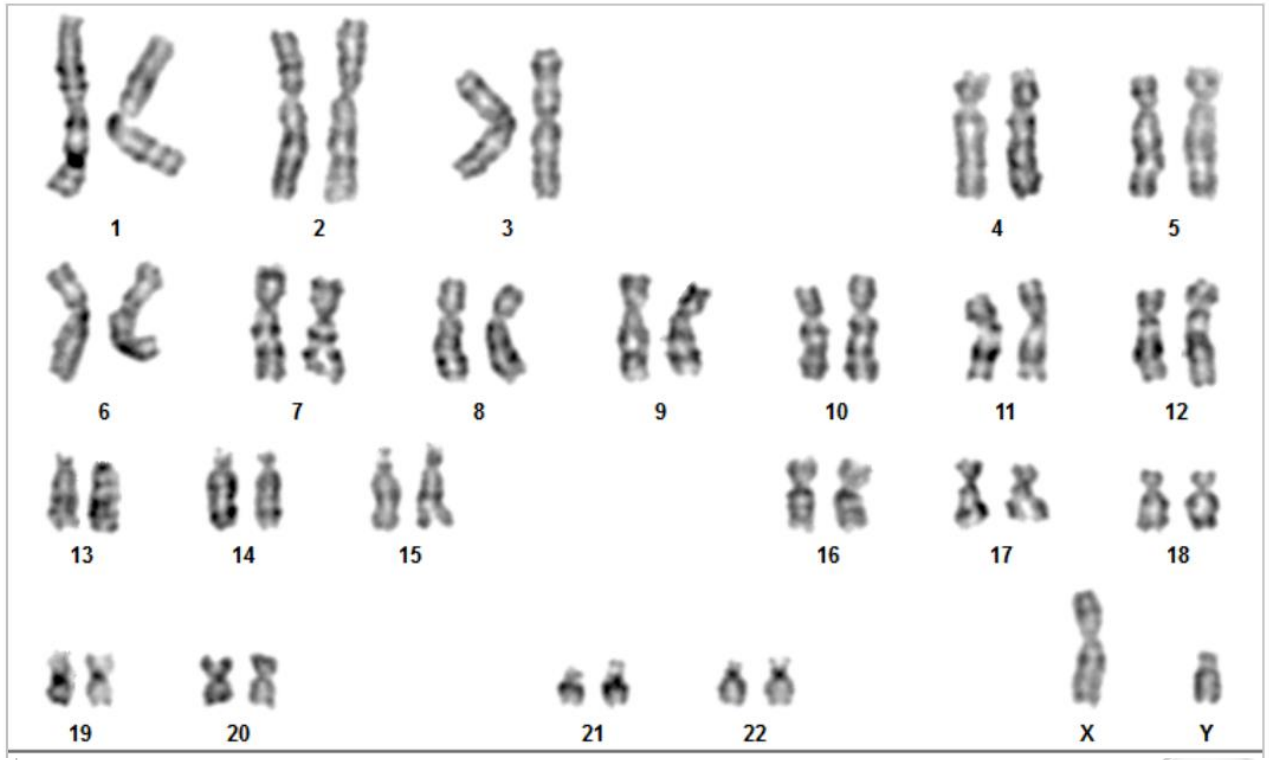


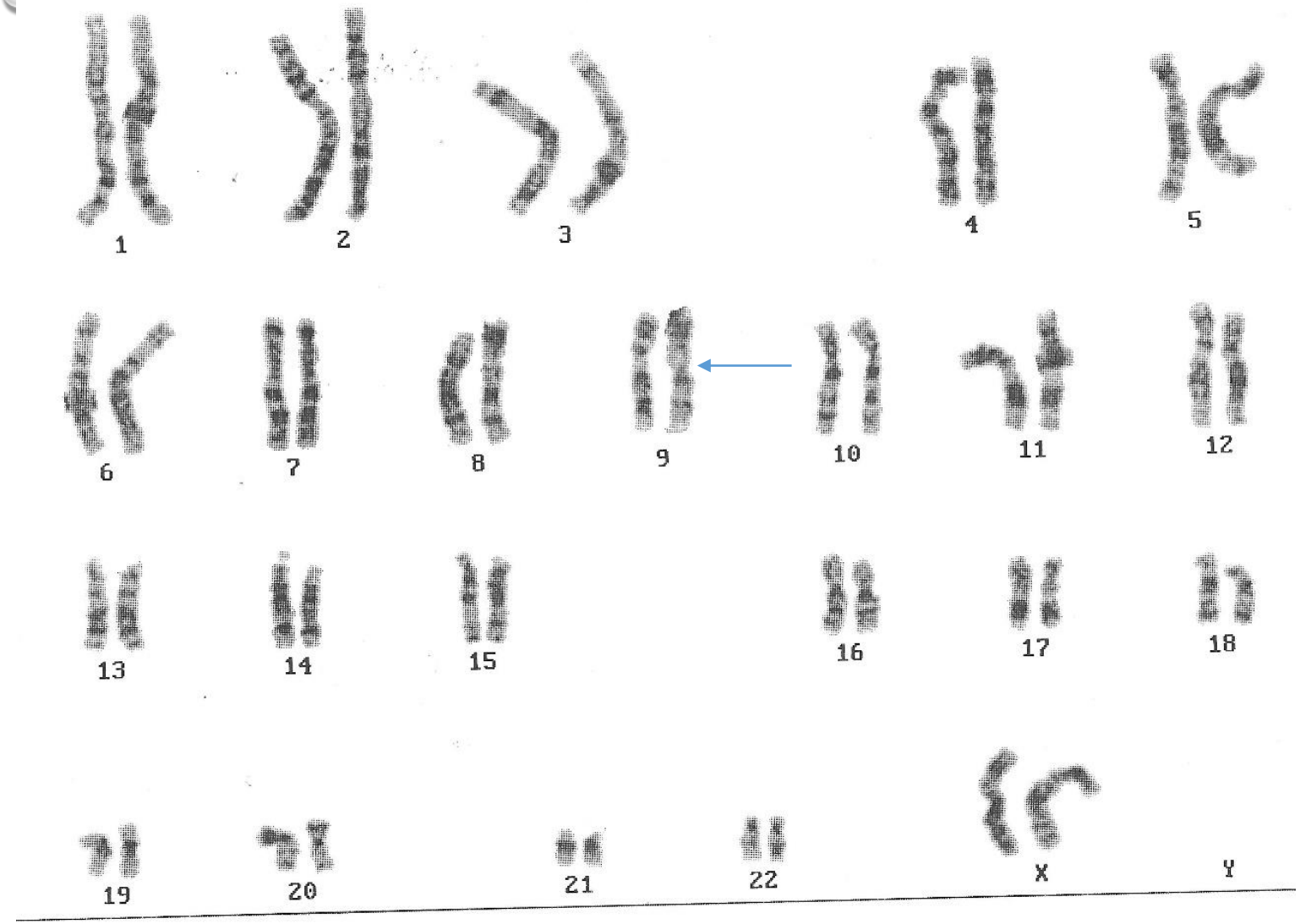
Material: Liquido Amniotico

Resultado: 46,X,der(Y)t(Y;1)(q12;q21)[10]/46,XY[40]

CARIOTIPO ALTERADO

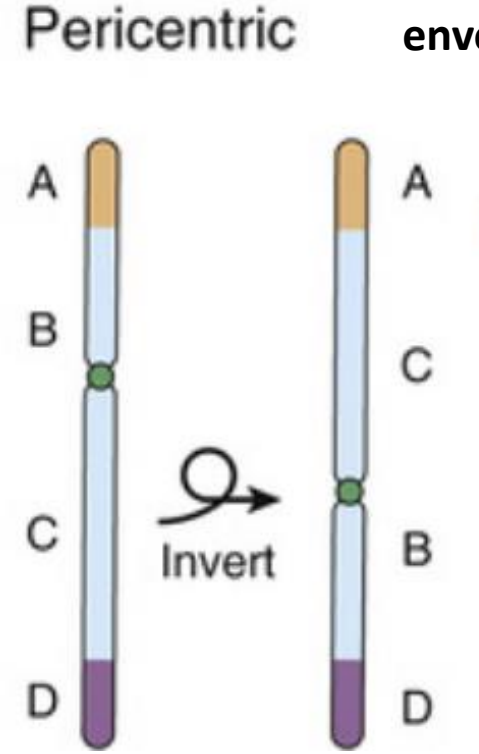






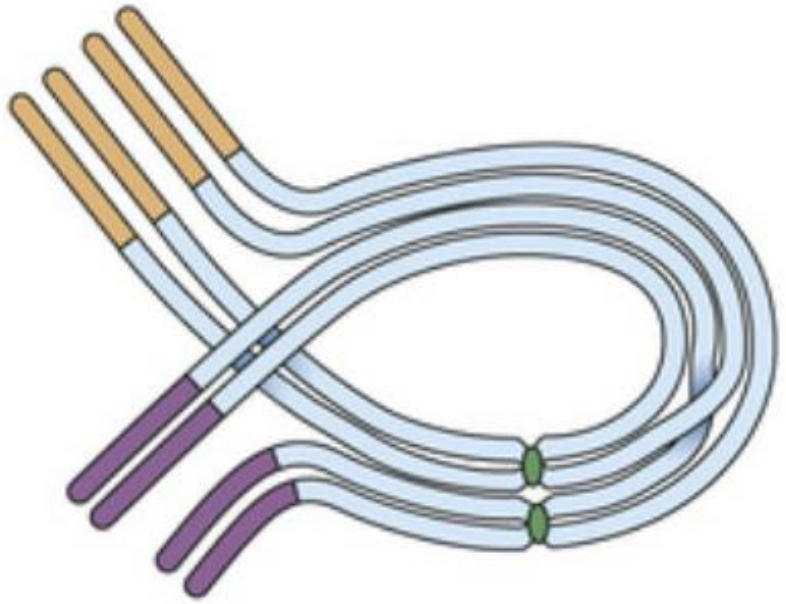
Resultado : 46,XX,inv(9)(p13q21)

inversões



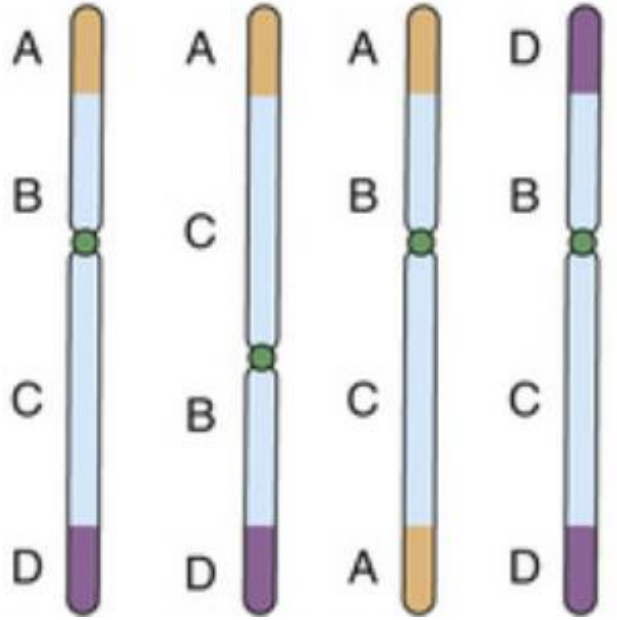
envolve o centrômero = 2 quebras em braços diferentes

PORTADOR balanceado



MEIOSE I (“loop”)

GAMETAS

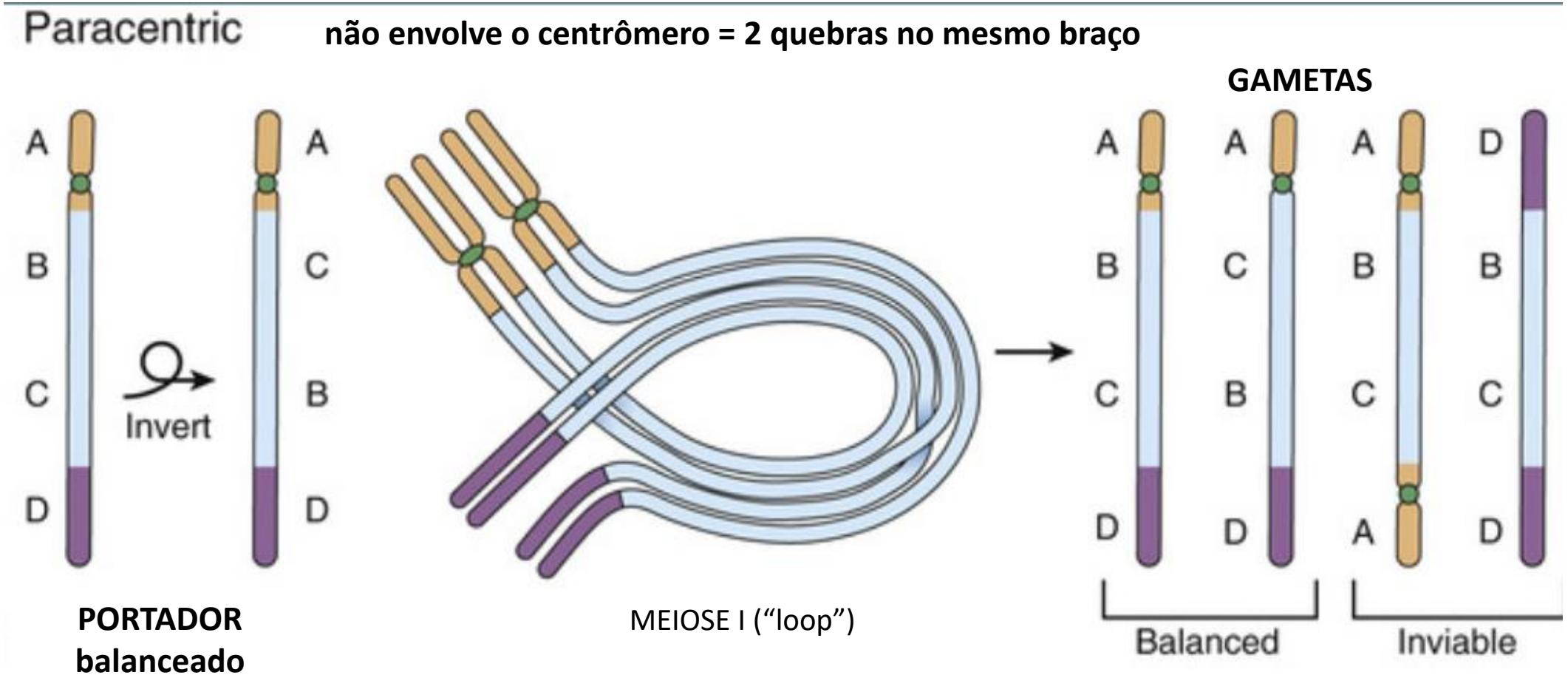


balanceado **não balanceados viáveis**

a chance de nascer uma criança não-balanceada depende do tamanho do segmento não balanceado!

~5-10%

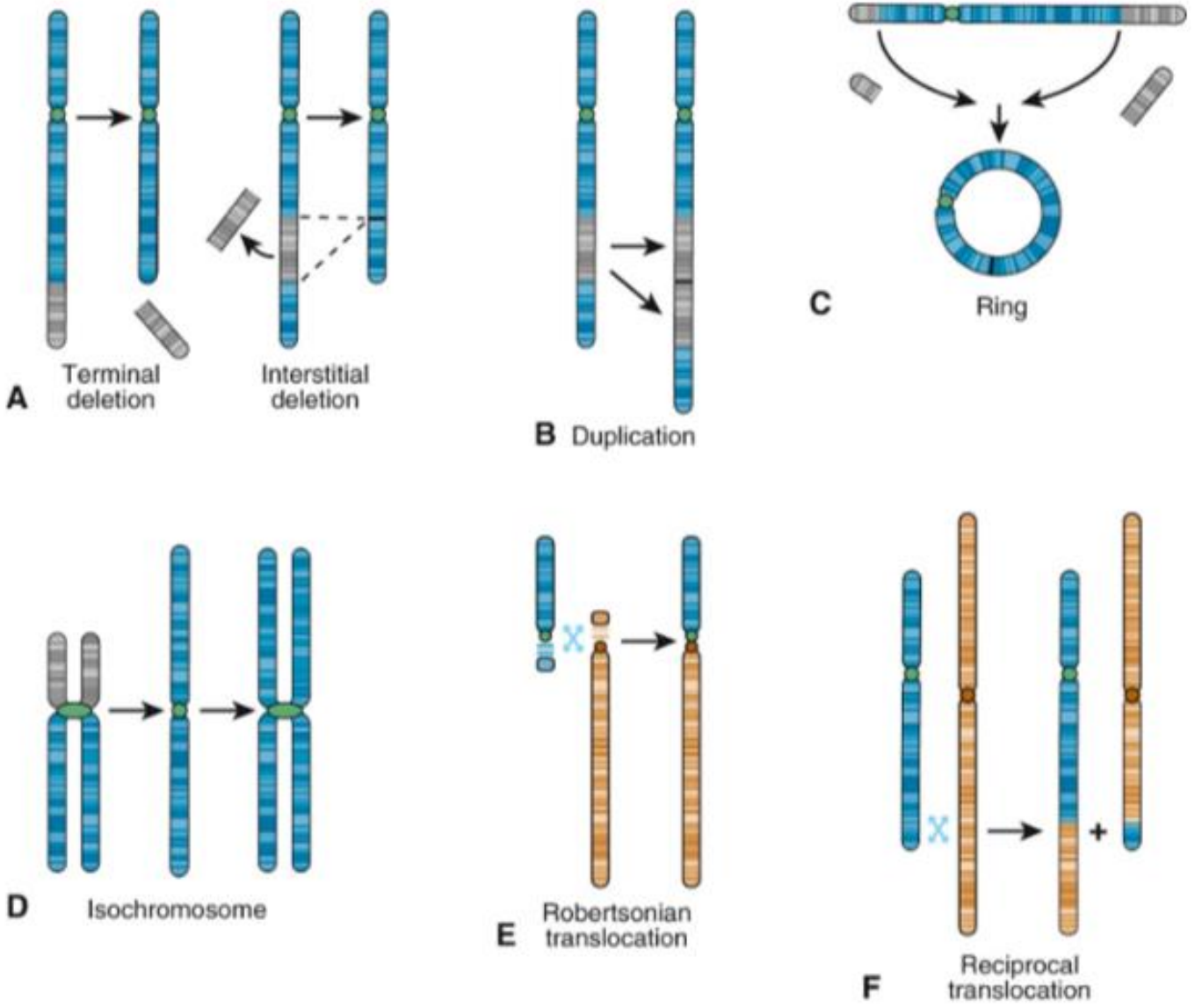
inversões



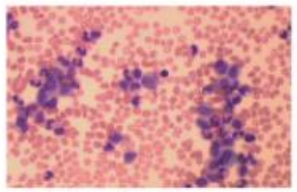
PORTADOR balanceado

a chance de nascer uma criança não-balanceada (afetada) é muito baixa!

- **ANOMALIAS ESTRUTURAIS**



LMC

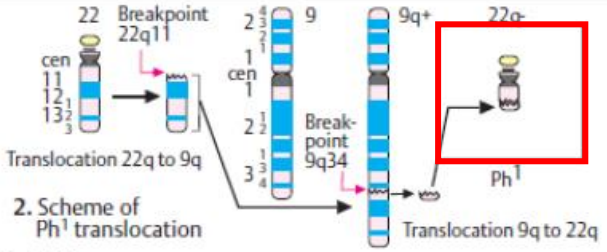


1. Accumulation of white blood cells (blue)

2. The Philadelphia translocation 9q;22q

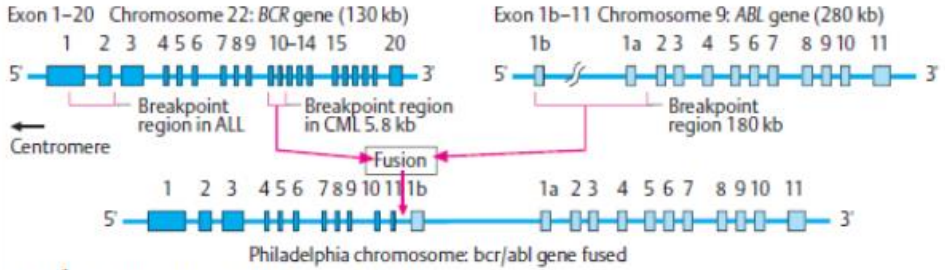
A. Main features

1. Ph[1] translocation

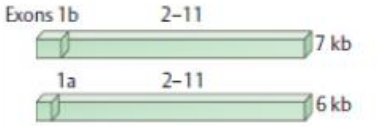


2. Scheme of Ph[1] translocation

B. Ph[1] translocation [t(9;22) (q34;q11)]

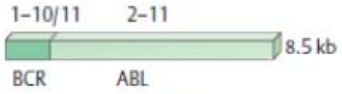


C. Ph[1] translocation causes fusion of two genes



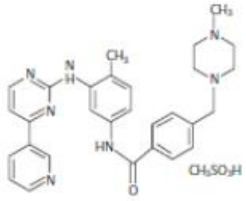
1. Normal ABL mRNA

2. Normal ABL protein (145 kDa)

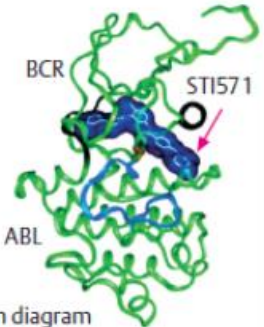


3. Abnormal BCR/ABL fusion

4. Abnormal fusion protein (210 kDa)



5. Chemical structure of STI571 (Gleevec)



6. Ribbon diagram

D. The BCR/ABL fusion protein

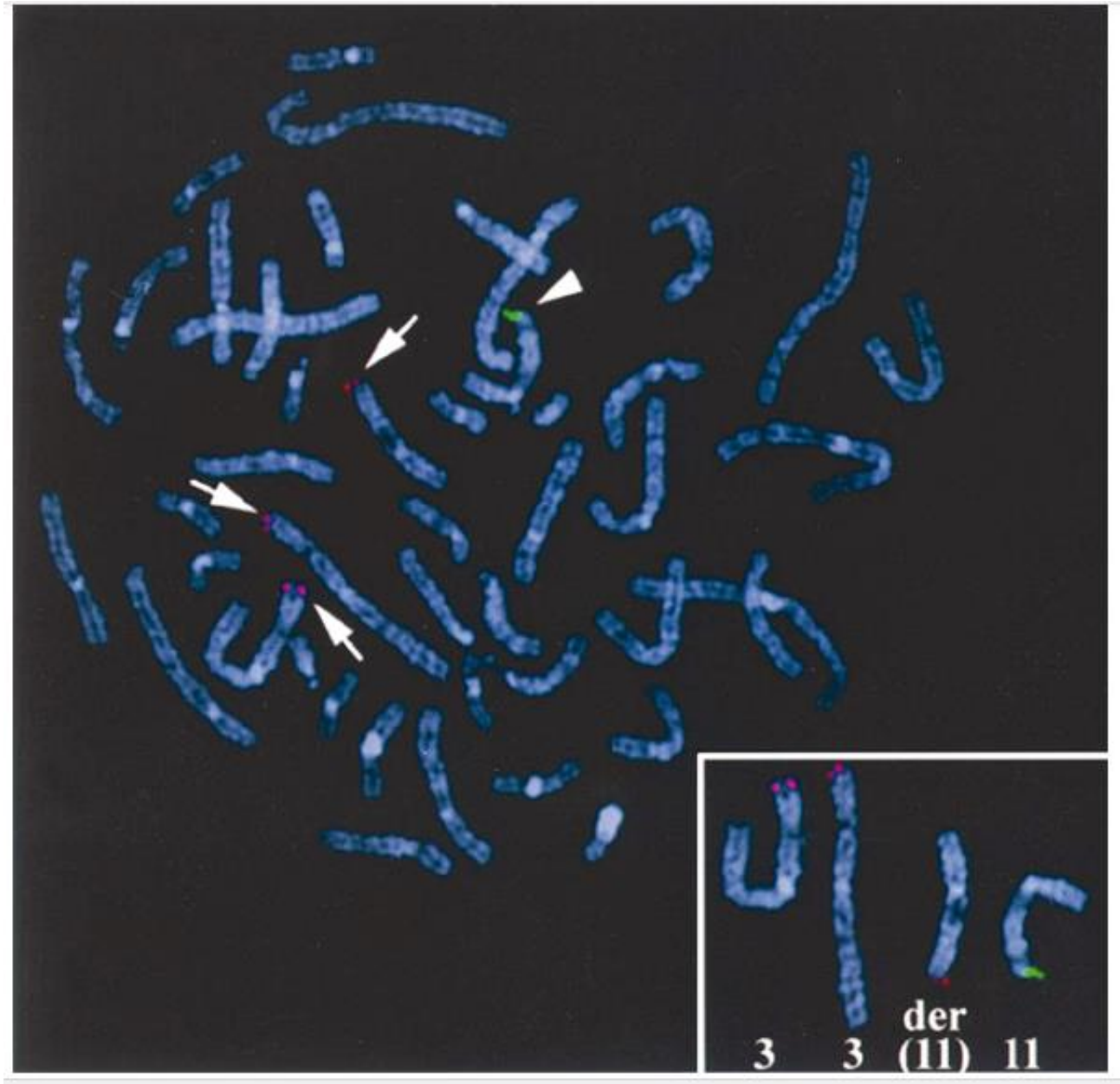
oncoproteína quimérica

IMATINIBE

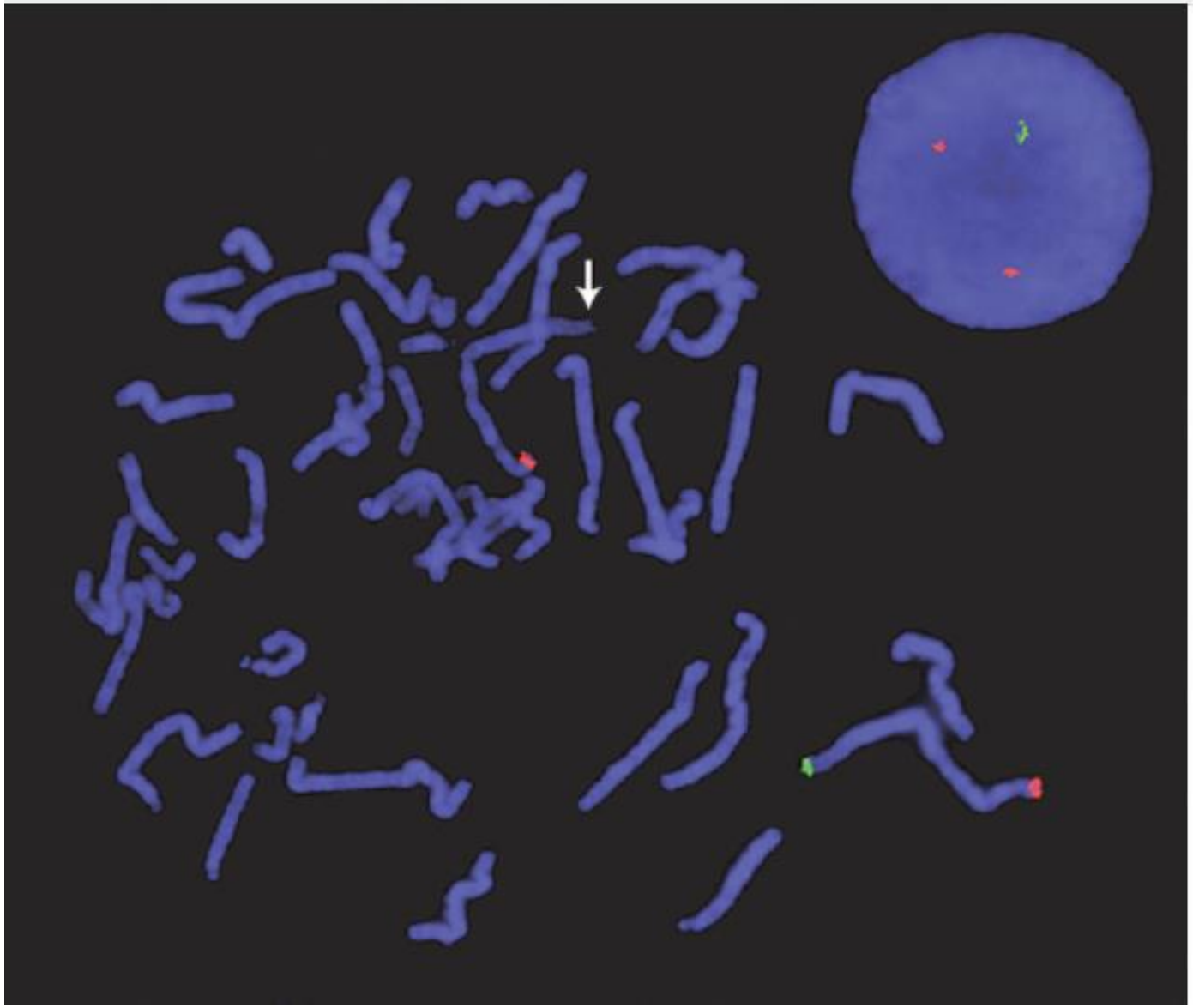
Resultado: 46,XX,dup(11)(q13q23)

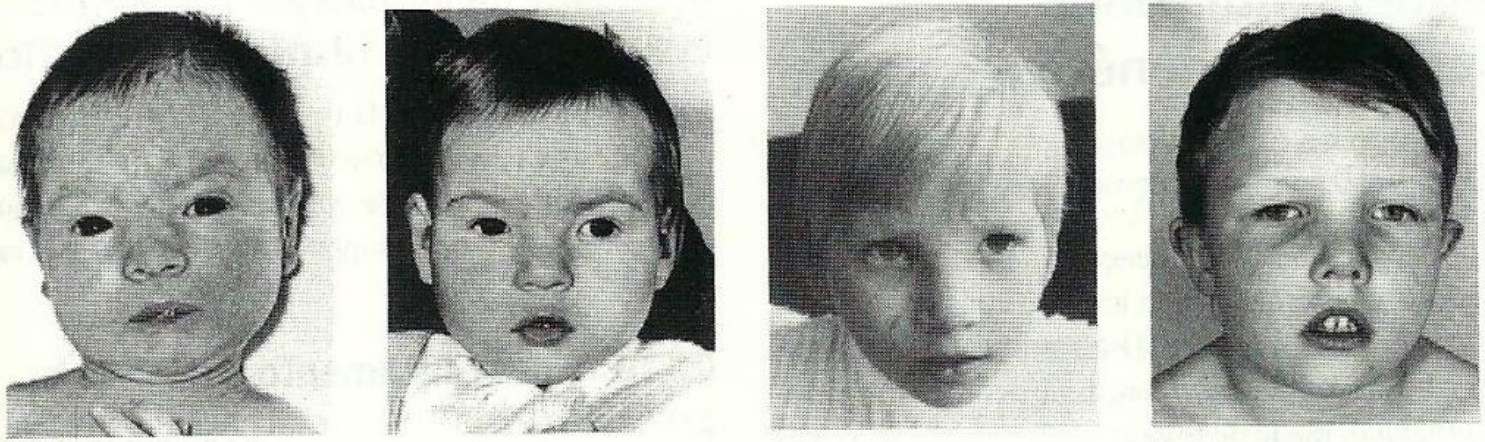
CARIOTIPO ALTERADO

- FISH (hibridação in situ fluorescente)
- sondas com fluorocromos
- translocação recíproca 3 e 11
- trissomia parcial 3p (*red*)
- monossomia parcial 11q (*green)*



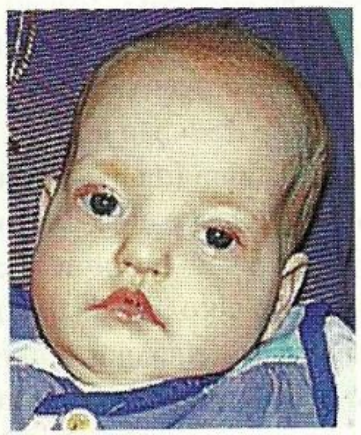
- FISH (hibridação in situ fluorescente)
- sondas com fluorocromos (clones)
- deleção 1p terminal

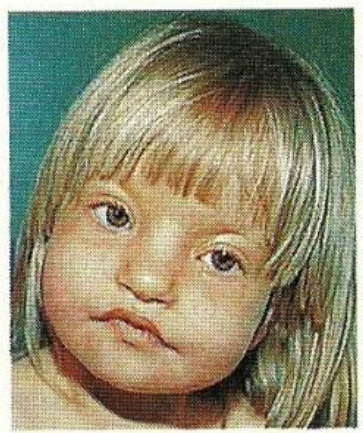


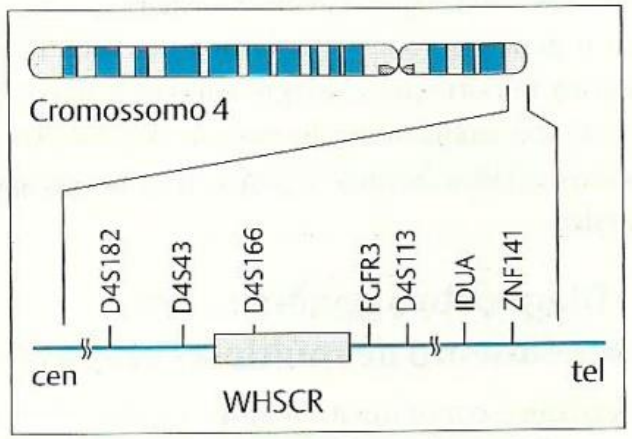


7 dias | 9 meses | 3 anos | 6 anos

A. Deleção 5p-: síndrome do miado de gato

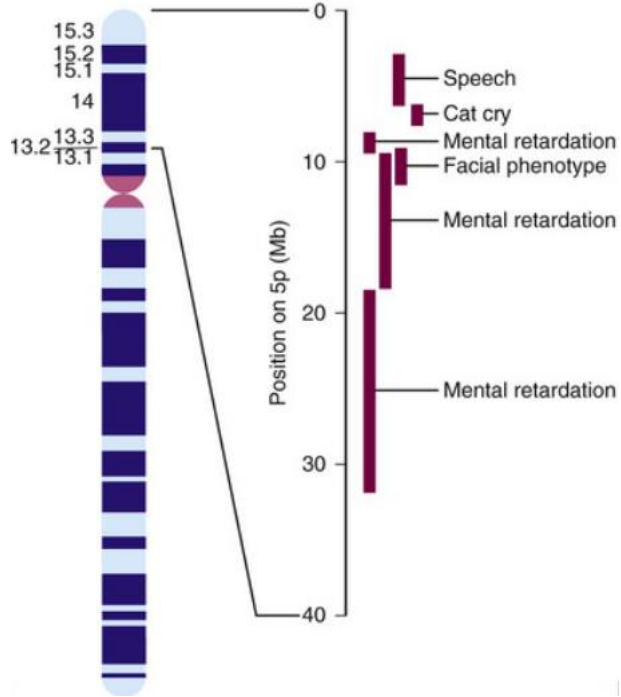




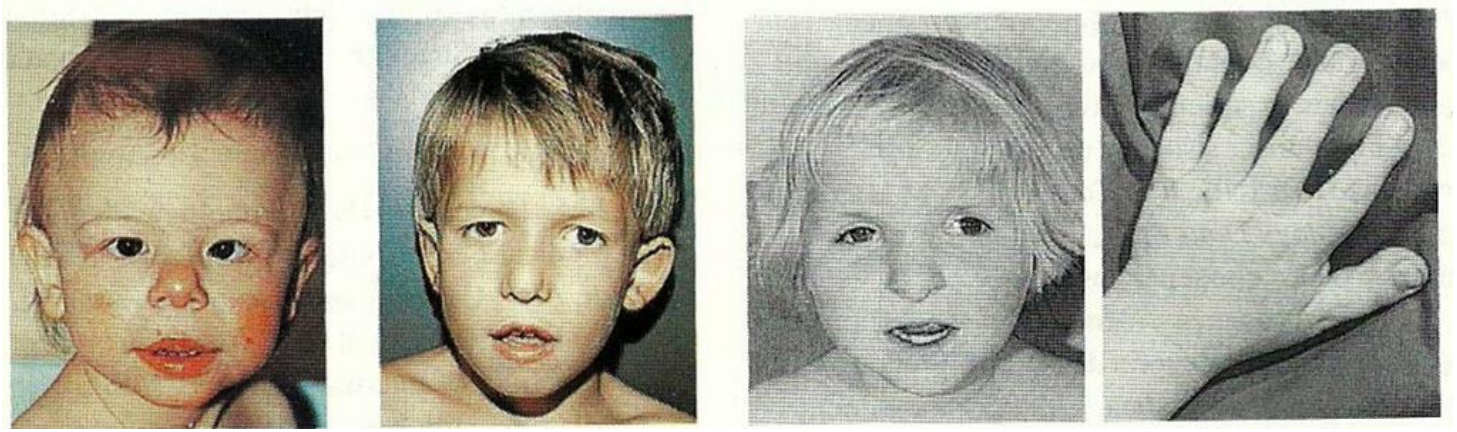


1. Idade: 1 ano e 3 meses **2.** Idade: 4 anos **3.** Esquema do mapa físico de 4p16

B. Deleção 4p-: síndrome de Wolf-Hirschhorn



MICRODELEÇÕES E MICRODUPLICAÇÕES



S. Williams del 7q11.23

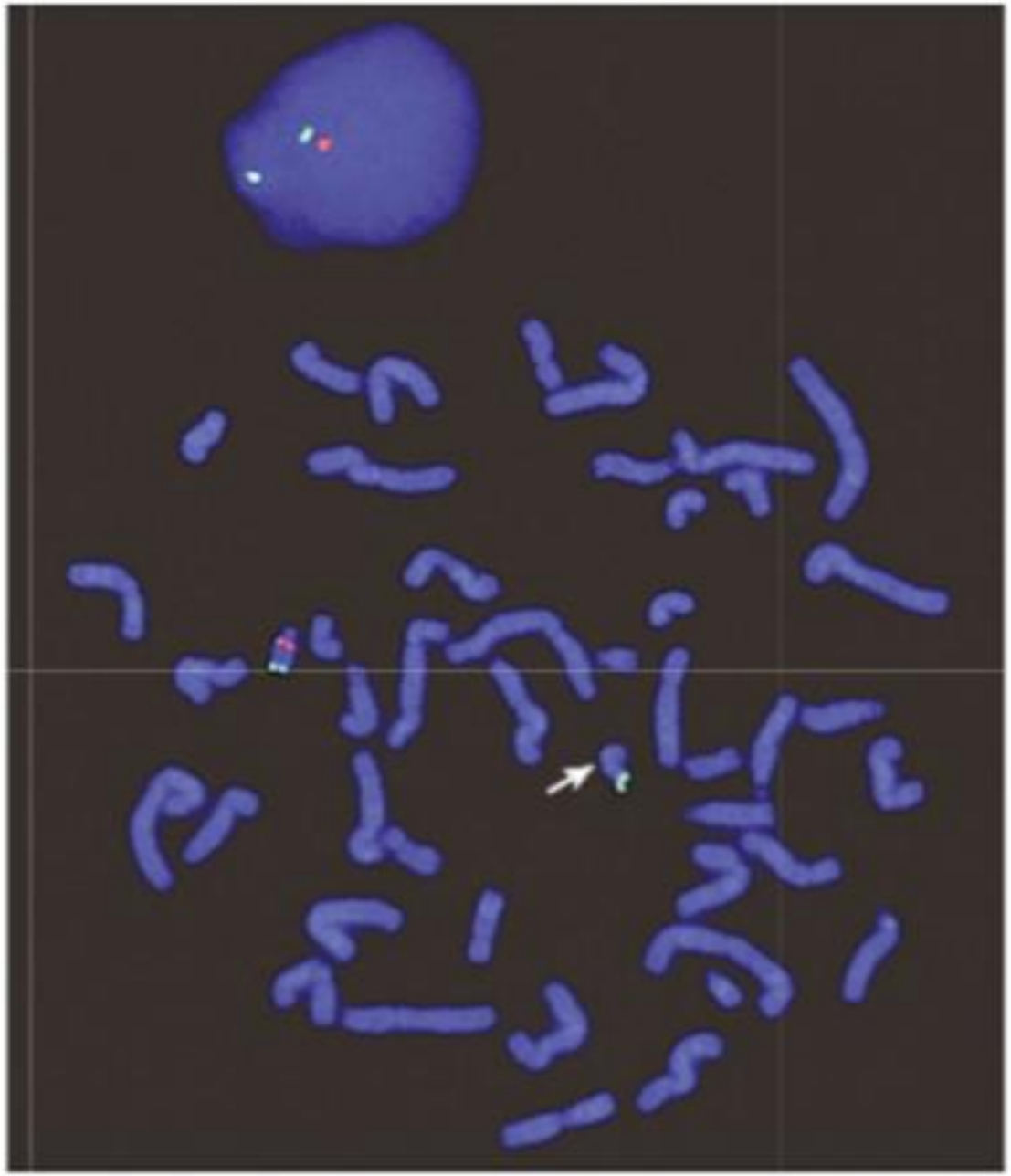
VCF/DiGeorge del 22q11.21

S. Rubinstein-Taybi del 16p13.3

- PRADER-WILLI/ANGELMAN : del15q11-q13
- SMITH-MAGENIS : del17p11.2
- POTOCKI-LUPSKI : dup17p11.2
- INFERTILIDADE MASCULINA: delYq11.2

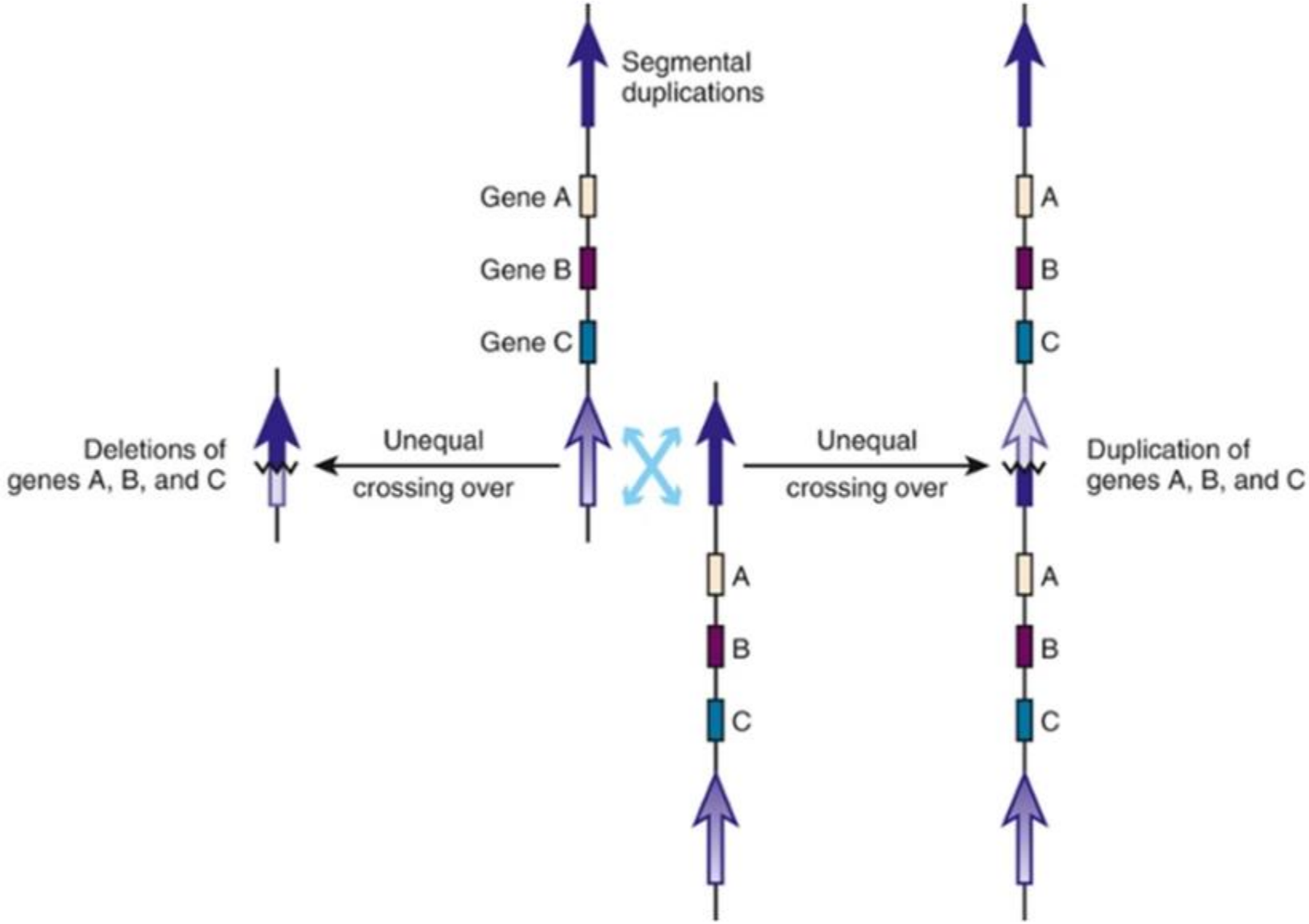
MICRODELEÇÃO 22q11.2

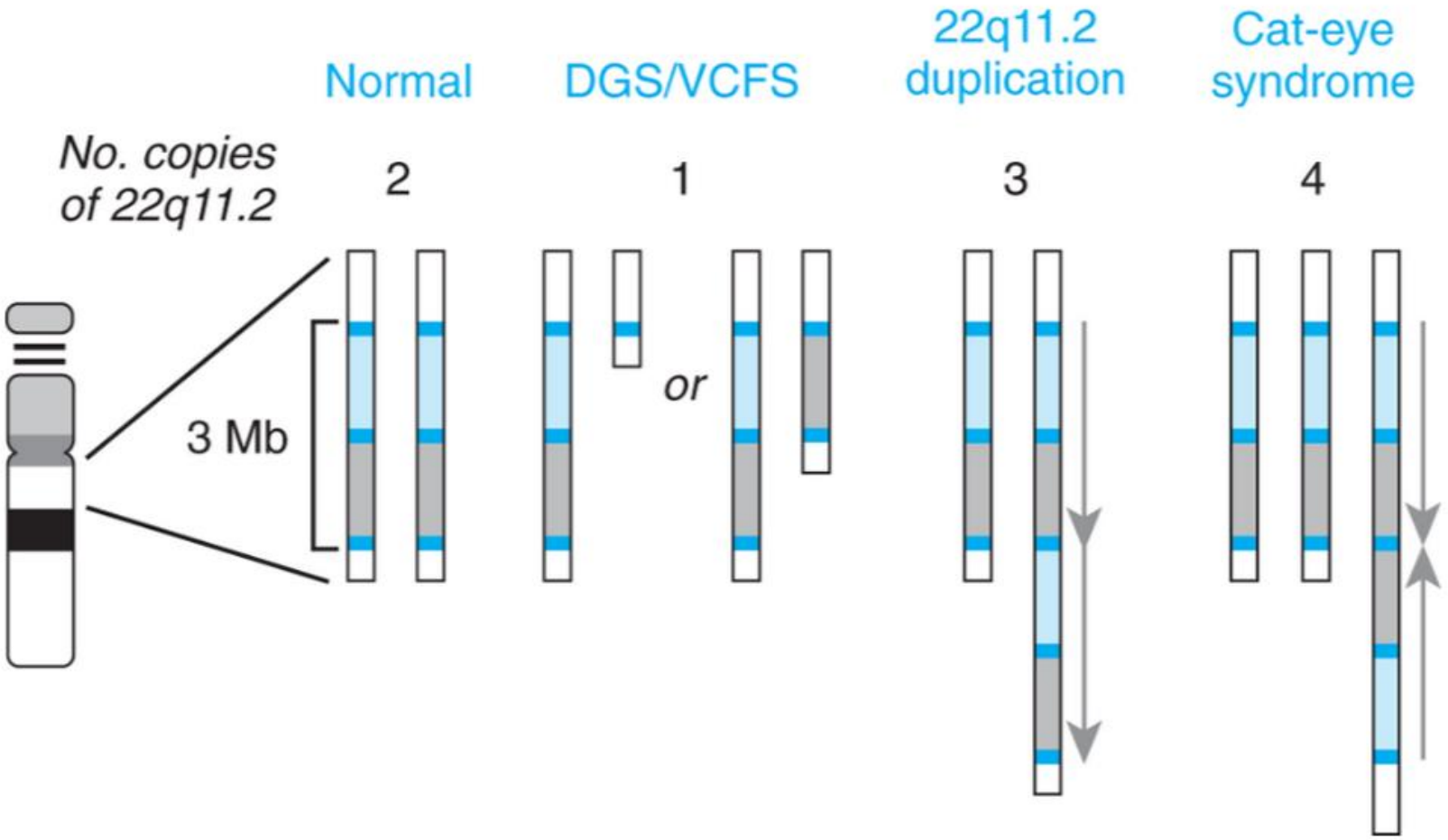
- FISH
- SONDA PARA REGIÃO DE INTERESSE
- VERDE (CONTROLE)
- VERMELHA (ÍNDICE)

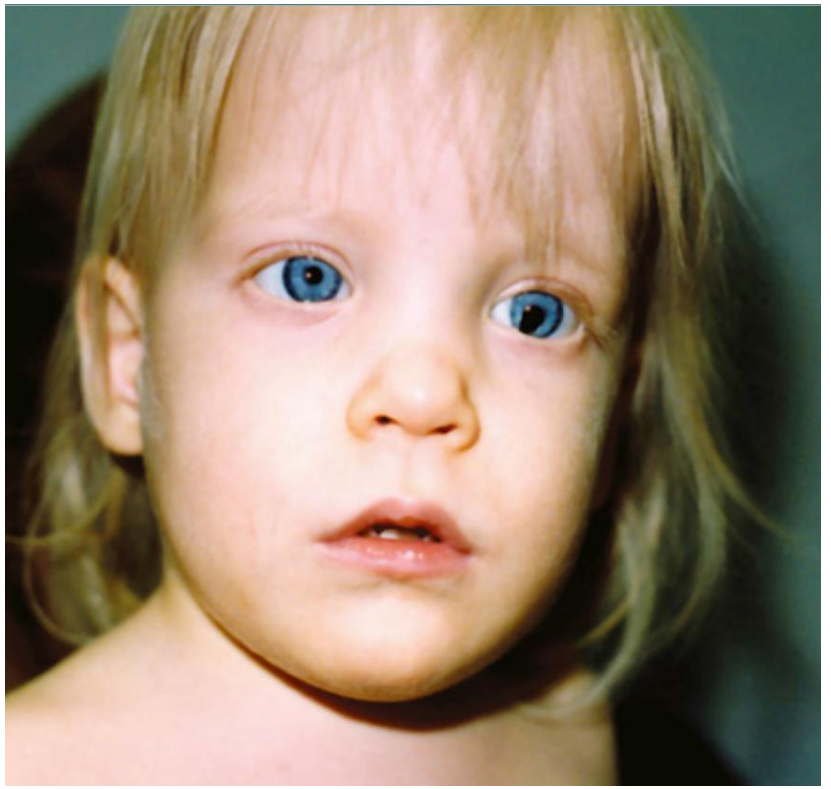


Microdeleções e microduplicações

- submicroscópicas (M.O.) < 10 Mb
  - aneussomia segmentar
  - perda ou ganho de mais de 1 gene = dosagem
  - CNV = variação no número de cópias
  - rearranjos gênicos
  - regiões repetitivas (LCR) = suscetíveis
  - *crossing-over* desigual
  - recombinação homóloga não-alélica
  - síndromes de genes contíguos = doenças genômicas
  - fenótipos reconhecidos que mudam após o nascimento
  - compatíveis com a vida


Segmental duplications
Gene A
Gene B
Gene C
Deletions of genes A, B, and C
Unequal crossing over
Unequal crossing over
Duplication of genes A, B, and C
A
B
C
A
B
C
A
B
C


Normal
DGS/VCFS
22q11.2 duplication
Cat-eye syndrome
No. copies of 22q11.2
2
1
3
4
3 Mb
or



Chromosomes and Disorders
Why we need your information
Disorder Guides - English
Disorder Guides - Translations
Registered Disorders
Request A Phenotype
Practical Guides for Families
New Members Pack
Little Yellow Book
Unique Tales for Siblings
Magazine Downloads

Registered Chromosome Disorders

(Database last updated 03 March 2016)

Unique has the following rare chromosome disorders in its membership. If you cannot see a disorder listed similar to your child's, please do not let this stop you from registering with us. New families are joining daily and if we do not have your details, we cannot put these families in touch with you

To search the database, pick from each drop list and press the button marked **"Search"**

Chromosome: Any ▾ **Arm:** Any ▾ **Disorder:** Any ▾

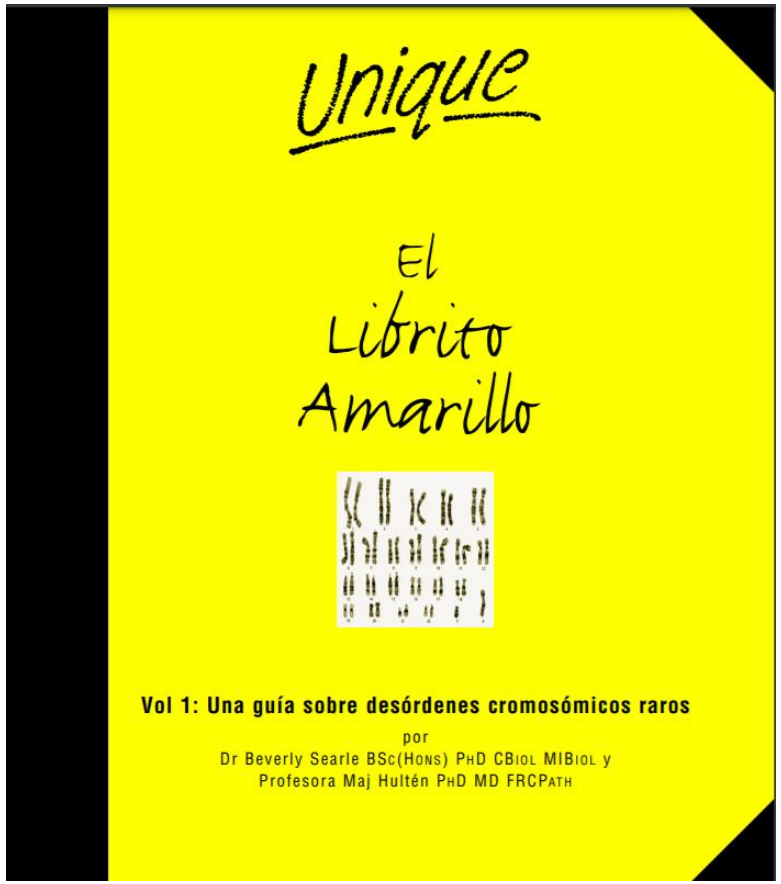
Search How many to display per page? 25

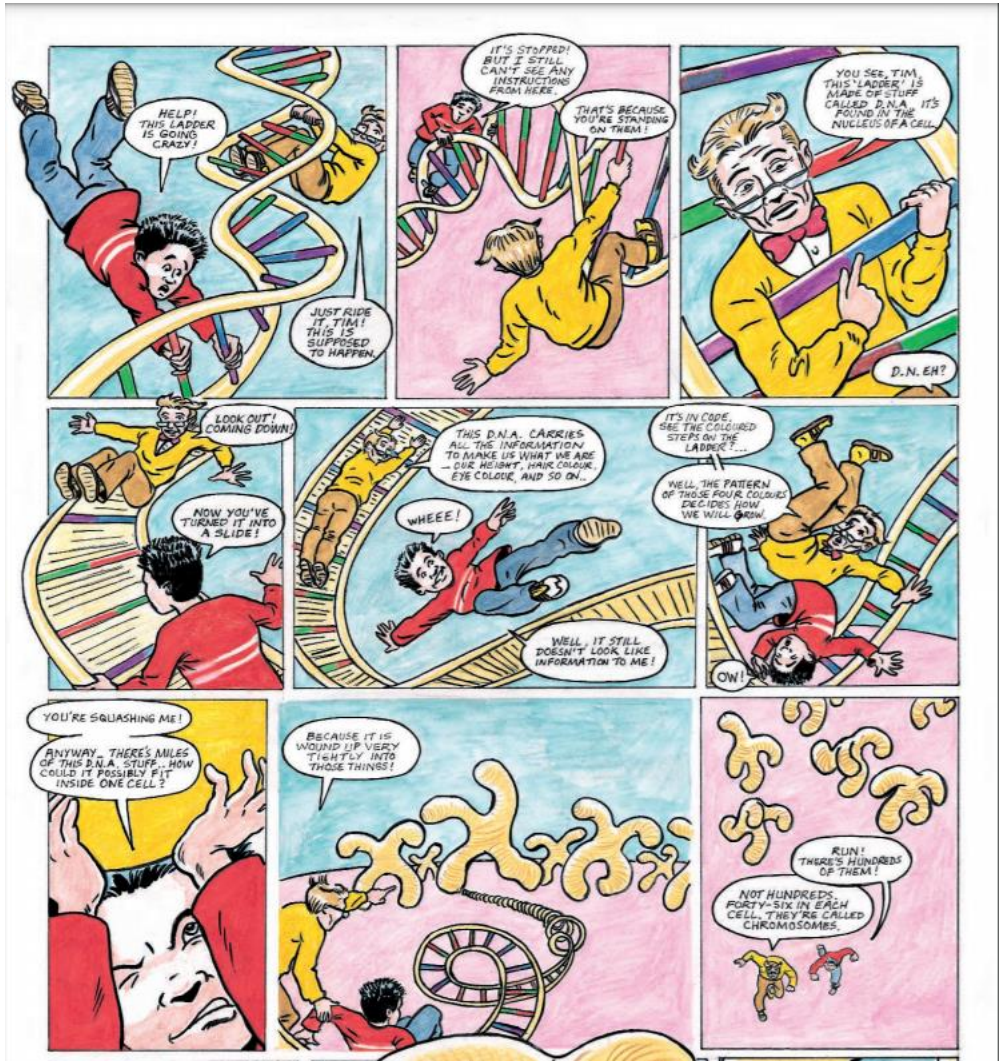
'

Results

The following list shows the chromosome conditions registered with ***Unique*** which match your search criteria. You may click on one to see specific karyotypes, FISH or arrayCGH analysis results registered against that condition

Select values and press Search





rarechromo.org