# Chromosome abnormalities

استاد:دکتر مریم اسلامی

ارائه دهندگان: کیمیا یلان، سارینا جامعی زاده،ساینا جامعی زاده

استاد:دکتر مریم اسلامی

# Types of Chromosomal Abnormalities

Numerical Abnormalities

Structural Abnormalities

**Numerical Abnormalities**

- Aneuploidy
  1. Trisomy
  2. Monosomy
- Polyploidy
  1. Triploidy

# NUMERICAL CHROMOSOMAL INSTABILITY

**Trisomy**

**1.Autosome**

**2.Sex Chromosomes**

# Autosome

Down Syndrome 21

Patue Syndrome 13

Edwards Syndrome 18

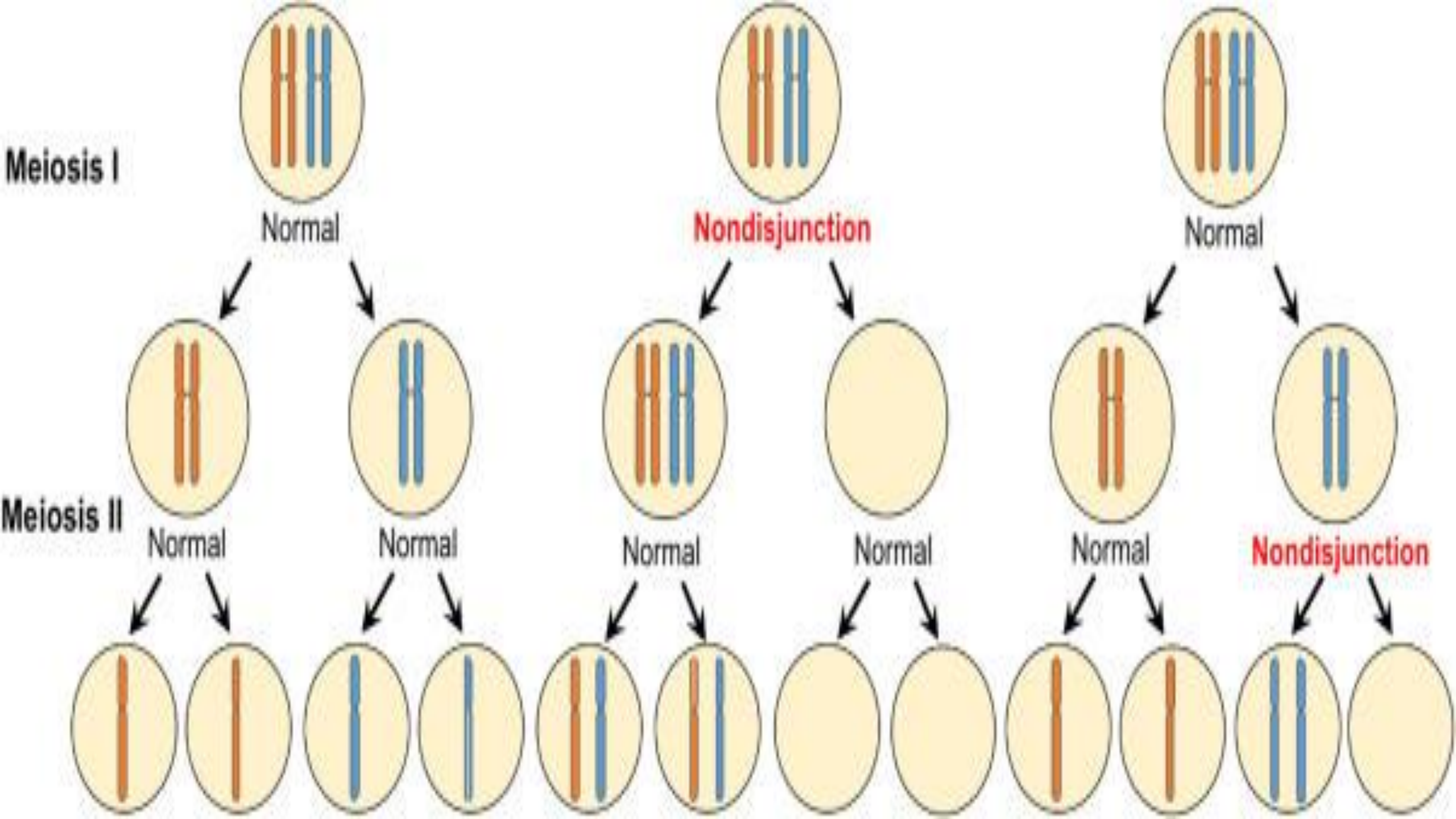
# Sex Chromosomes

**Klinefelter syndrome**
**<u>xxy</u>**

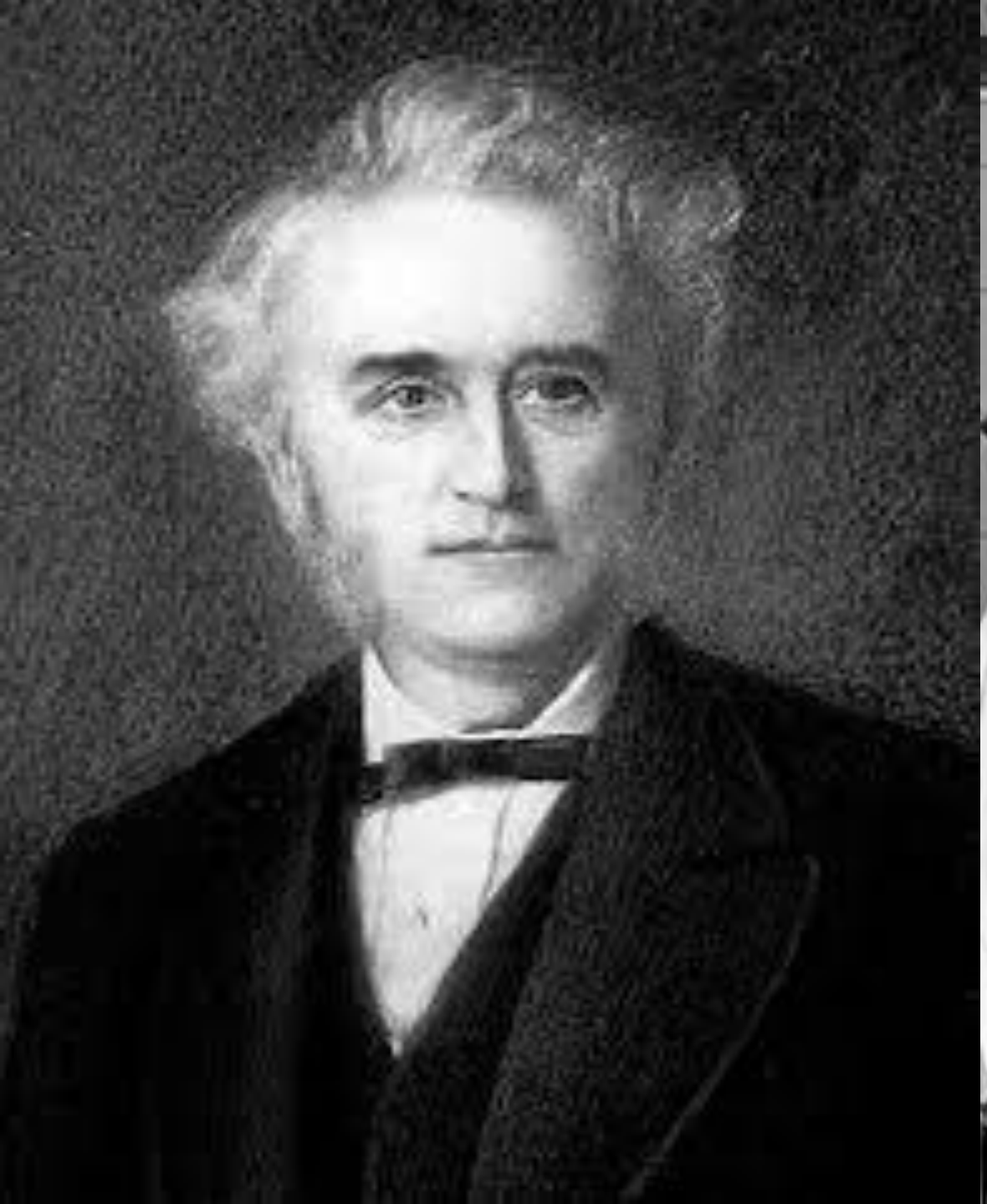
**Triple X syndrome**
**<u>xxx</u>**

**Jacobs syndrome**
**<u>xyy</u>**

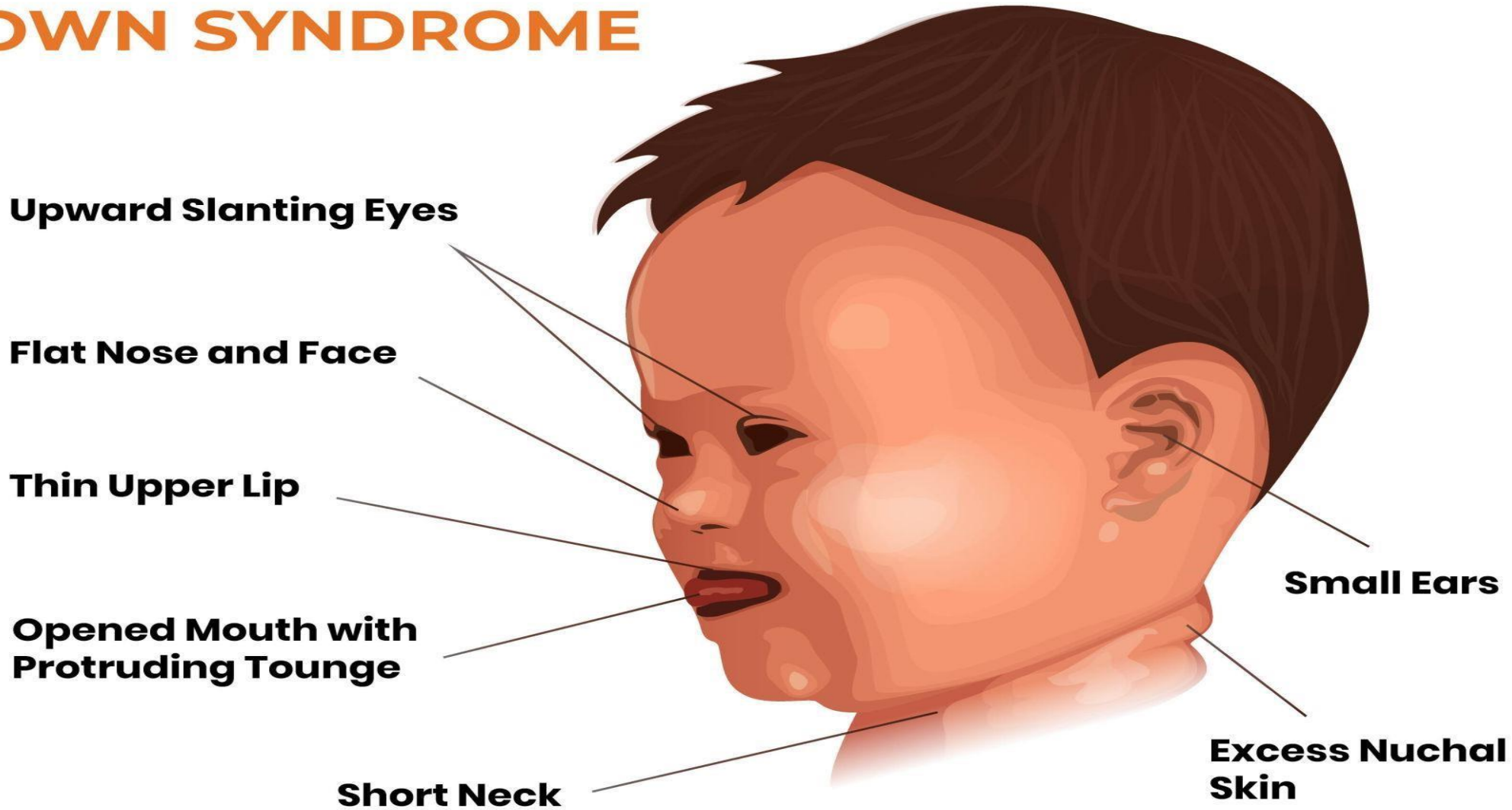
# What is the mechanism of trisomy?

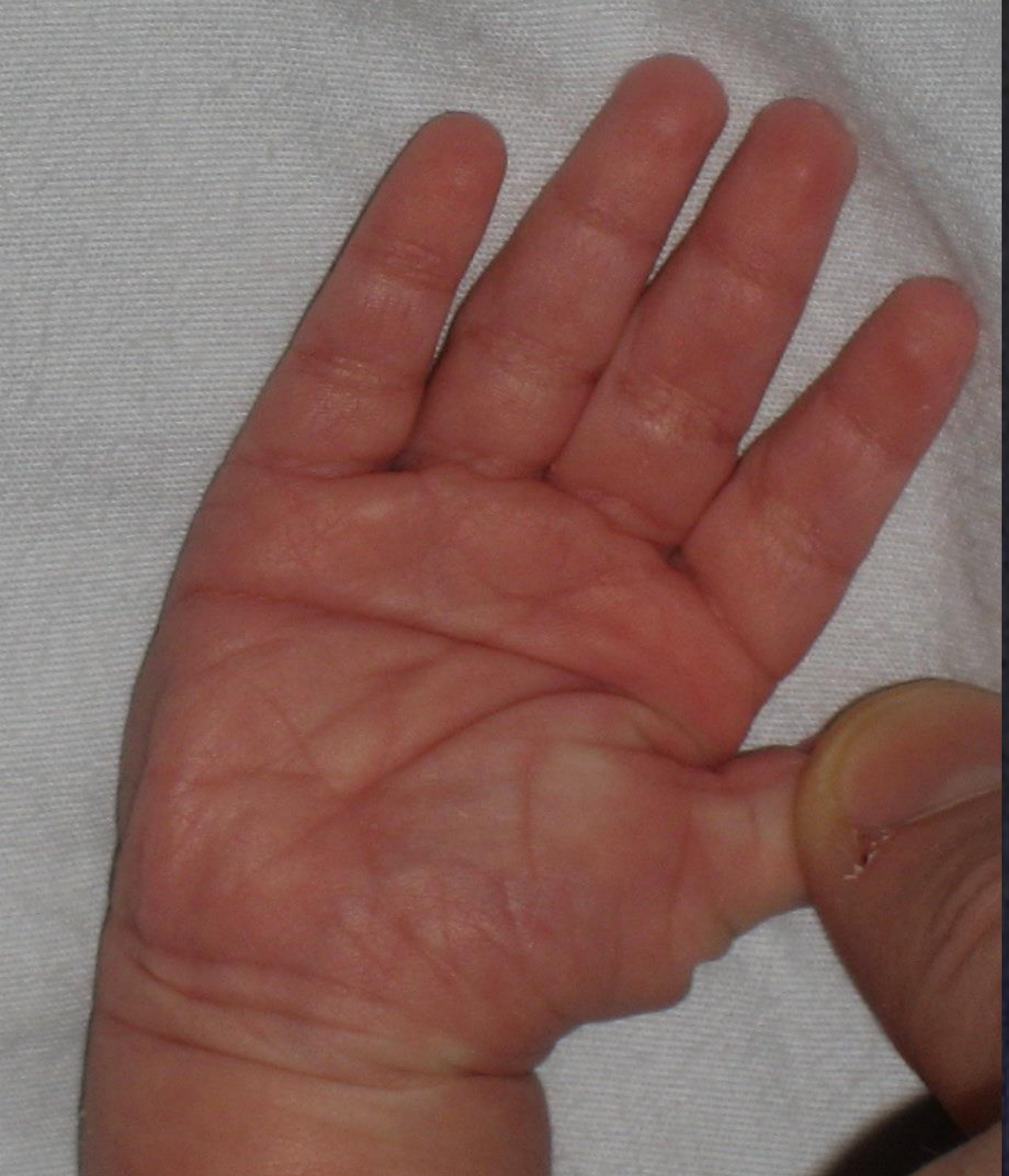

Meiosis I
Normal
Nondisjunction
Normal
Meiosis II
Normal
Normal
Normal
Normal
Normal
Nondisjunction

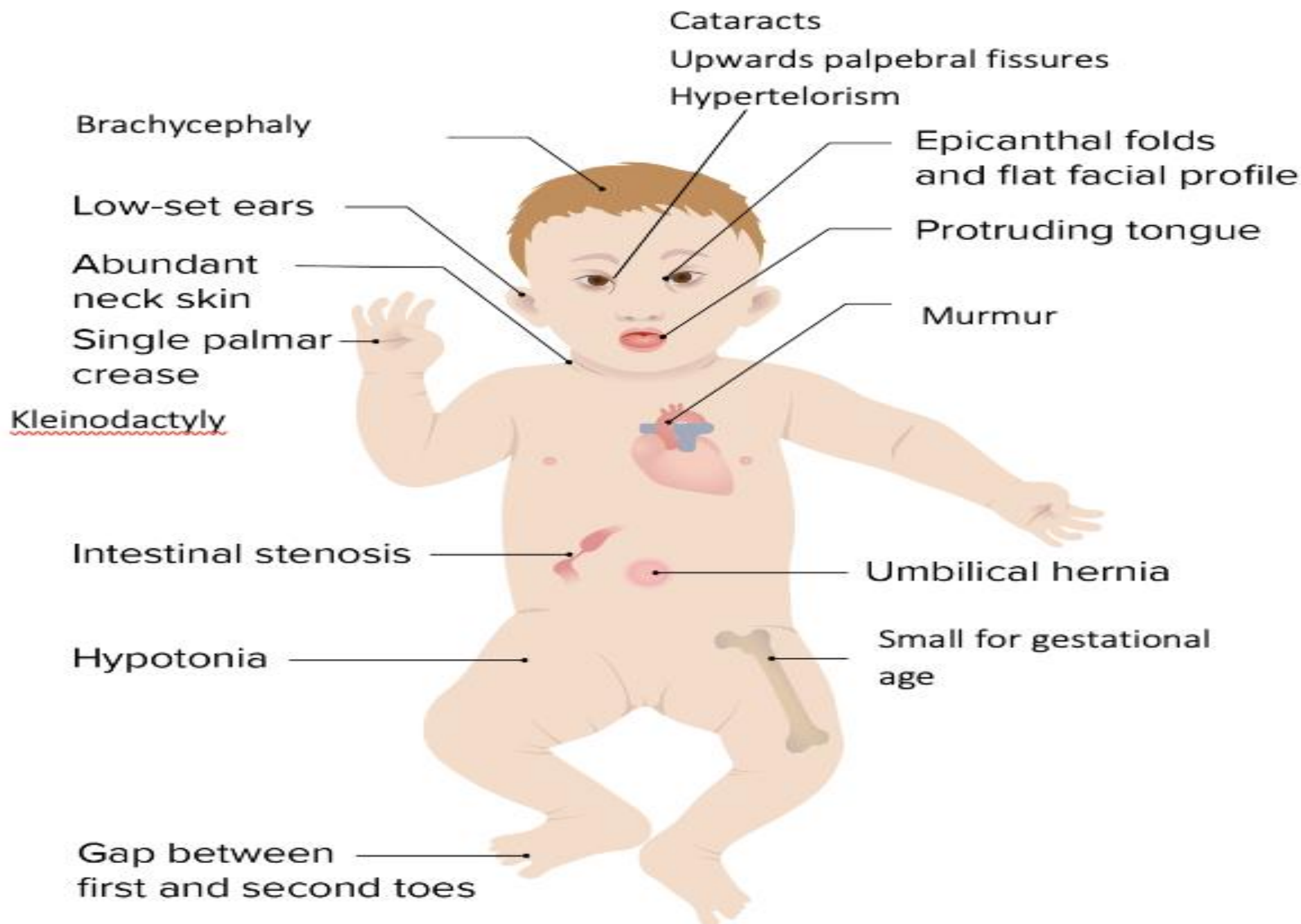
# DOWN
# *Syndrome*

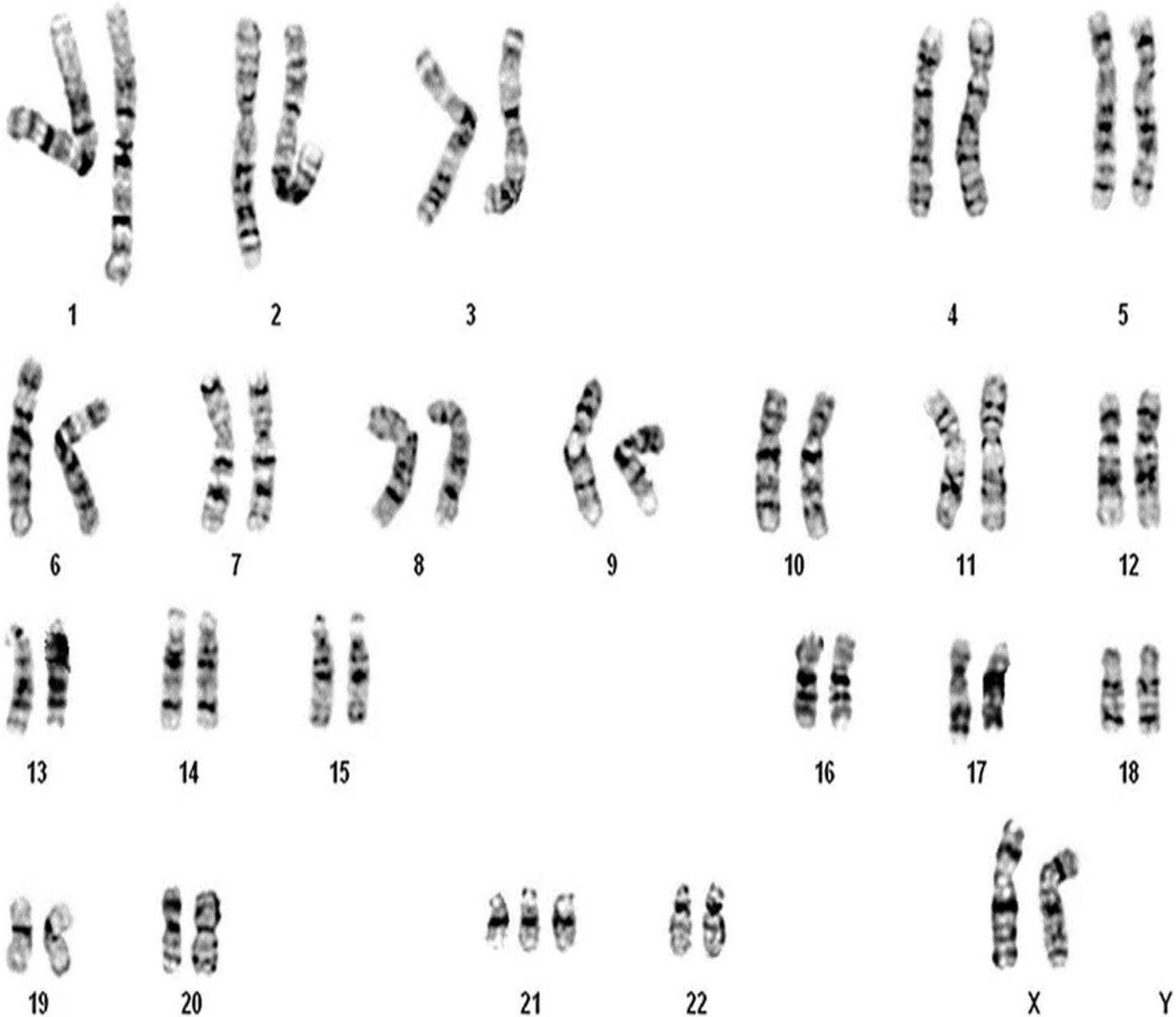


# DOWN SYNDROME






Cataracts
Upwards palpebral fissures
Hypertelorism
Brachycephaly
Epicanthal folds and flat facial profile
Low-set ears
Protruding tongue
Abundant neck skin
Murmur
Single palmar crease
Kleinodactyly
Intestinal stenosis
Umbilical hernia
Small for gestational age
Hypotonia
Gap between first and second toes




| ناهنجاری | فراوانی (%) |
|---|---|
| تریزومی | 95 |
| جابه جایی | 4 |
| موزائیسم | 1 |

PNAS NEXUS

PNAS Nexus, 2025, 4, pgaf022

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Research Report

# Trisomic rescue via allele-specific multiple chromosome cleavage using CRISPR-Cas9 in trisomy 21 cells

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**Guest Editor** Jorge Busciglio
**Accepted by Editor** David Brenner

## Abstract

Human trisomy 21, responsible for Down syndrome, is the most prevalent genetic cause of cognitive impairment and remains a key focus for prenatal and preimplantation diagnosis. However, research directed toward eliminating supernumerary chromosomes from trisomic cells is limited. The present study demonstrates that allele-specific multiple chromosome cleavage by clustered regularly interspaced palindromic repeats Cas9 can achieve trisomy rescue by eliminating the target chromosome from human trisomy 21 induced pluripotent stem cells and fibroblasts. Unlike previously reported allele-nonspecific strategies, we have developed a comprehensive allele-specific (AS) Cas9 target sequence extraction method that efficiently removes the target chromosome. The temporary knockdown of DNA damage response genes increases the chromosome loss rate, while chromosomal rescue reversibly restores gene signatures and ameliorates cellular phenotypes. Additionally, this strategy proves effective in differentiated, nondividing cells. We anticipate that an AS approach will lay the groundwork for more sophisticated medical interventions targeting trisomy 21.

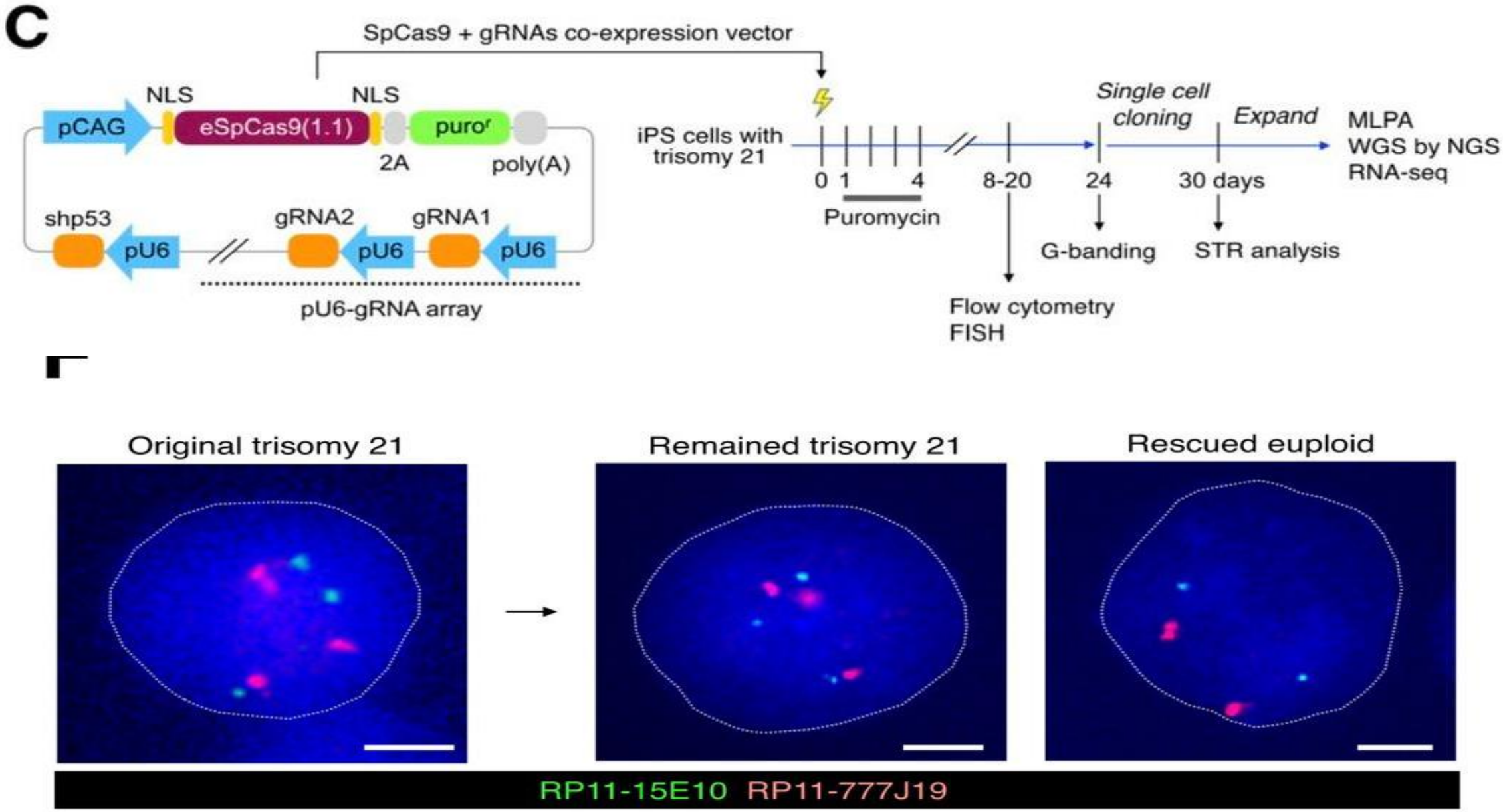
**Keywords:** human trisomy 21, chromosome loss, CRISPR/Cas, allele specificity, chromosome cut, Down syndrome

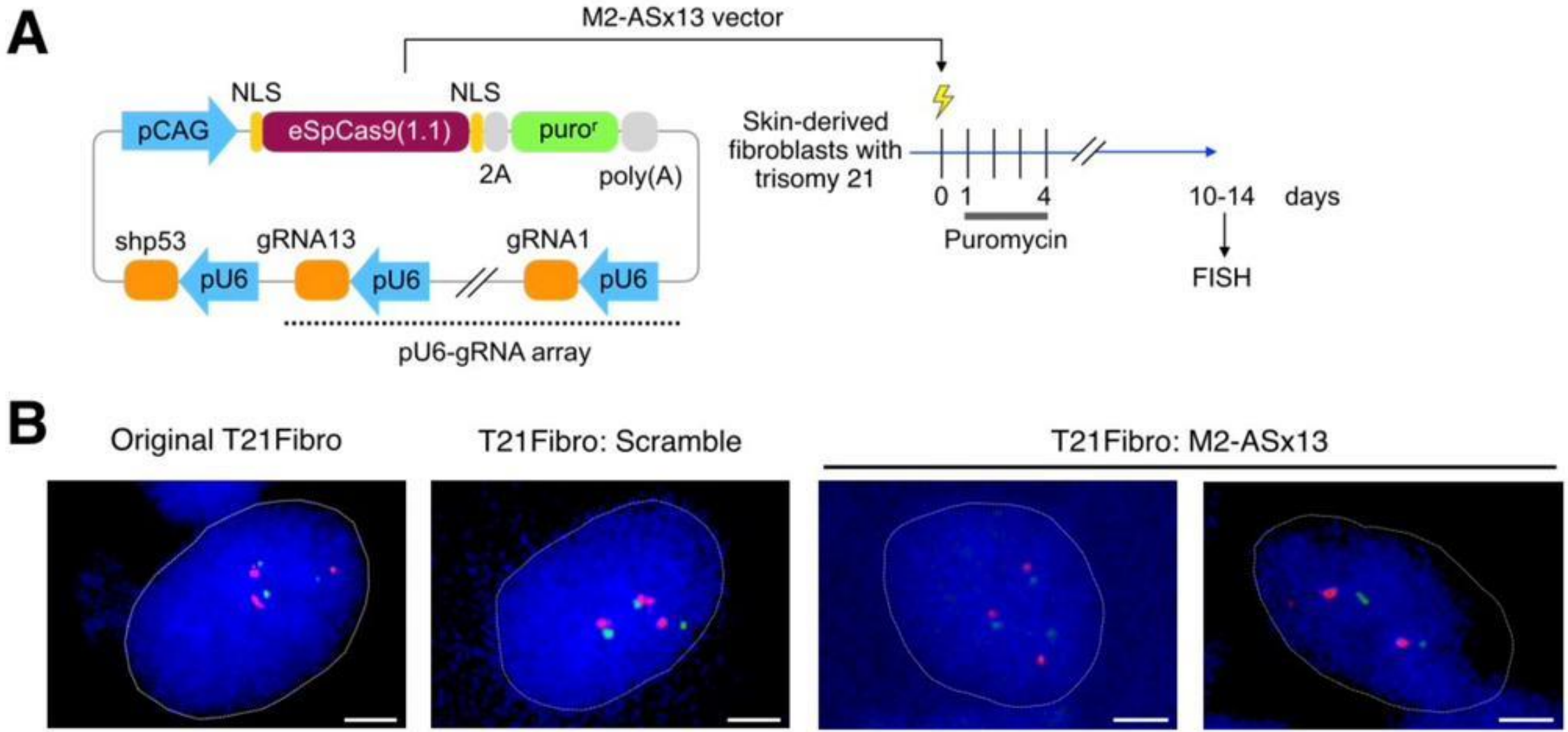
**iPS cells**

pluripotent ✓

**Fibroblast**

pluripotent ✗


C
SpCas9 + gRNAs co-expression vector
NLS
NLS
pCAG
eSpCas9(1.1)
puro^r
2A
poly(A)
shp53
gRNA2
gRNA1
pU6
pU6
pU6
pU6-gRNA array
iPS cells with trisomy 21
0 1 4
Puromycin
8-20
Flow cytometry
FISH
Single cell cloning
24
G-banding
Expand
30 days
STR analysis
MLPA
WGS by NGS
RNA-seq
Original trisomy 21
Remained trisomy 21
Rescued euploid
RP11-15E10 RP11-777J19


A
M2-ASx13 vector
NLS
NLS
pCAG
eSpCas9(1.1)
puro^r
2A
poly(A)
shp53
gRNA13
gRNA1
pU6
pU6
pU6
pU6-gRNA array
Skin-derived fibroblasts with trisomy 21
0 1 4
Puromycin
10-14 days
FISH
B
Original T21Fibro
T21Fibro: Scramble
T21Fibro: M2-ASx13

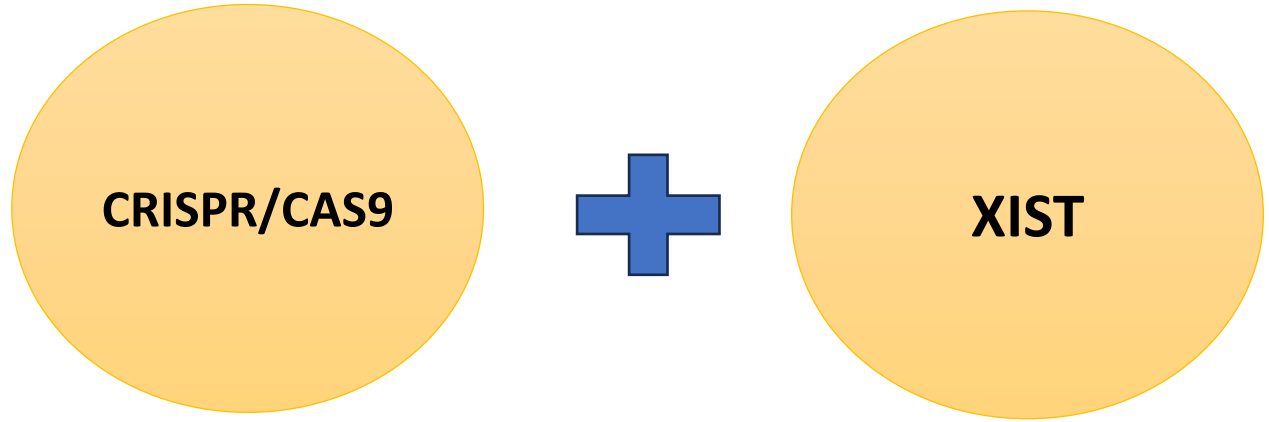
Article

# A modified CRISPR/Cas9 approach in silencing the triplication in Down syndrome: A treatment path XISTs

April 2026 · Proceedings of the National Academy of Sciences
123(16)

DOI:10.1073/pnas.2517953123






4 sgRNA

↓

PX459

↓

SNP

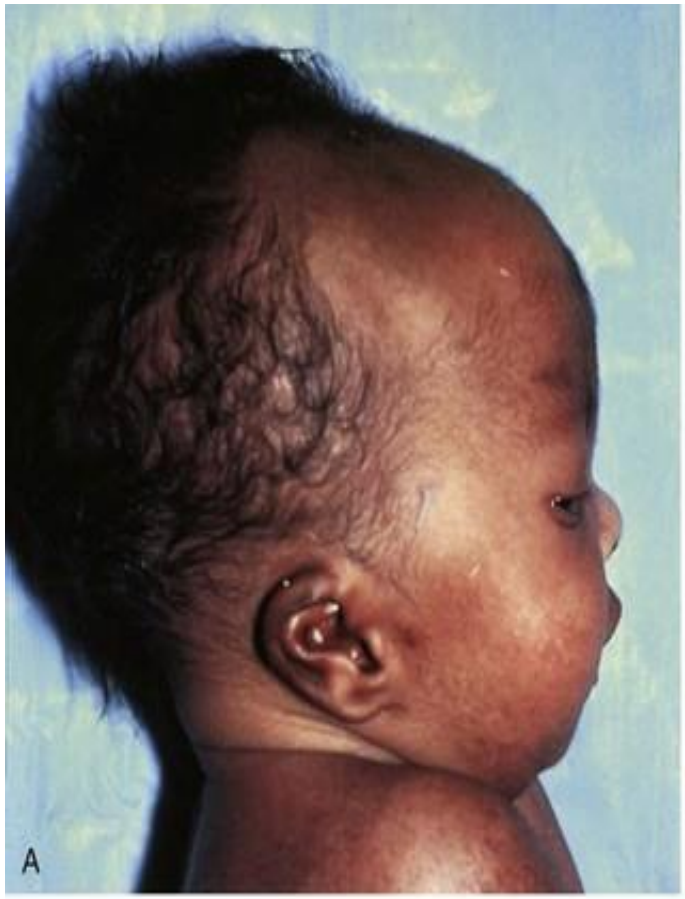
↓

PAM

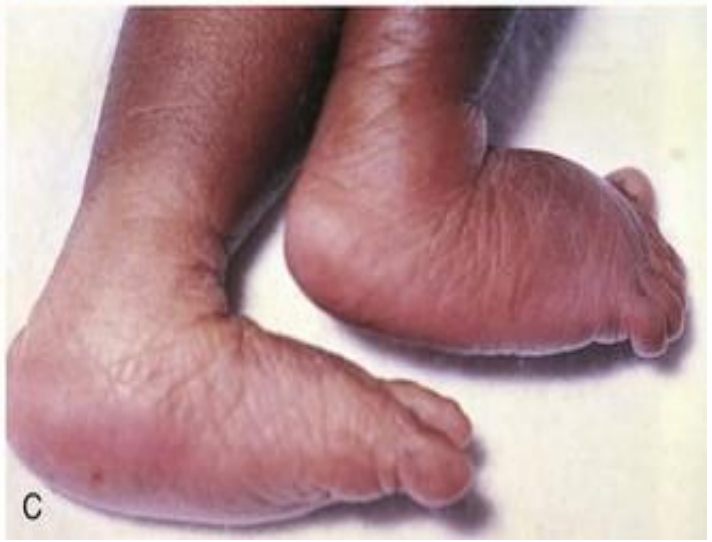
↓

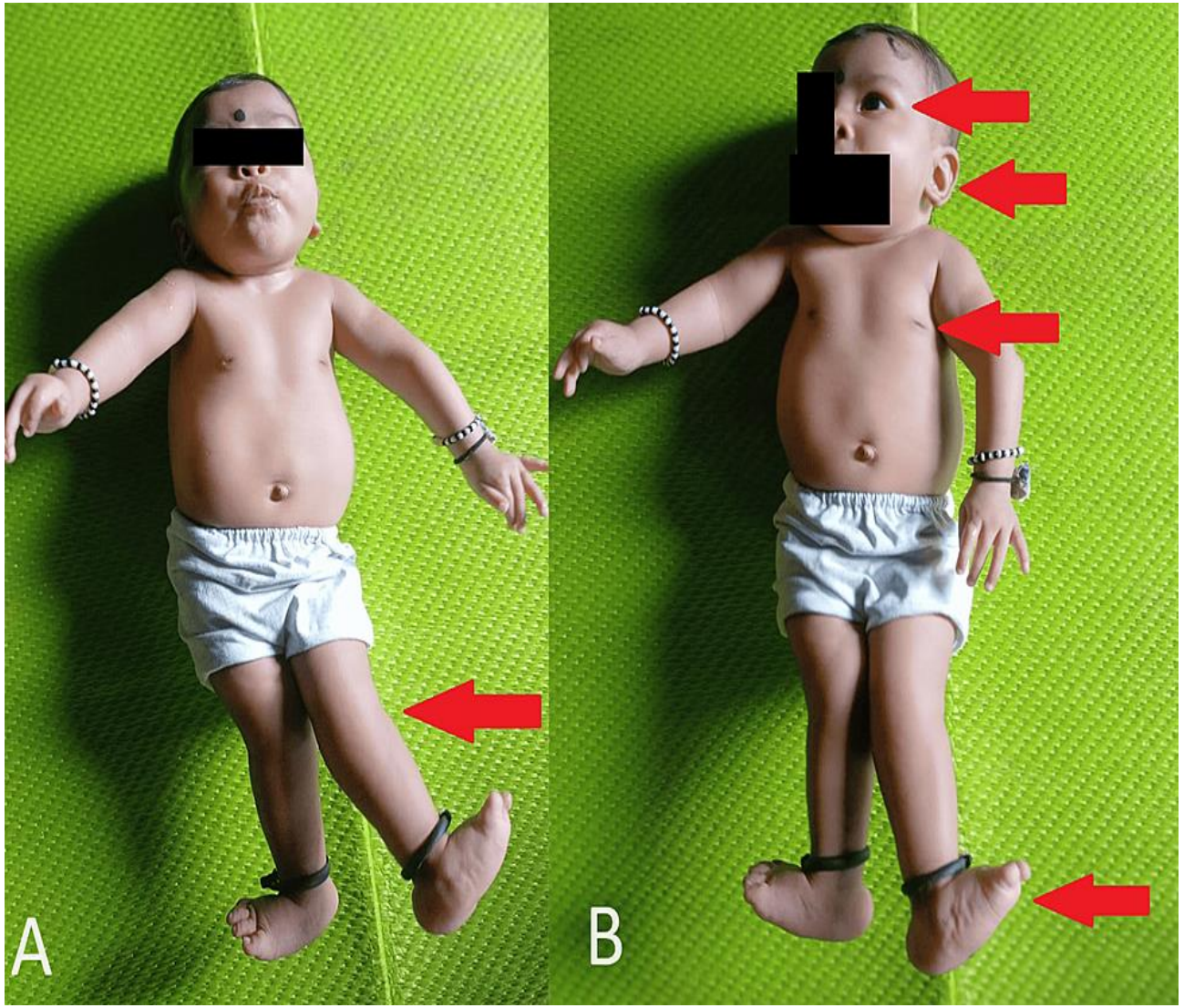
RNA-seq

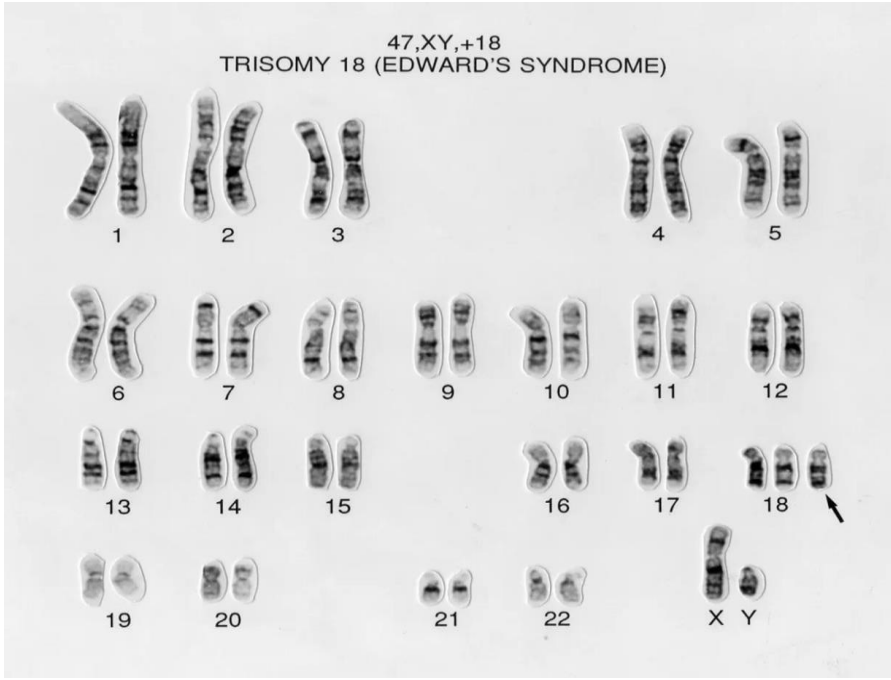
# Edwards Syndrome









A
B


47,XY,+18
TRISOMY 18 (EDWARD'S SYNDROME)
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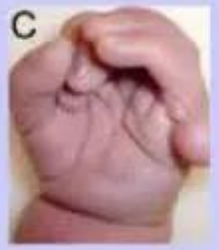
X Y

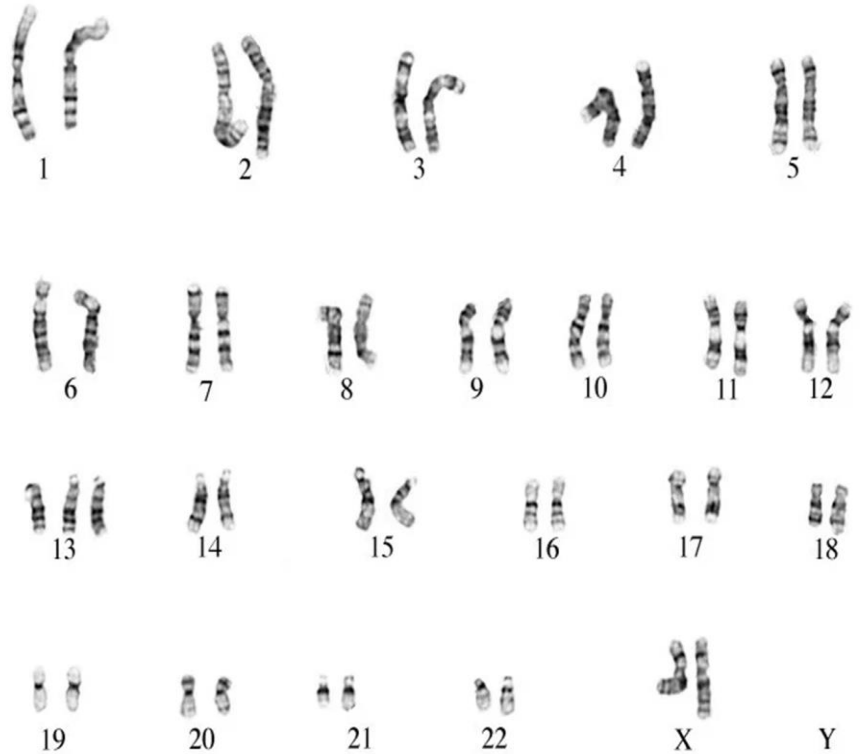
# Trisomy 13
## Patau Syndrome
### Symptoms

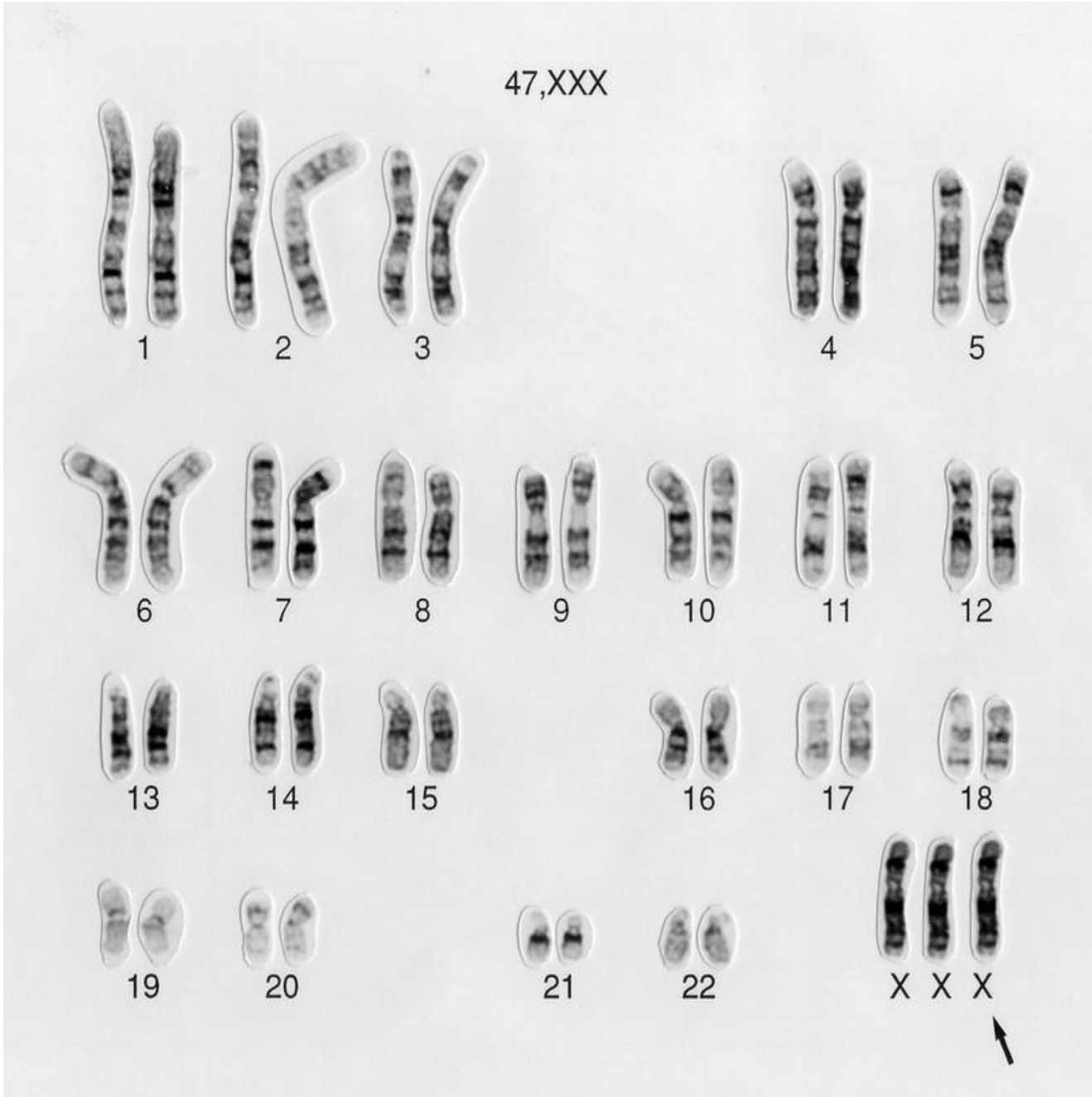



Cleft lip or palate
Clenched hands (with outer fingers on top of the inner fingers)
Close-set eyes -- eyes may actually fuse together into one
Decreased muscle tone

Extra fingers or toes
Hole, split, or cleft in the iris
Low-set ears
Mental Retardation,severe
Scalp defects (missing skin)

Small eyes
Small head
Small lower jaw




47,XXX
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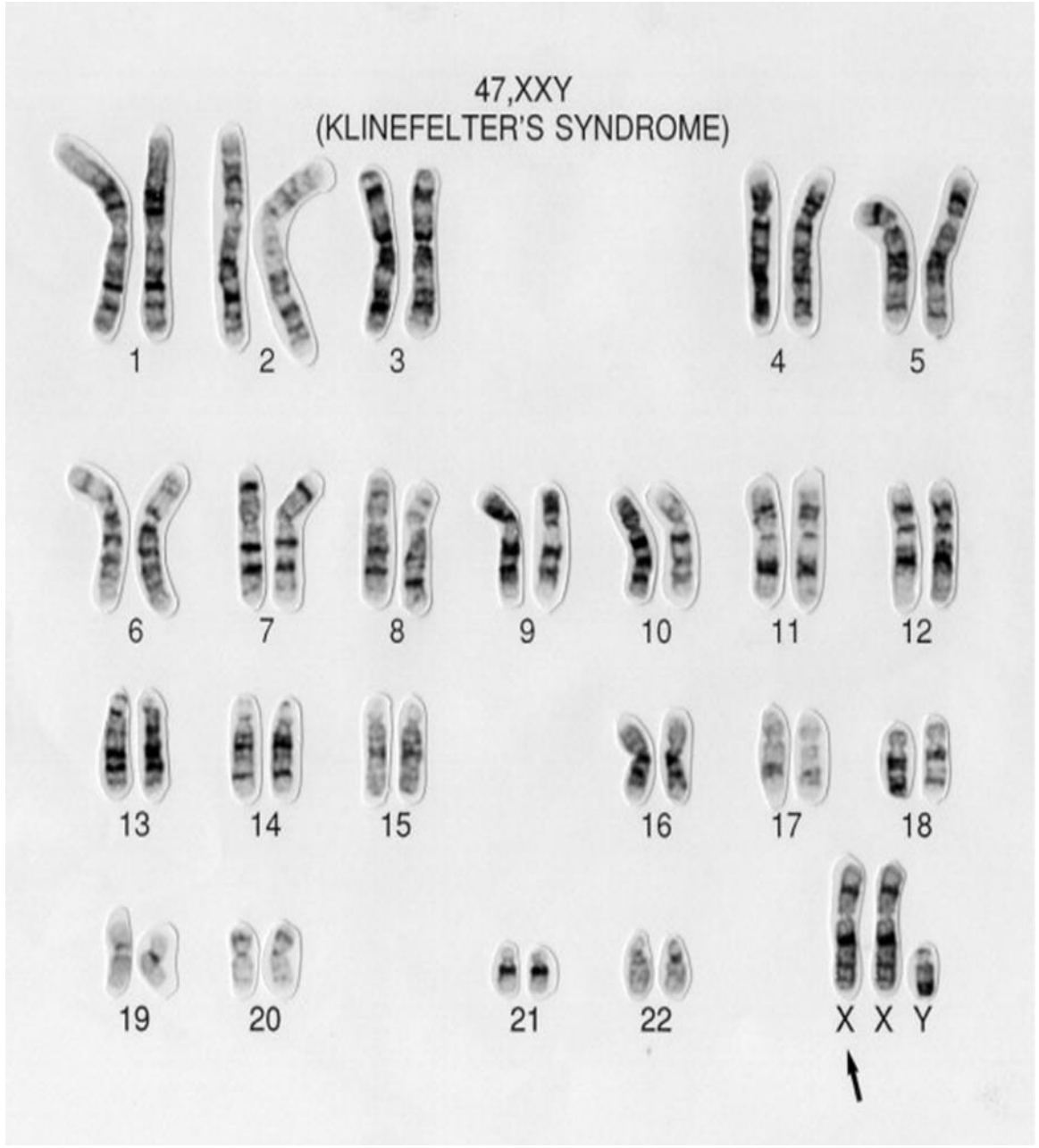
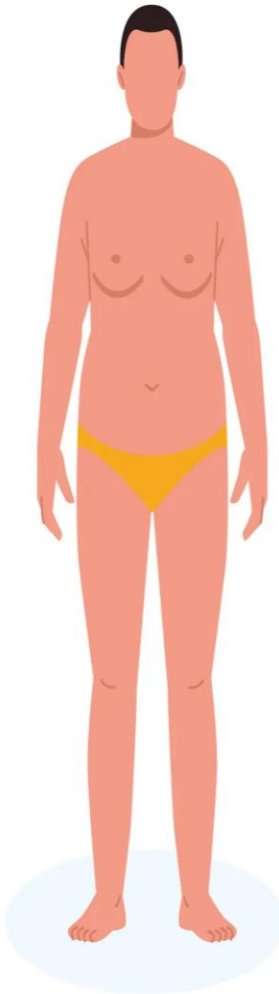
X X X



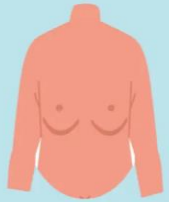

# KLINEFELTER SYNDROME



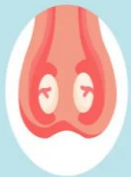
## Main symptoms

Psychomotor delays and learning difficulties

Tall stature



Enlarged breast tissue and increased belly fat



Small penis and testes

Reduced facial and body hair and less muscle

Azoospermia

*Not all symptoms are listed, and symptoms may vary in type and severity between affected people.*

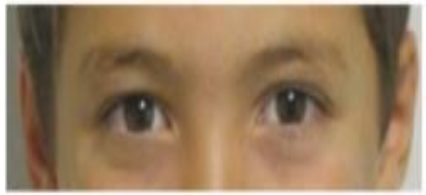
## TRT

درمان علائم کمبود تستسترون
کیفیت زندگی بهتر
ناباروری را درمان نمیکند

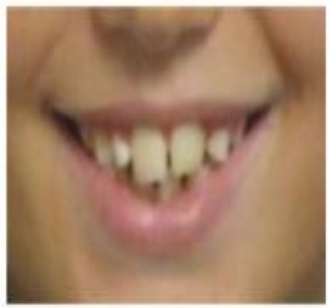
## ICSI

کمک به فرزندآوری
درمان ناباروری
وابسته به پیدا شدن اسپرم در بیضه

A

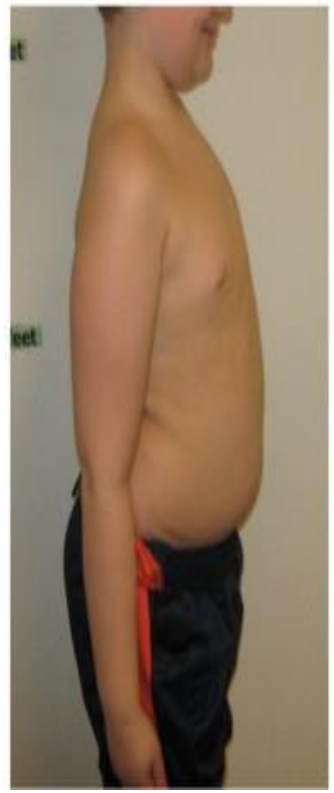


B

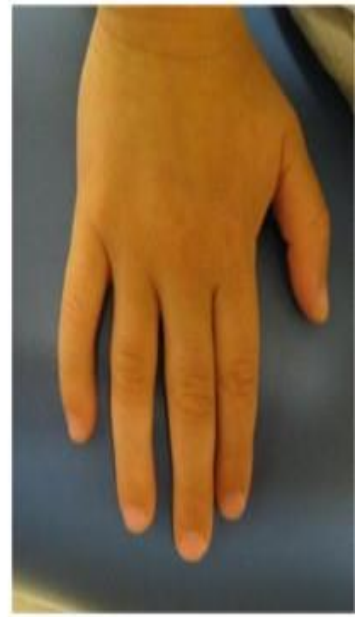


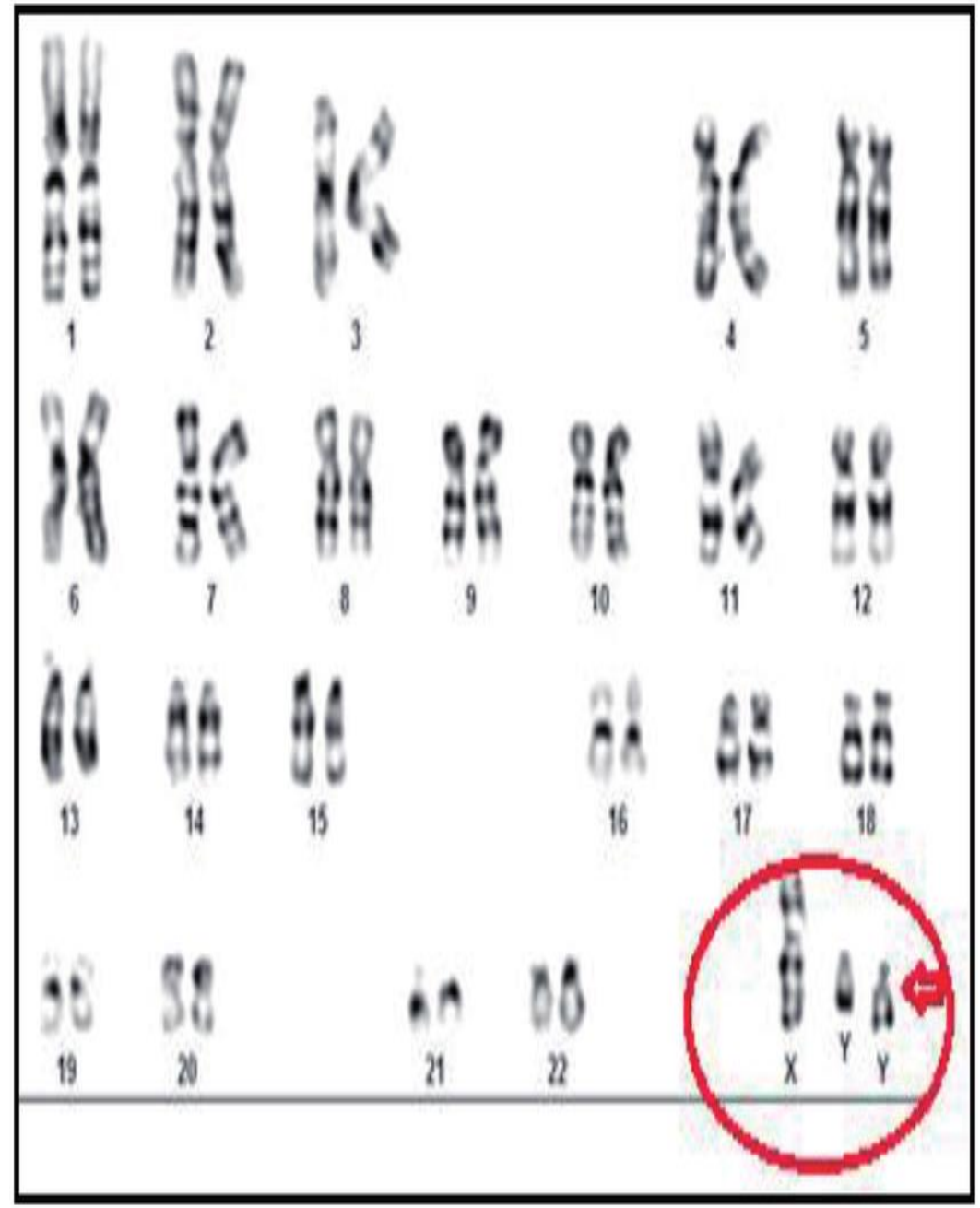
C

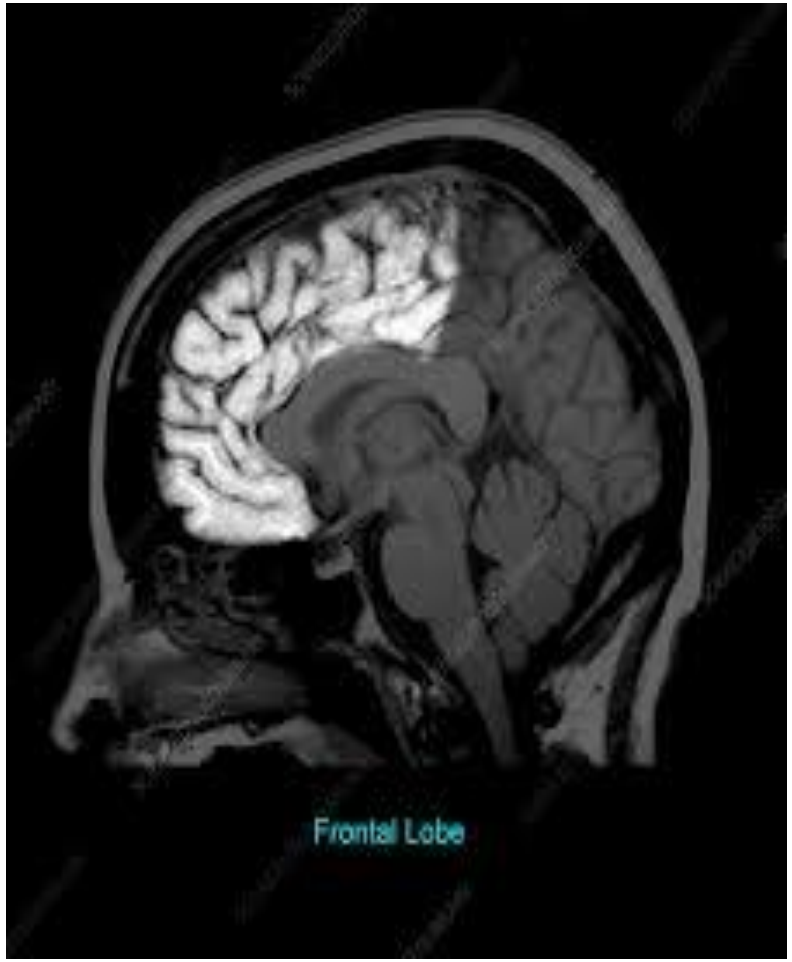
D

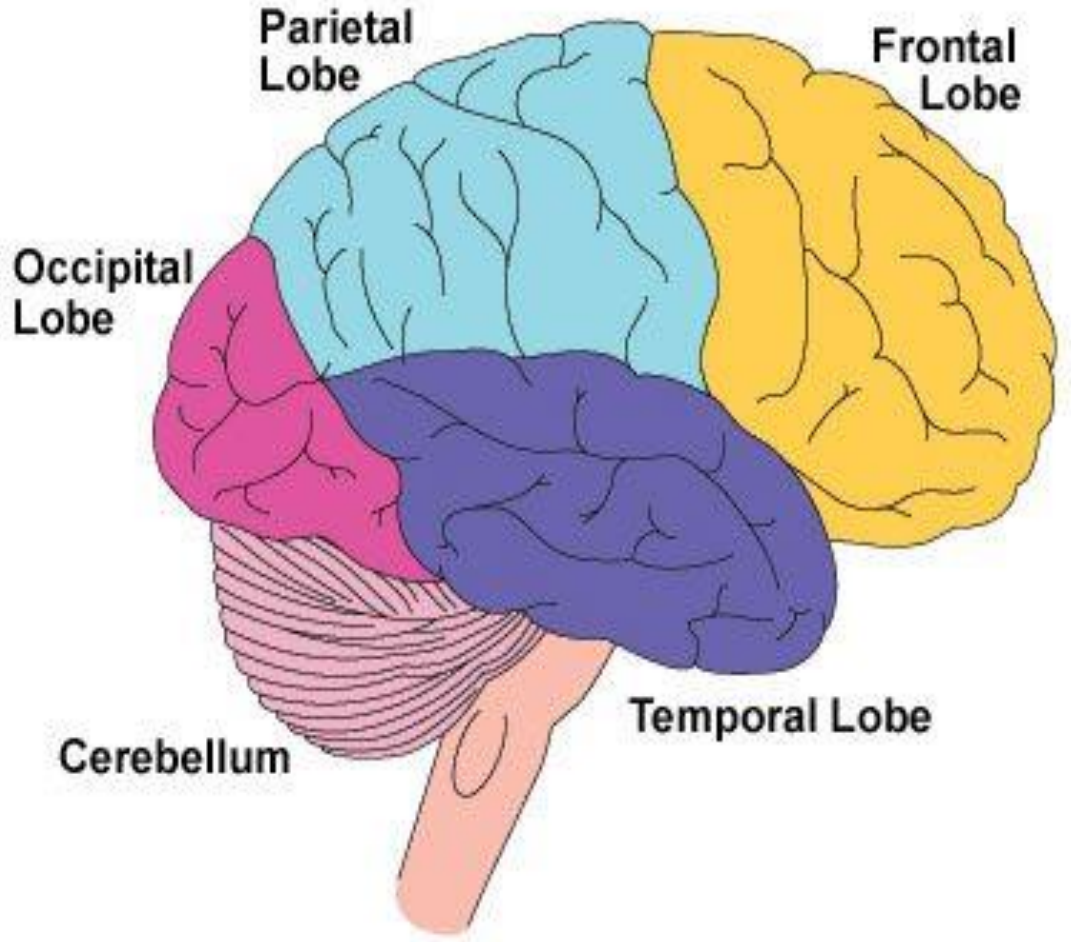


E








★ رفتار های بی توجهی، بیش فعالی،تکانشی ★

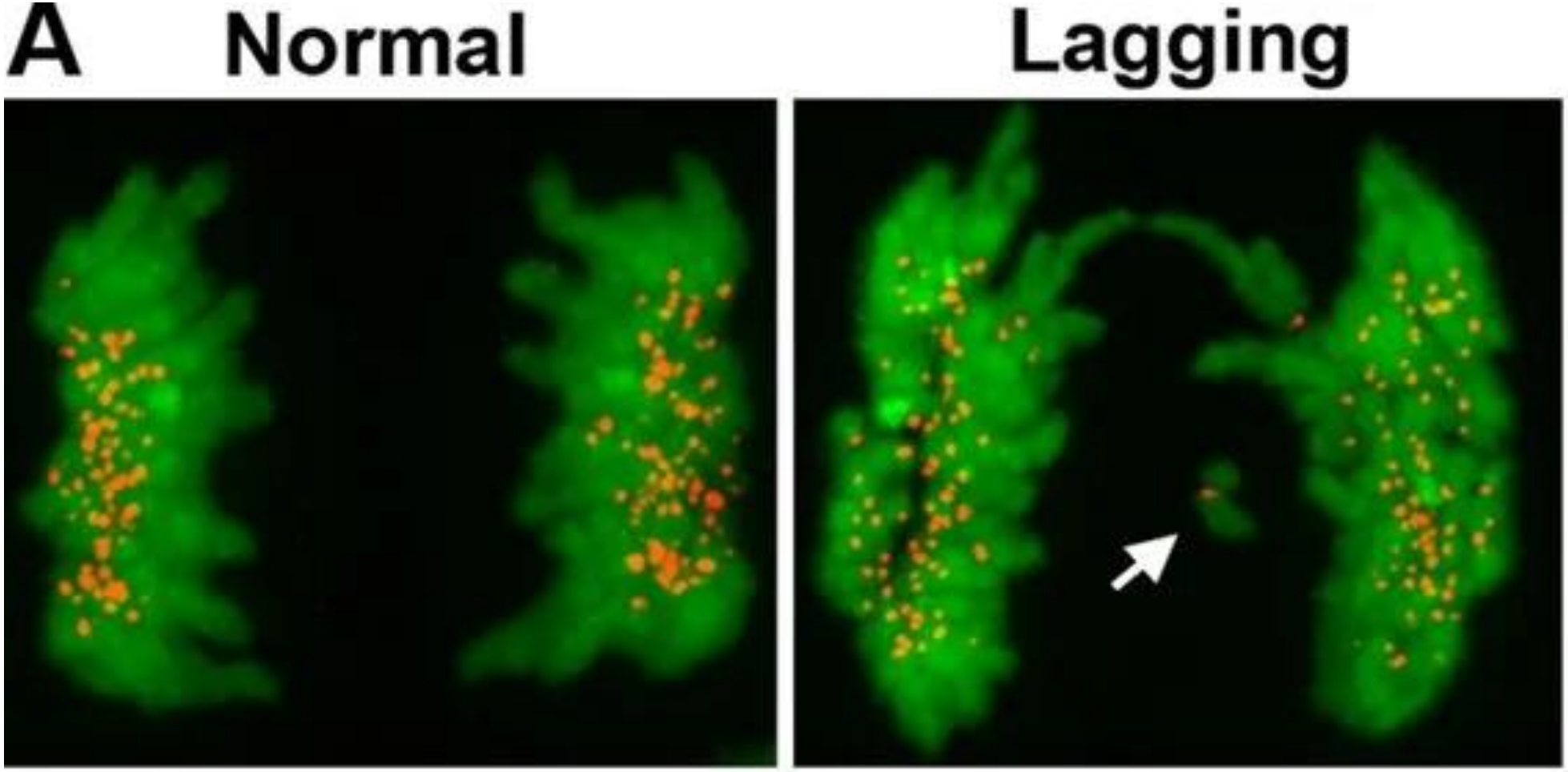
1.Autosome

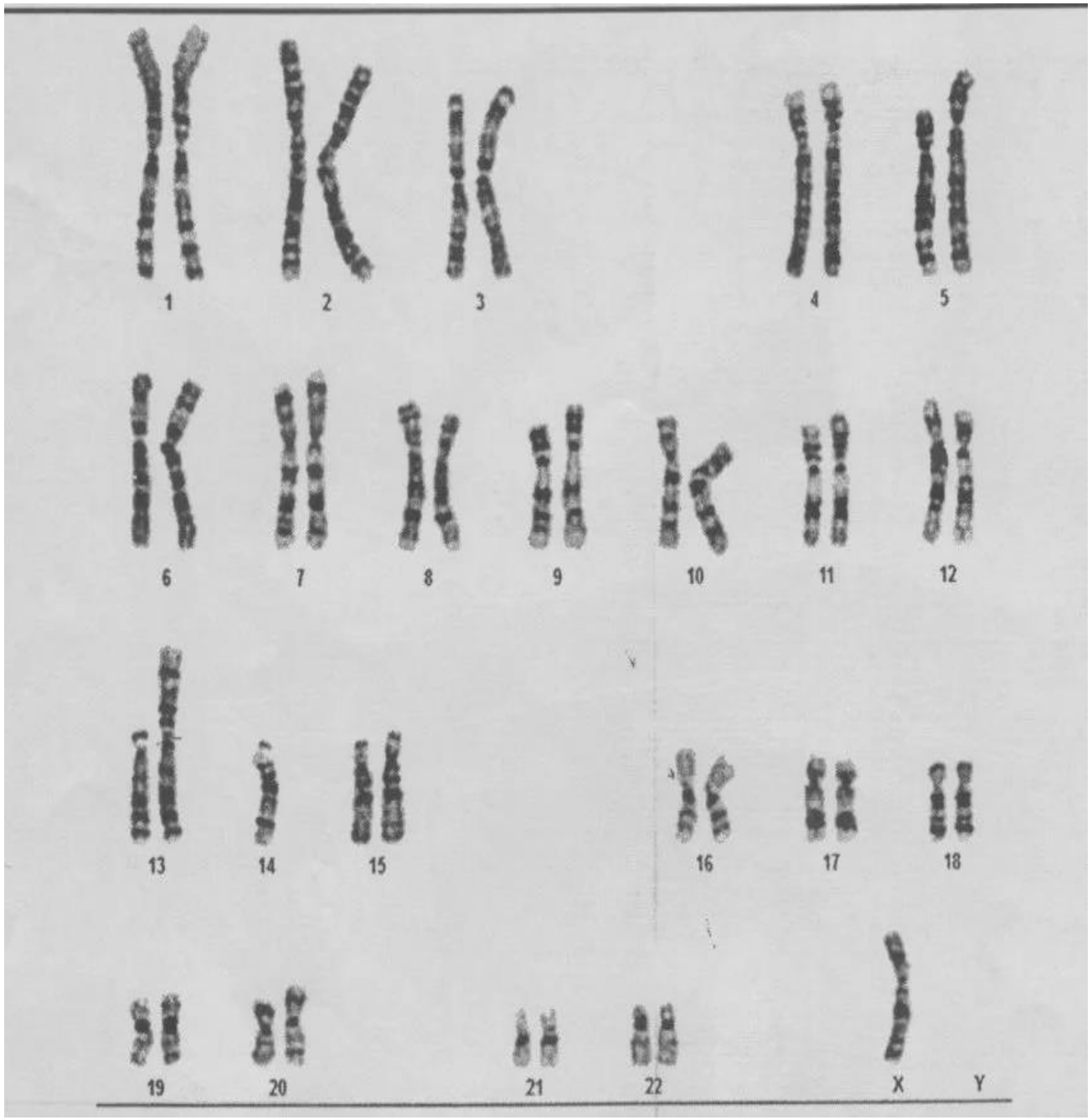
Monosomy

2.Sex Chromosomes

*Turner syndrome*

# What are the causes of monosomy?

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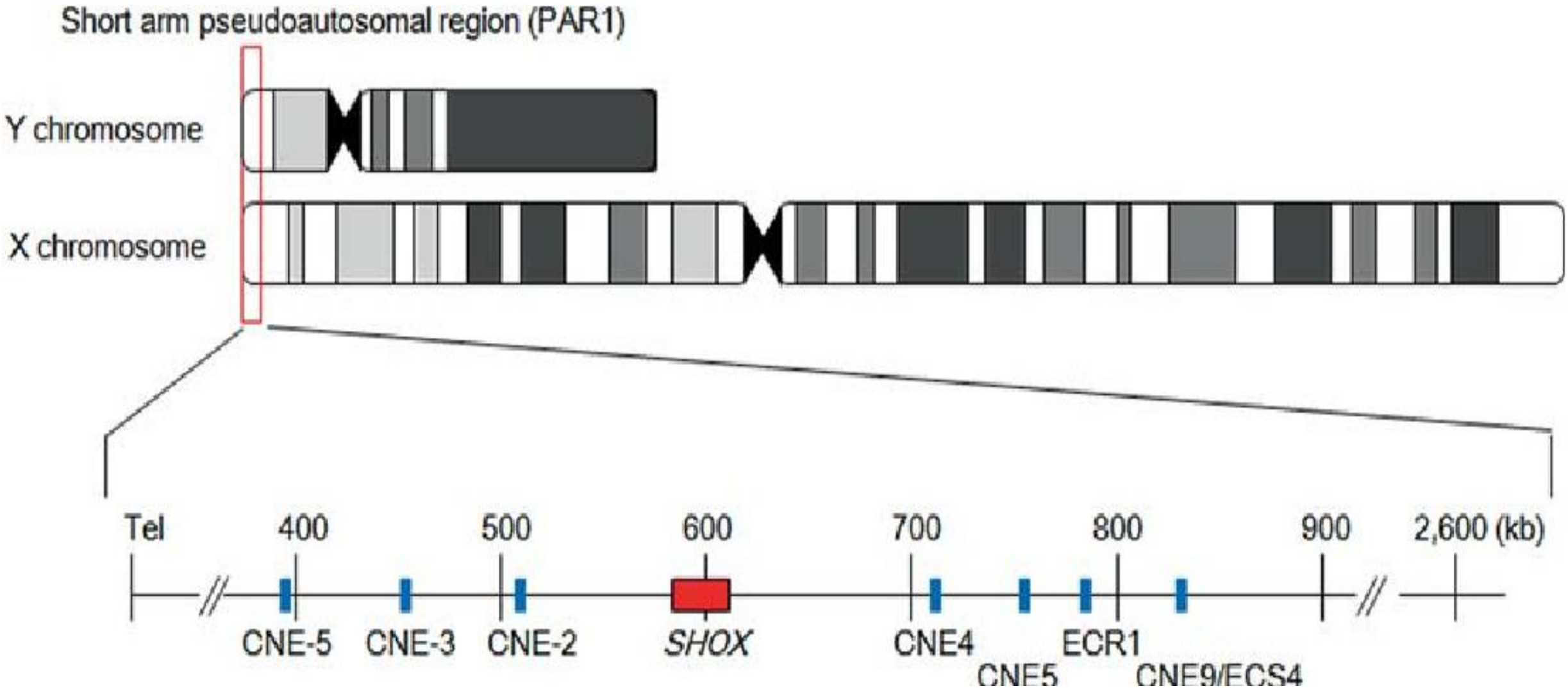
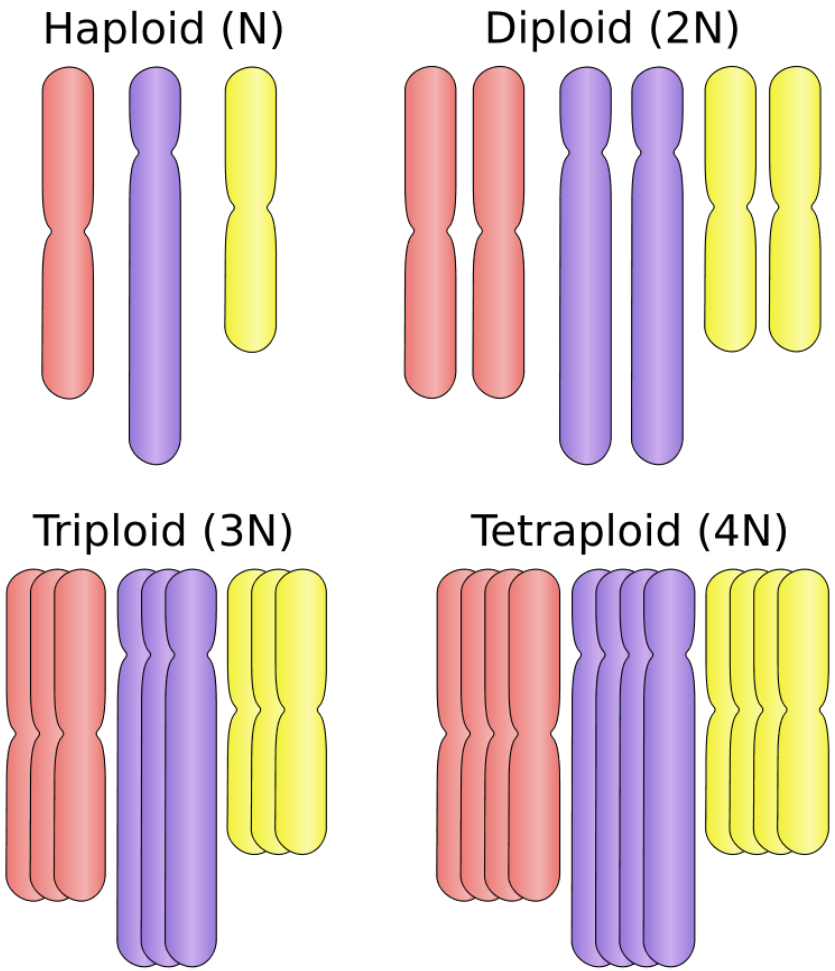
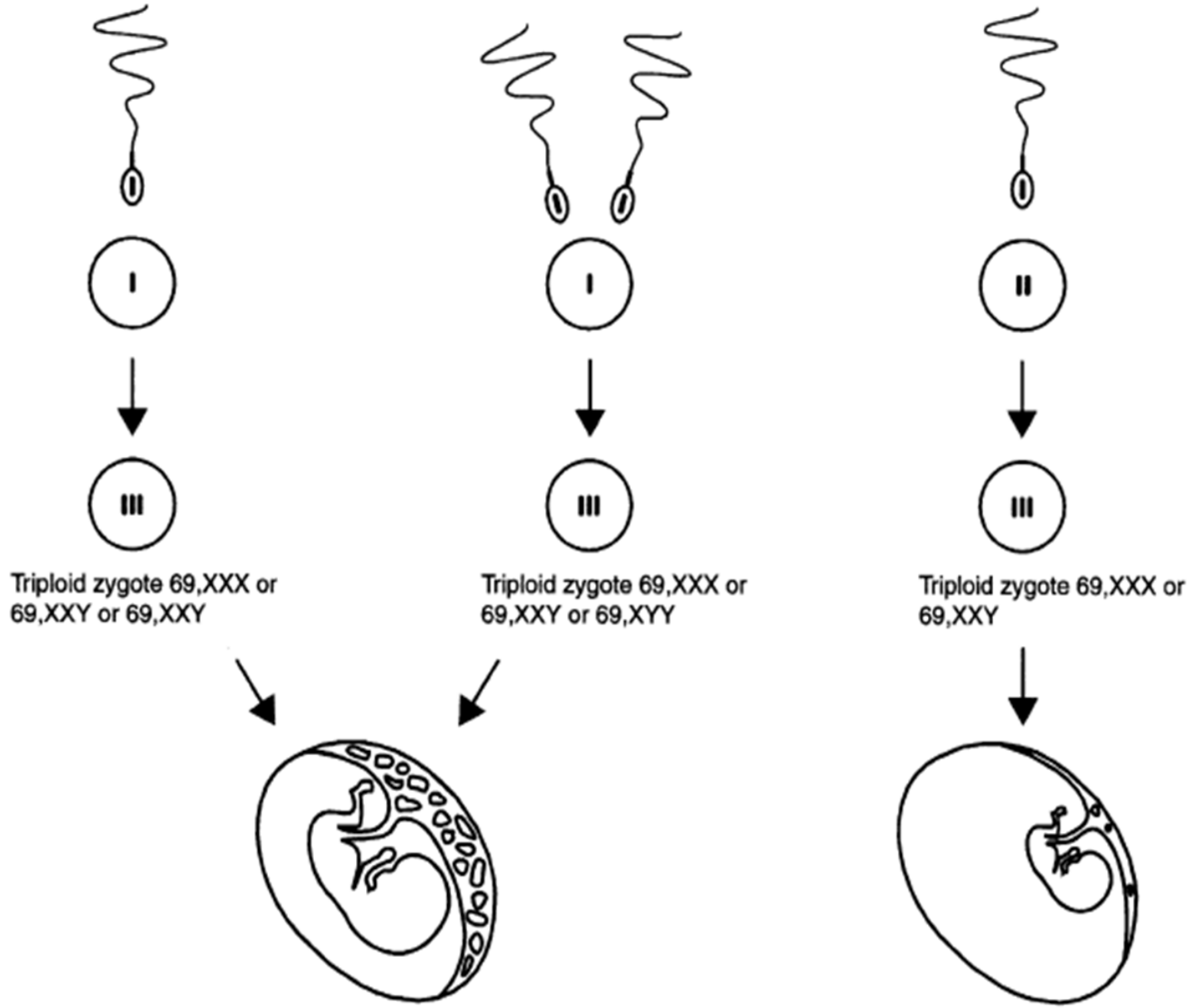
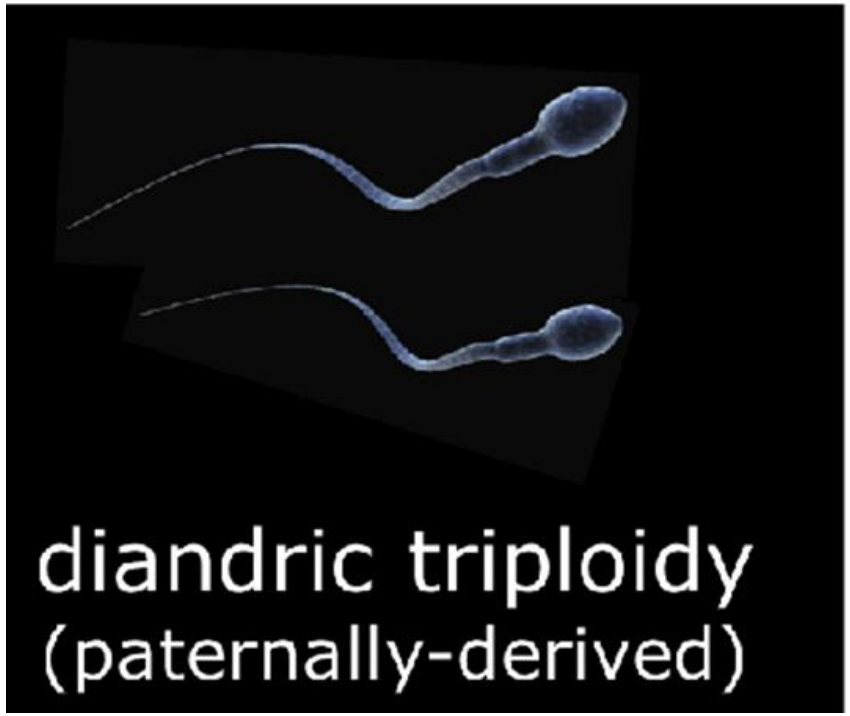
22
X
Y


Short arm pseudoautosomal region (PAR1)
Y chromosome
X chromosome
Tel
400
500
600
700
800
900
2,600 (kb)
CNE-5
CNE-3
CNE-2
SHOX
CNE4
ECR1
CNE5
CNE9/ECS4

# Polyploidy

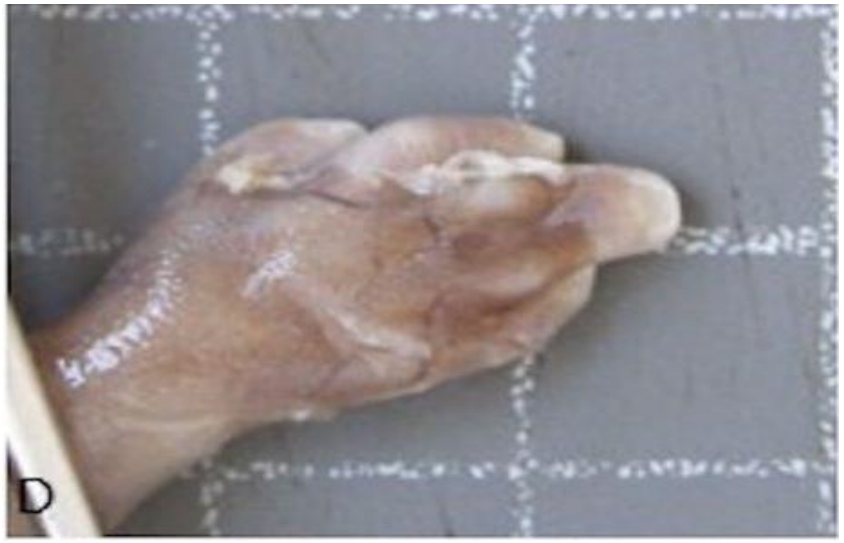

Haploid (N)
Diploid (2N)
Triploid (3N)
Tetraploid (4N)

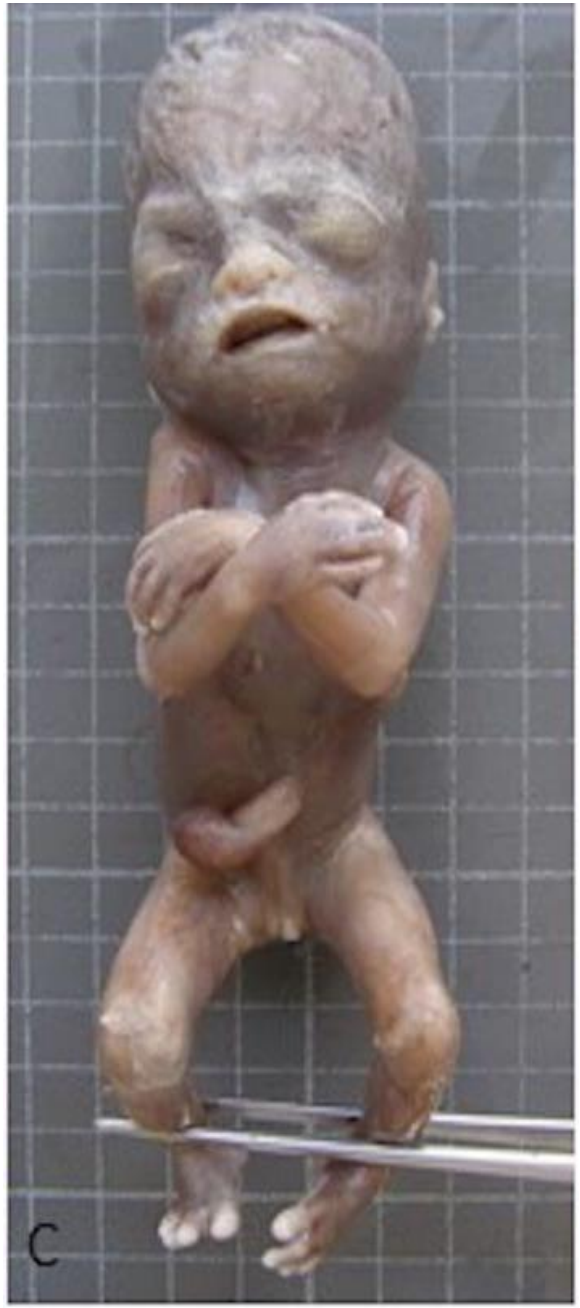

I
III
Triploid zygote 69,XXX or 69,XXY or 69,XXY
I
III
Triploid zygote 69,XXX or 69,XXY or 69,XYY
II
III
Triploid zygote 69,XXX or 69,XXY



diandric triploidy
(paternally-derived)

digynic triploidy
(maternally-derived)

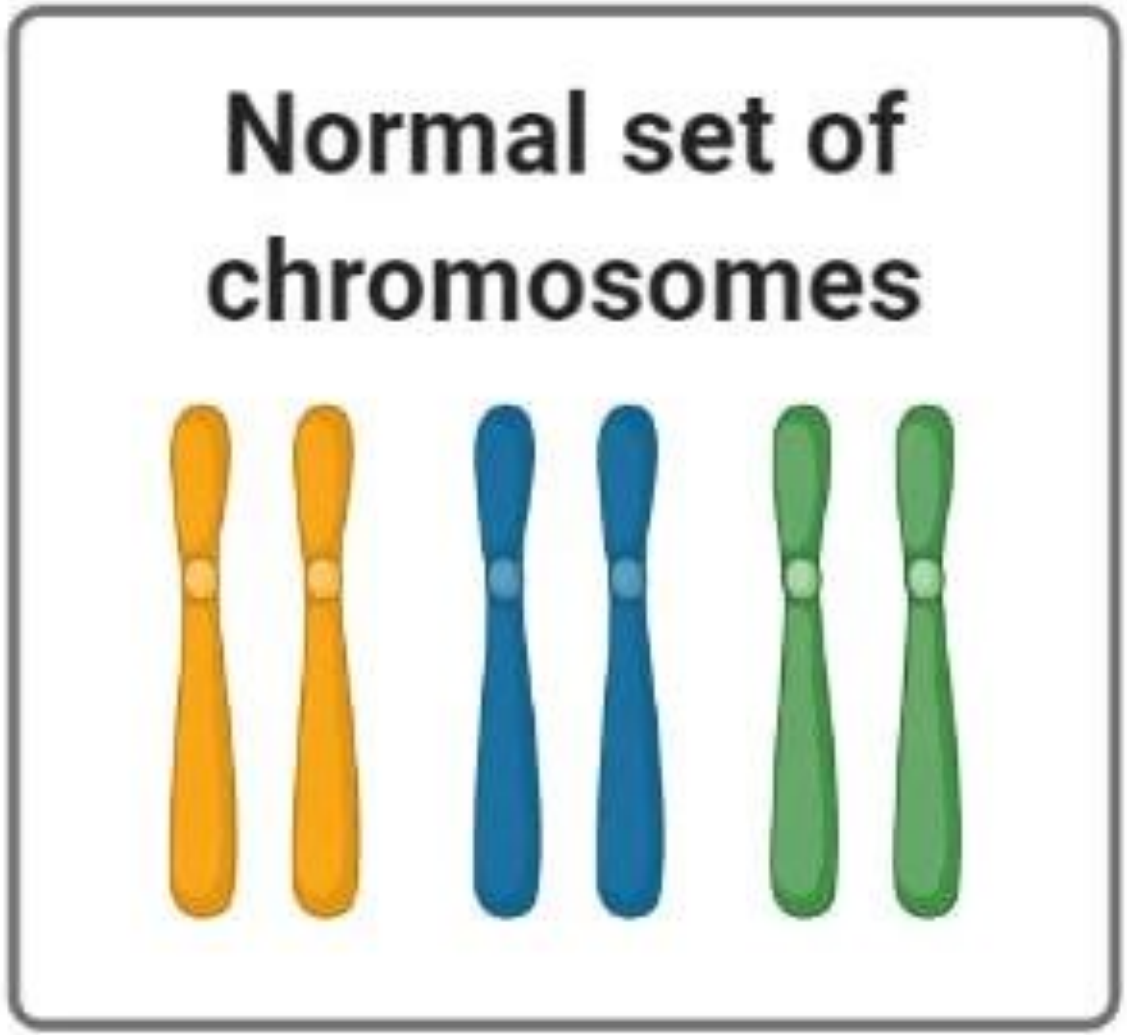
| نام سندرم | NIPT | Ultrasound | تست ترکیبی سه ماهه اول | تست سه ماهه دوم |
|---|---|---|---|---|
| Edwards syndrome | هفته 10 بارداری<br>غیر تهاجمی<br>خون مادر | سه ماهه اول و دوم<br>تاخیر رشد داخل راحمی،<br>قلب غیرطبیعی و دست های گره کرده | سونو NT افزایش یا طبیعی<br>Beta-hCG کاهش<br>PAPP-A کاهش | |
| Patau syndrome | هفته 10 بارداری<br>تشخیص قطعی نیست | شکاف لب و کام،<br>ناهنجاری قلب، ناهنجاری شدید مغز و انگشت اضافه | سونو NT بالا<br>Beta-Hcg پایین<br>PAPP-A پایین | |
| Dawn syndrome | هفته 10 بارداری<br>فقط احتمال را نشان میدهد | افزایشNT ، تاخیر رشد،<br>ضخیم شدن گردن،<br>استخوان بینی کوچک | سونو NT افزایش<br>Beta-hCG بالا<br>PAPP-A پایین | AFP پایین<br>Beta-hCG بالا<br>uE3 پایین<br>Inhibin A بالا |
| Klinefelter syndrome | هفته 10 بارداری | تاخیر رشد خفیف، طبیعی بودن کامل<br>نشانه های واضحی دیده نمیشود | | برای این سندرم اختصاصی نیستند |
| Triple X syndrome | هفته 10 بارداری<br>فقط احتمال را نشان میدهد | معمولا طبیعی است و<br>نشانه خاصی ندارد | | |

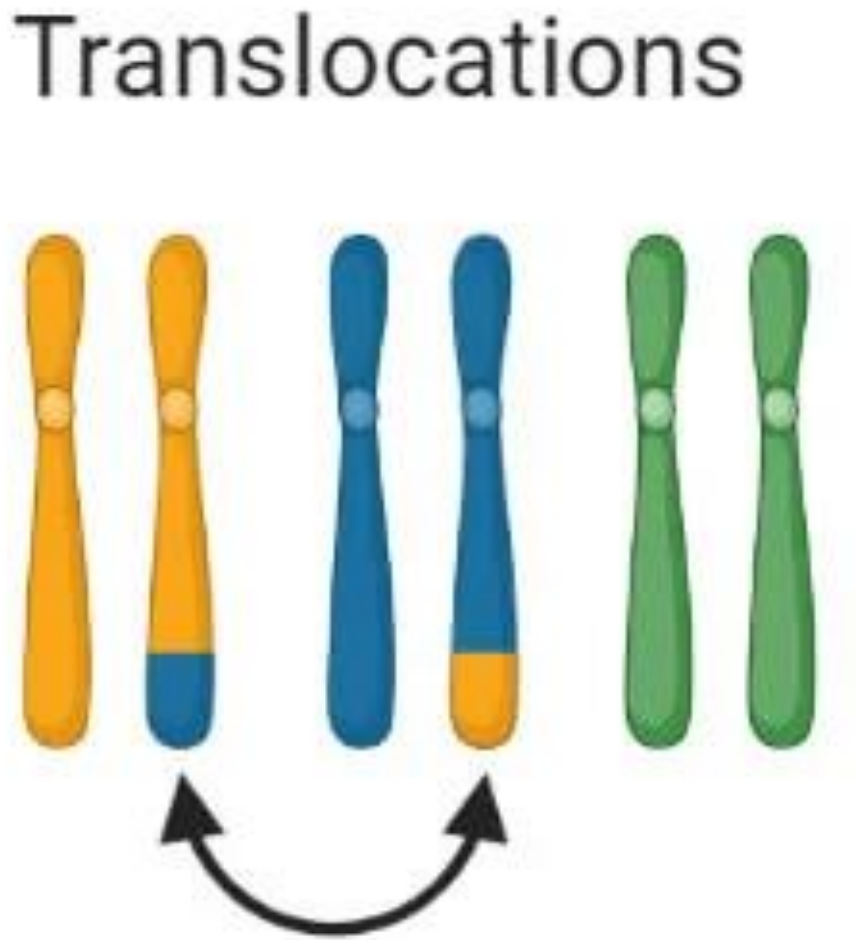
| نام سندرم | Amniocentesis | CVS | Karyotyping | FISH |
|---|---|---|---|---|
| Edwars syndrome | هفته 10-15 بارداری مایع آمنیوتیک بررسی DNAجنین | هفته 10-13 بارداری نمونه:جفت بررسی: کروموزوم جنین | تشخیص نوع تریزومی قطعی و دقیق | روش سریع 24-48 ساعت |
| Patau syndrome | هفته 15-20 بارداری نمونه مایع امنیوتیک بررسی: کاریوتایپ و DNA جنین | هفته 10-13 بارداری نمونه: پرز های جفت | تشخیص قطعی نوع تریزومی | روش سریع 24-48 ساعت |
| Dawn syndrome | هفته 15-20 بارداری | هفته 10-13 بارداری | تشخیص قطعی و نوع تریزومی | روش سریع 24-48 ساعت |
| Klinefelter syndrome | هفته 15-20 بارداری | هفته 10-13 بارداری | تشخیص قطعی سندرم و نوع | روش سریع 24-48 ساعت |
| Triple X syndrome | هفته 15-20 بارداری | هفته 10-13 بارداری | تشخیص قطعی و تعداد دقیق کروموزوم های X | روش سریع 24-48 ساعت |
| Turner syndrome | هفته 15-20 بارداری | هفته 10-13 بارداری | مهم ترین و قطعی ترین تست | روش سریع 24-48 ساعت |

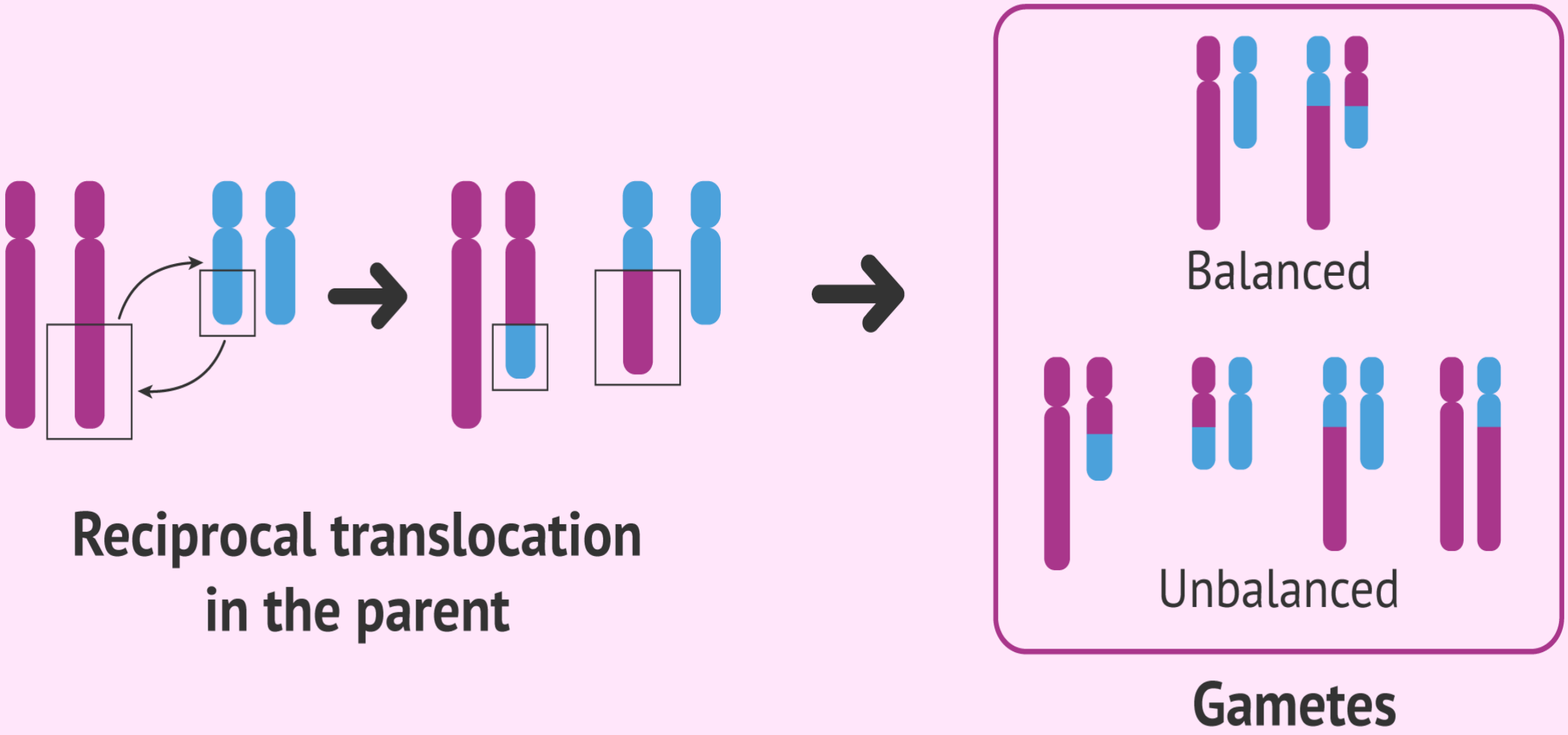
| نام سندرم | کاریوتایپ خون محیطی | بررسی های تکمیلی |
| --- | --- | --- |
| Edwards syndrome | تایید قطعی بیماری | اکو قلب، سونو کلیه و شکم،MRI/CT مغز |
| Patau syndrome | تایید قطعی بیماری | MRI مغز، اکوقلب، بررسی اندام ها |
| Dawn syndrome | تایید قطعی بیماری | اکو قلب(خیلی مهم)، بررسی شنوایی، ارزیابی رشد ذهنی و جسمی |
| Klinefelter syndrome | قطعی ترین روش تشخیص | تست های هورمونی که معمولا تستوسترون پایین،FSH بالا،LH بالا و آنالیز اسپرم |
| Triple X syndrome | بهترین روش | رشد طبیعی یا کمی بلندی قد، اختلالات خفیف گفتاری |
| Turner syndrome | تایید قطعی بیماری | علائم بالینی کوتاهی قد، گردن پره دار، قفسه سینه پهن و بررسی های هورمونی: FSHبالا LH بالا و استروژن پایین |

**Structural Abnormalities**

- Balanced Rearrengment
  1. Translocation
  2. Inversion
  3. Insertion
- Un Balanced Rearrengment
  1. Deletion
  2. Duplicatin
  3. Ring chromosome
  4. Iso chromosome


Normal set of chromosomes

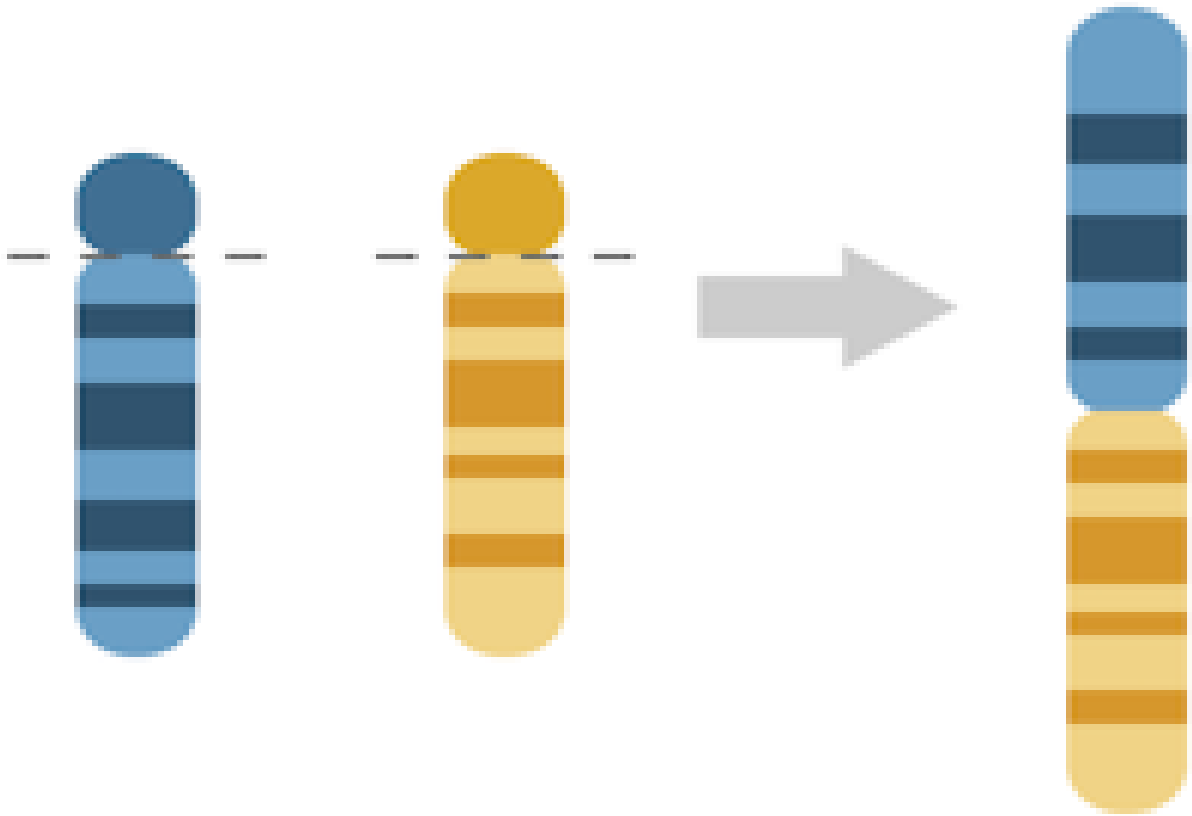

Translocations




Reciprocal translocation in the parent

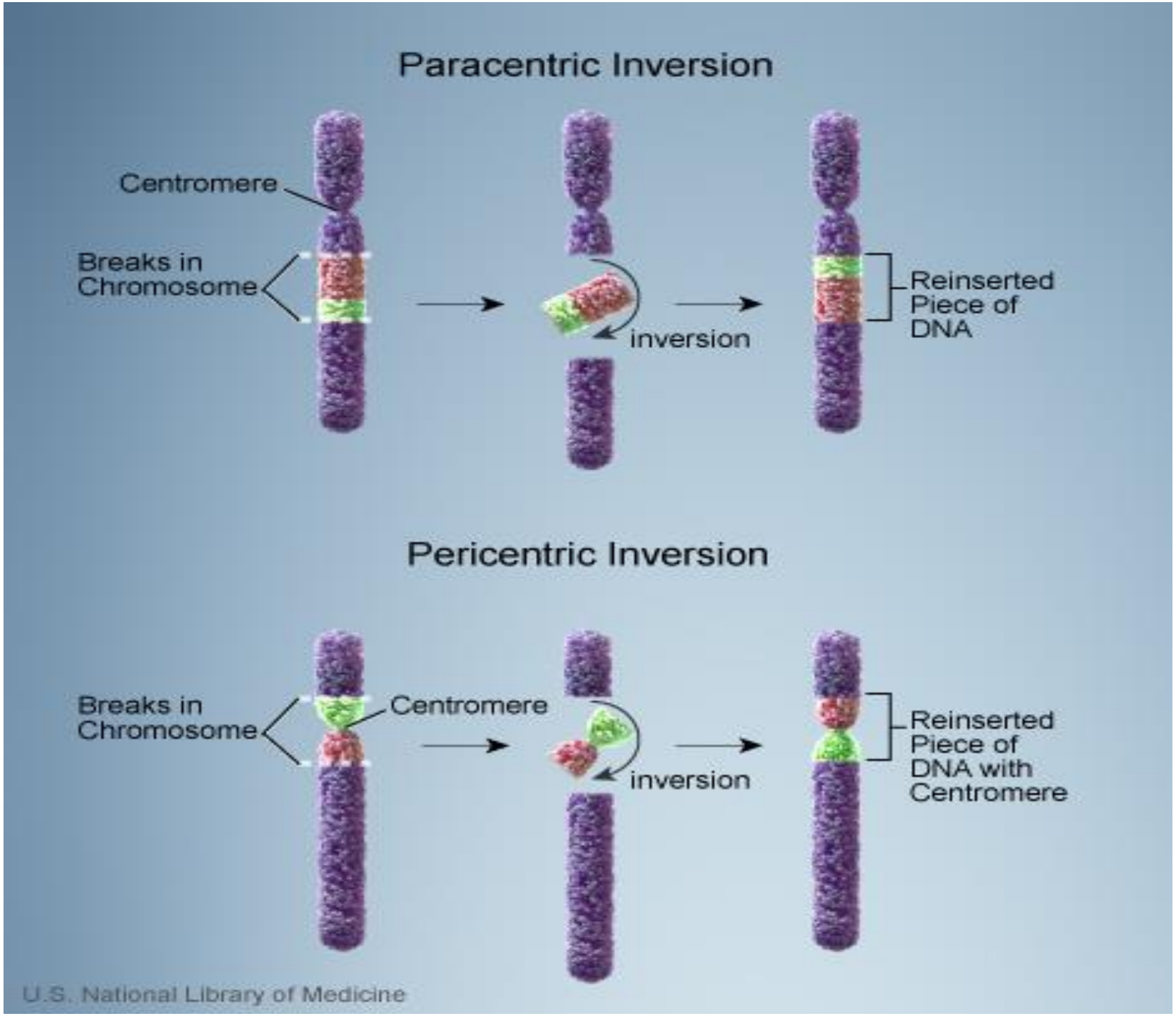
Gametes

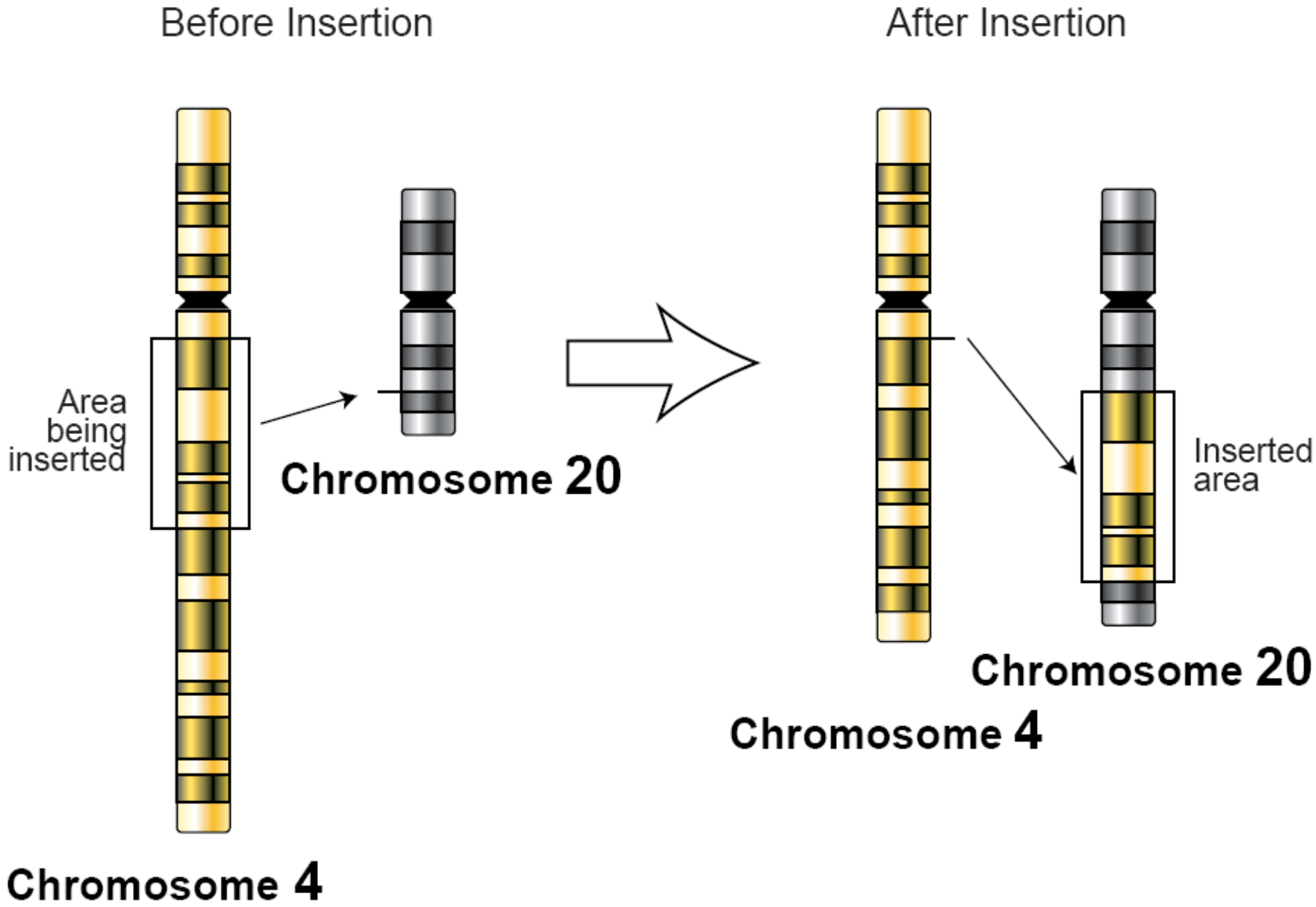
# Robertsonian translocation



**Normal set of chromosomes**

Inversions


Paracentric Inversion
Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA
Pericentric Inversion
Breaks in Chromosome
Centromere
inversion
Reinserted Piece of DNA with Centromere
U.S. National Library of Medicine


Before Insertion
After Insertion
Area being inserted
Chromosome 20
Chromosome 4
Inserted area
Chromosome 20
Chromosome 4

## Normal set of chromosomes

## Deletions

**Deletion**

## Large deletions

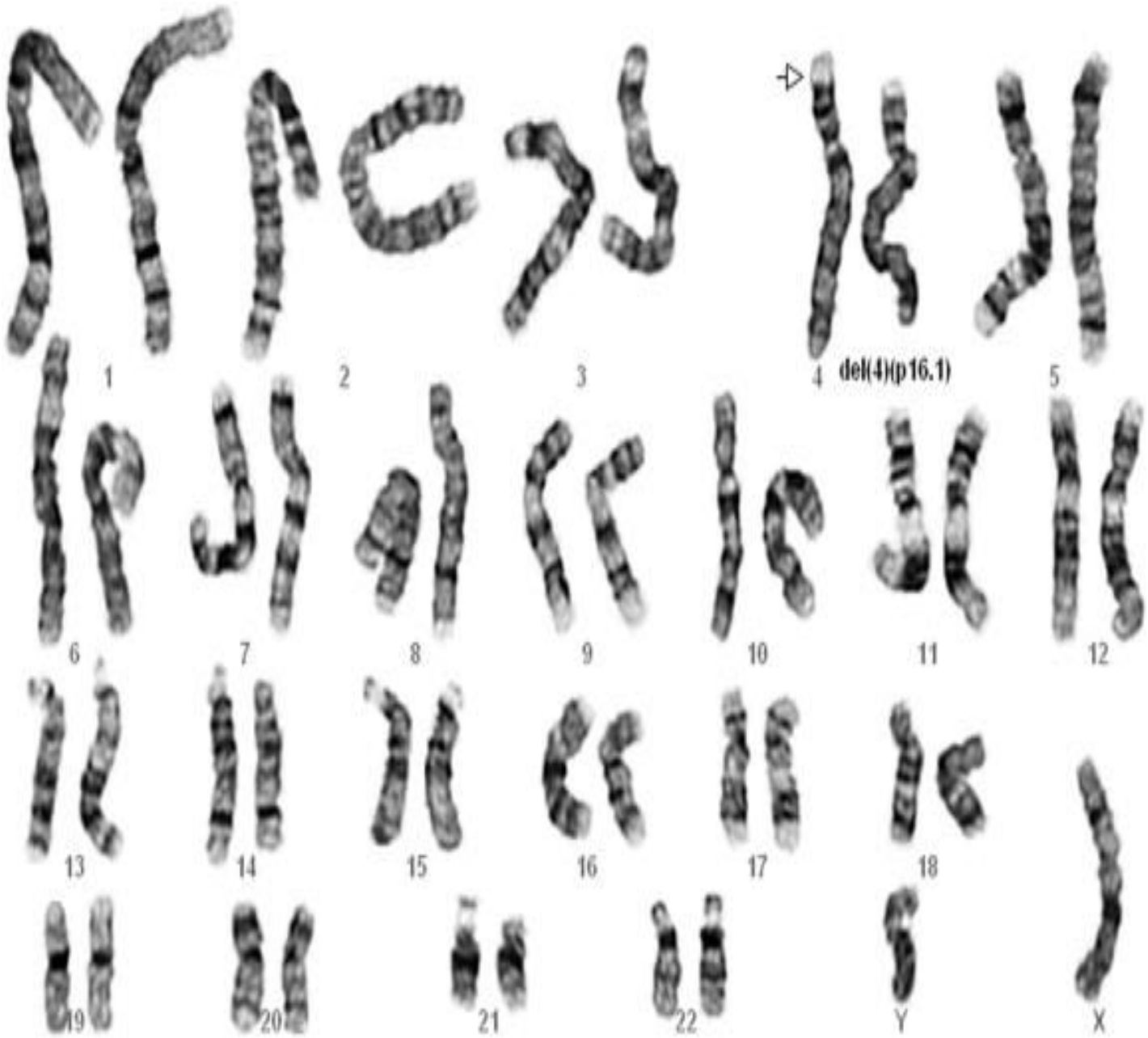
1. Wolf-Hirschhorn syndrome
2. Cri-du-chat syndrome

## Micro deletions

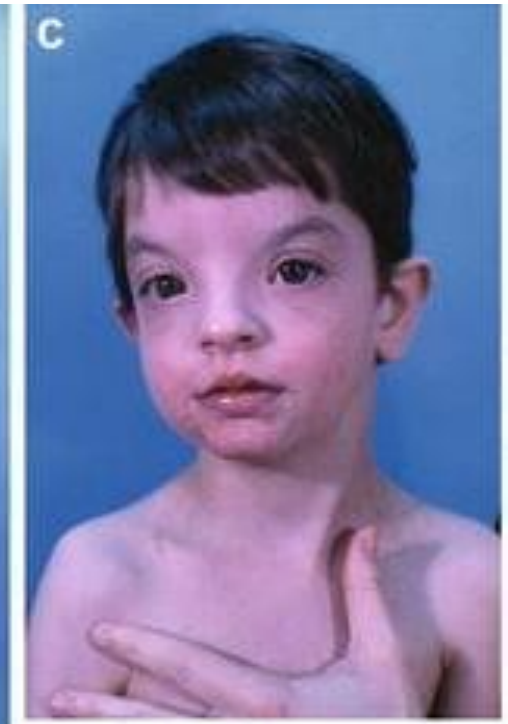
1. Prader–Willi syndrome
2. Angelman syndrome
3. Wilms tumor
4. DiGeorge syndrome
5. Williams syndrome

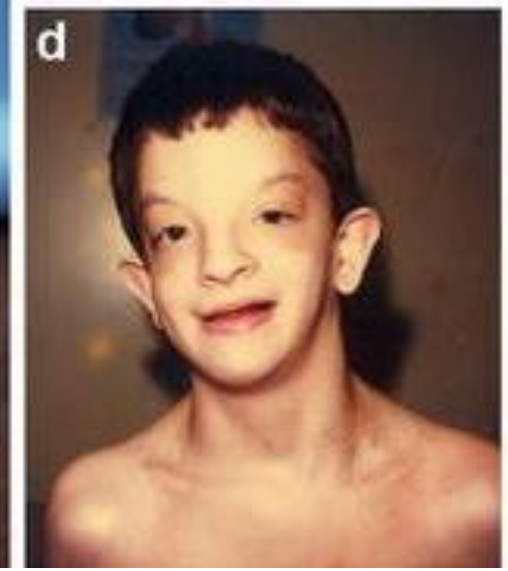

Main facial symptoms
Large, wide-spaced eyes
Eye abnormalities
High forehead
Broad nasal bridge
Small chin and head
(microcephaly)
Cleft lip and cleft palate

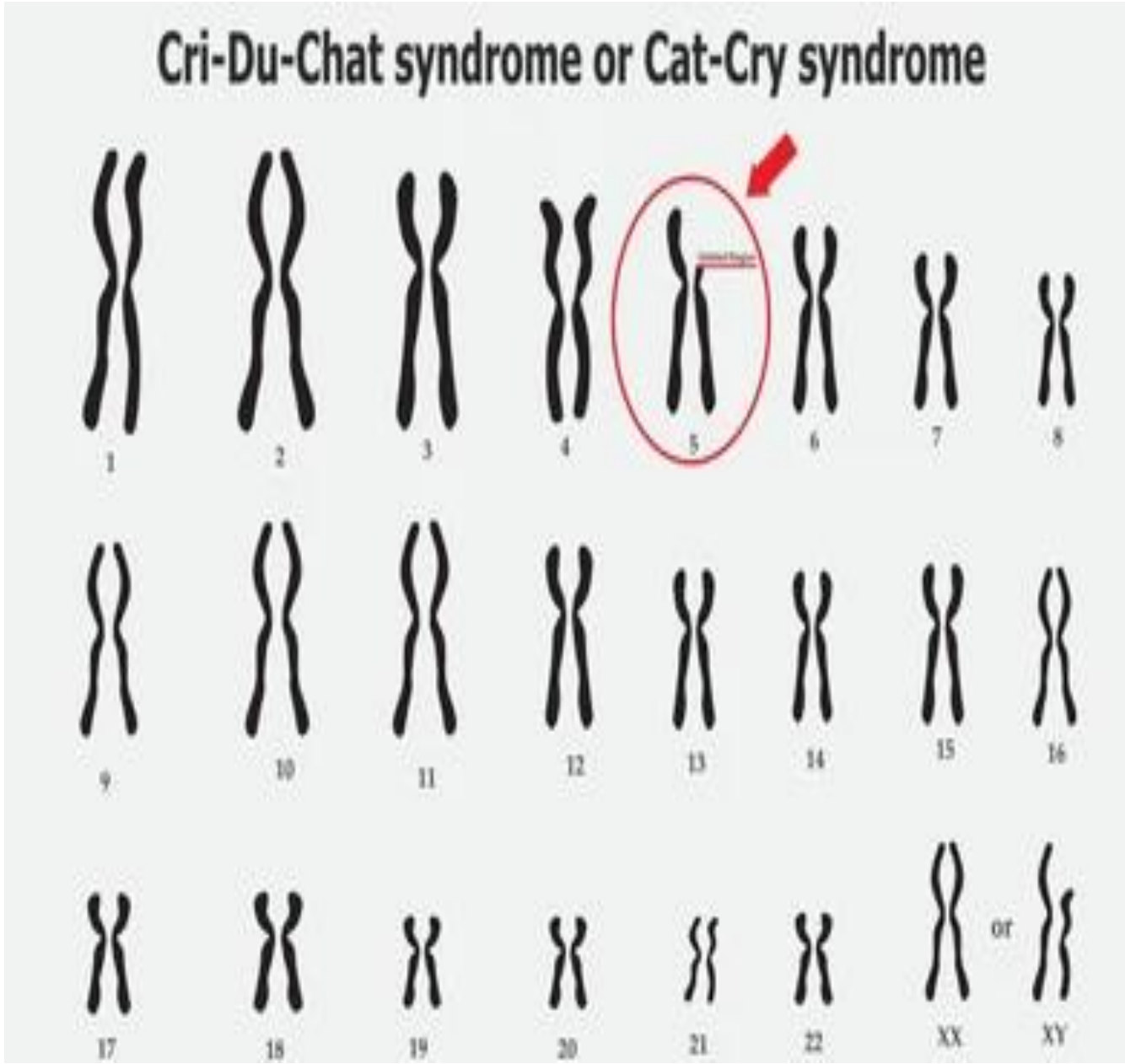

867
648
372
312
214
311
999
412


del(4)(p16.1)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Y
X


b


c


d


Cri-Du-Chat syndrome or Cat-Cry syndrome
1
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11
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13
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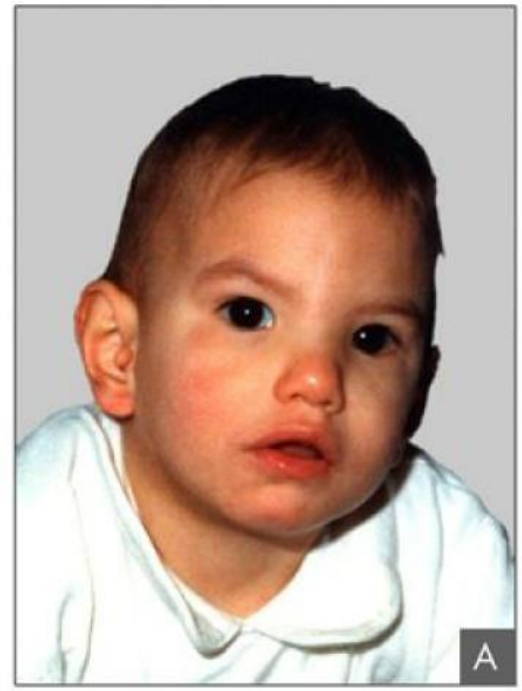
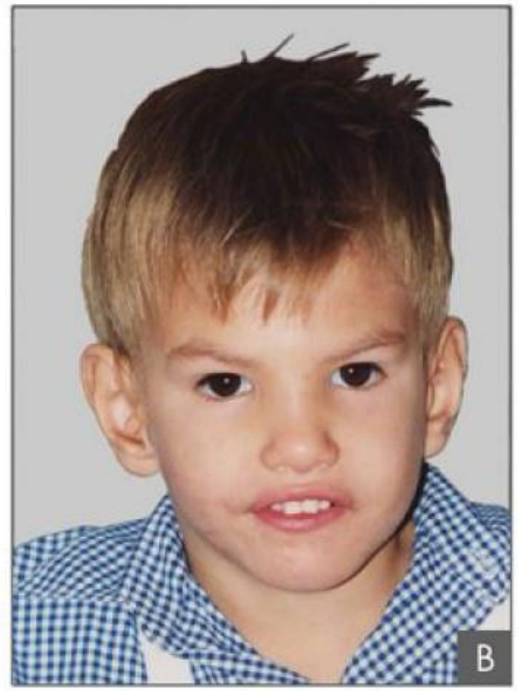
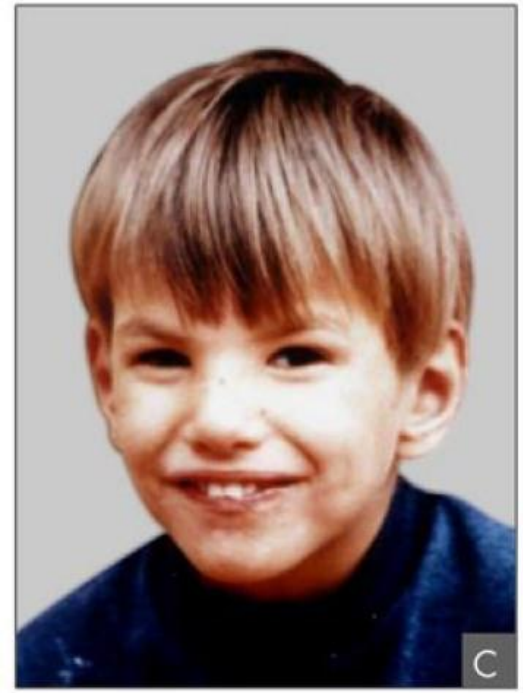
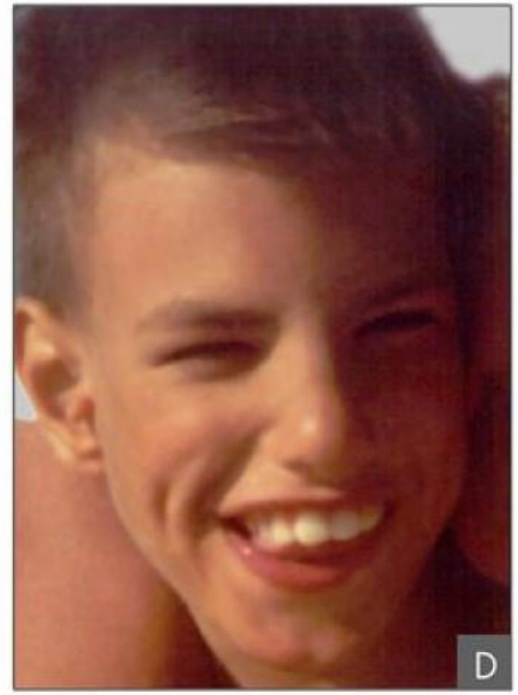
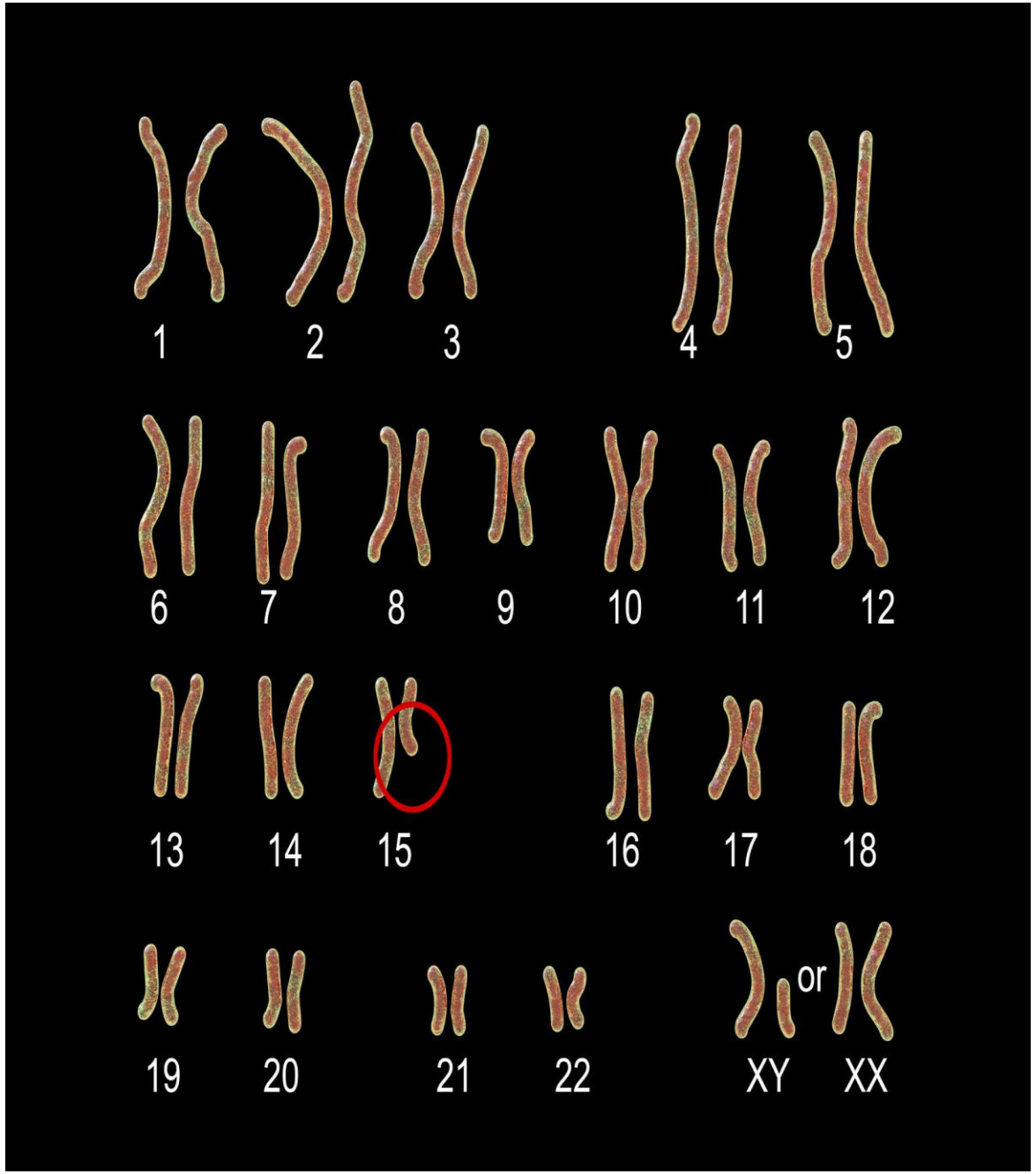
15
16
17
18
19
20
21
22
XX
or
XY


A


B


C

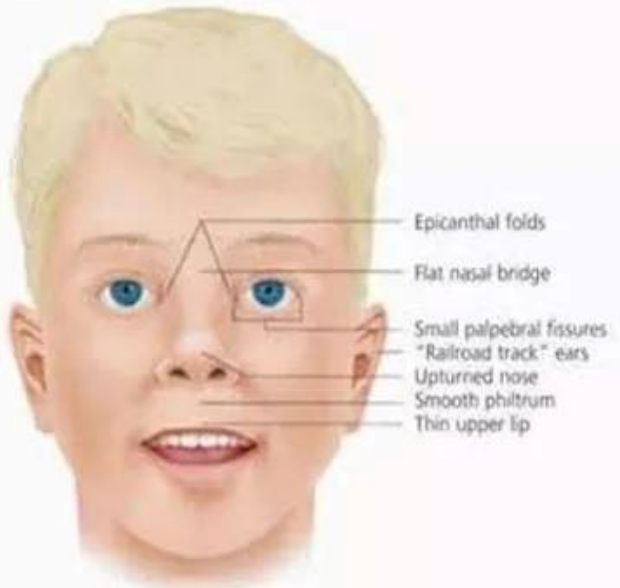

D

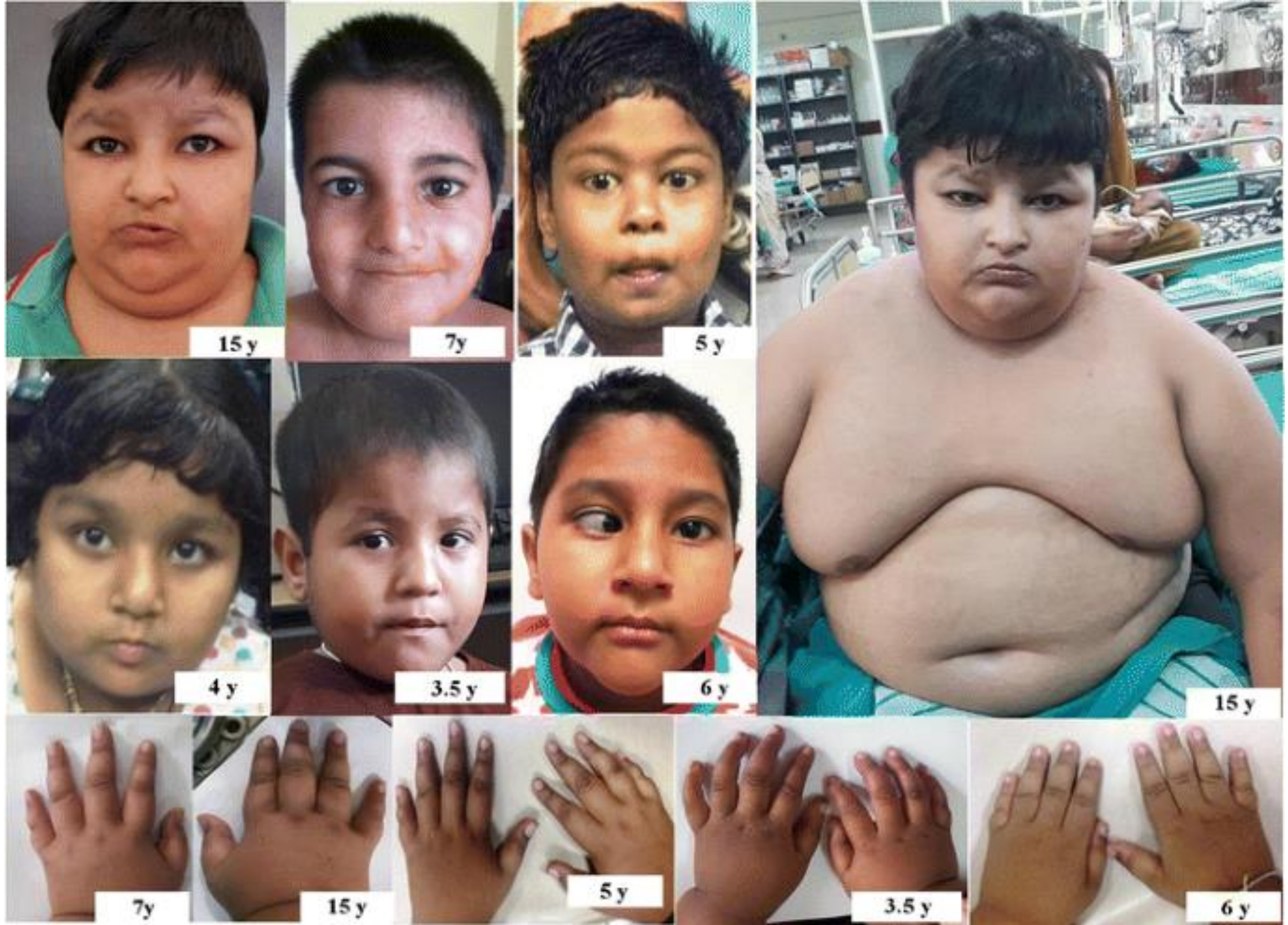


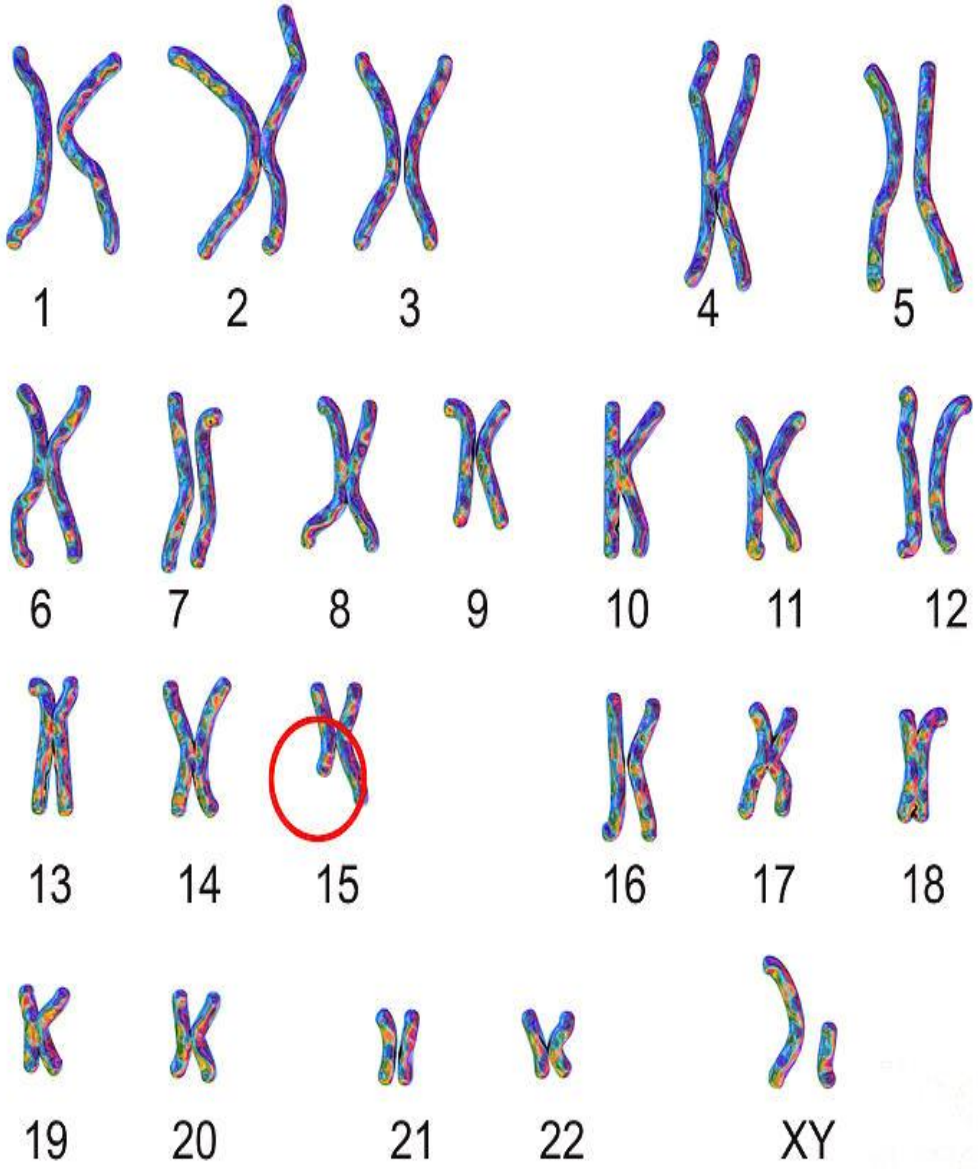

# PRADER WILLI FEATURES

**Mnemonic : H30**

- **Hyperphagia**
- **Hypotonia**
- **Hypopigmentation**
- **Obesity**




15 y
7y
5 y
4 y
3.5 y
6 y
15 y
7y
15 y
5 y
3.5 y
6 y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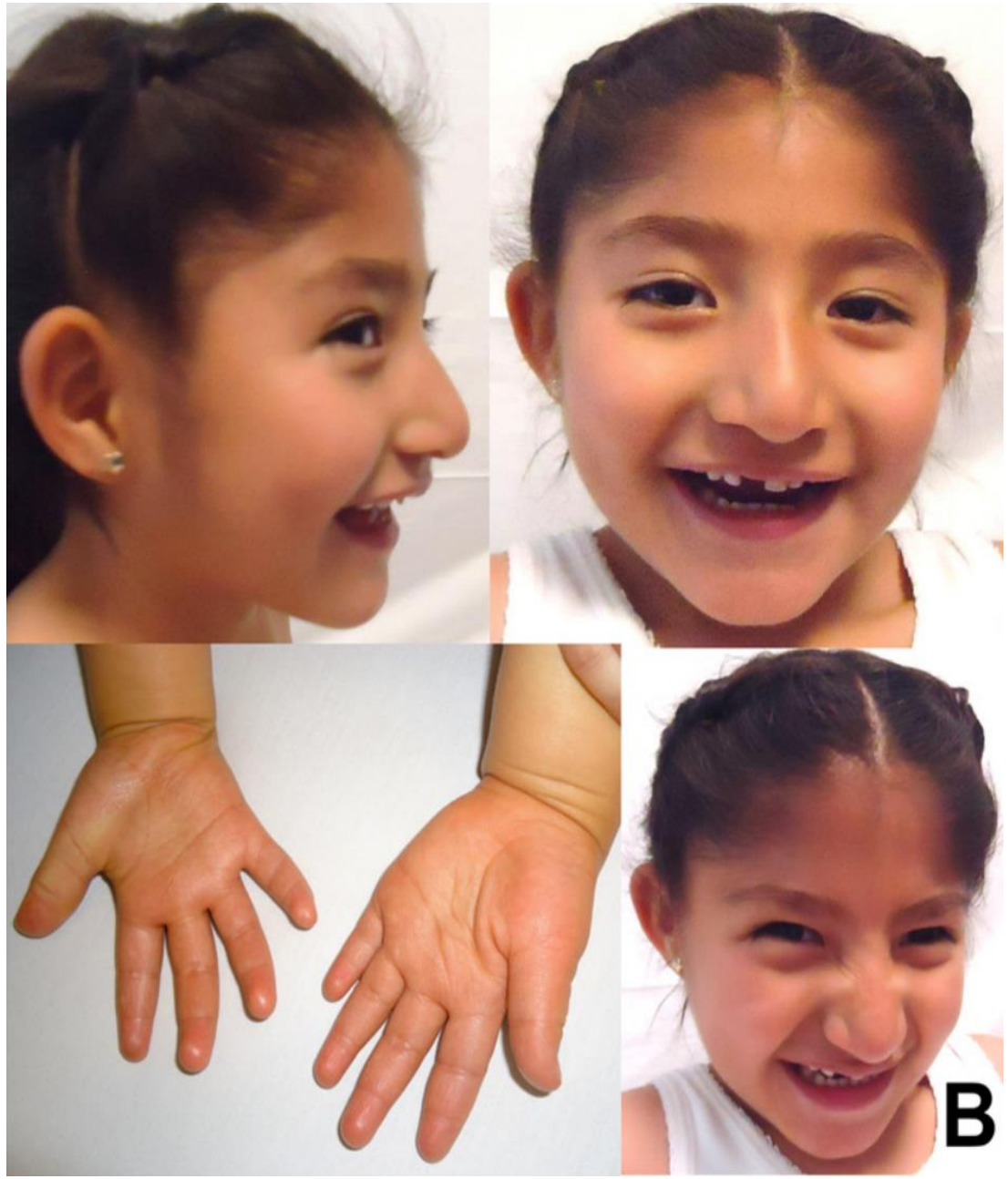
19
20
21
22
XY


B

# WAGR Syndrome

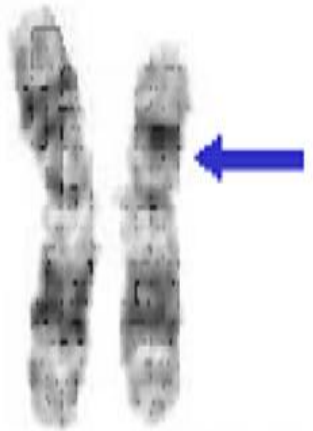
→ Results from deletion on chromosome 11 (11p13)

**W**ilms tumor
(Nephroblastoma)

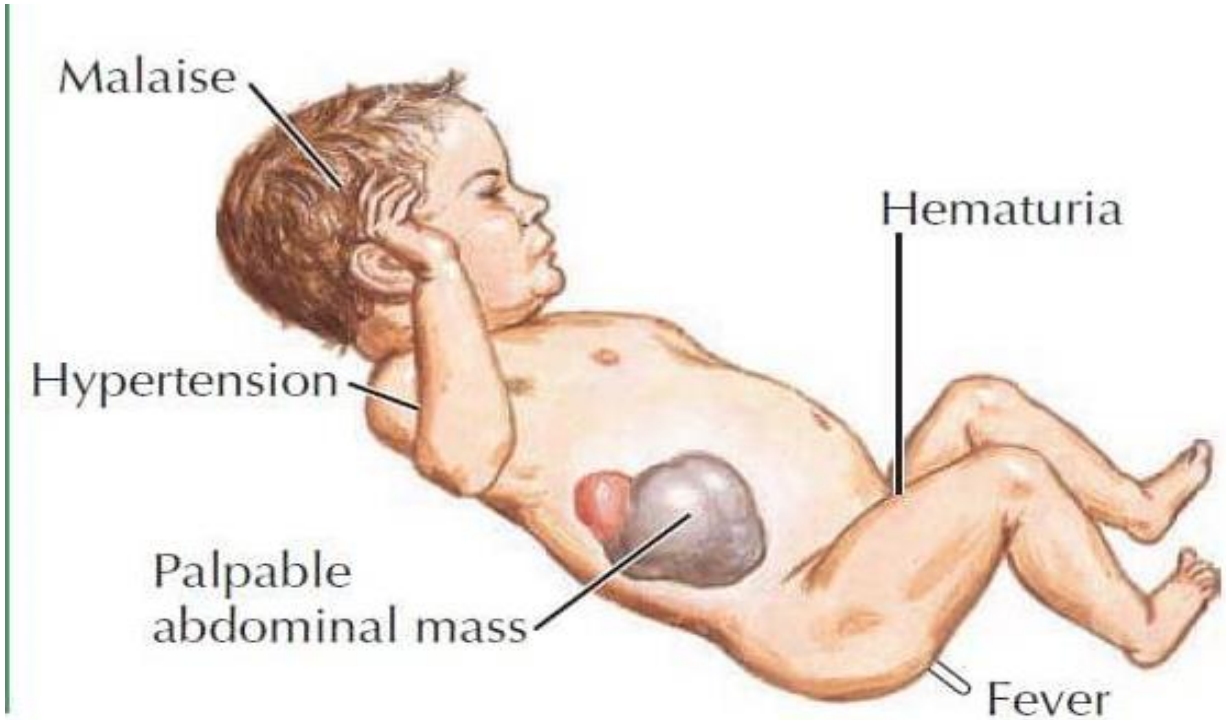
**A**niridia

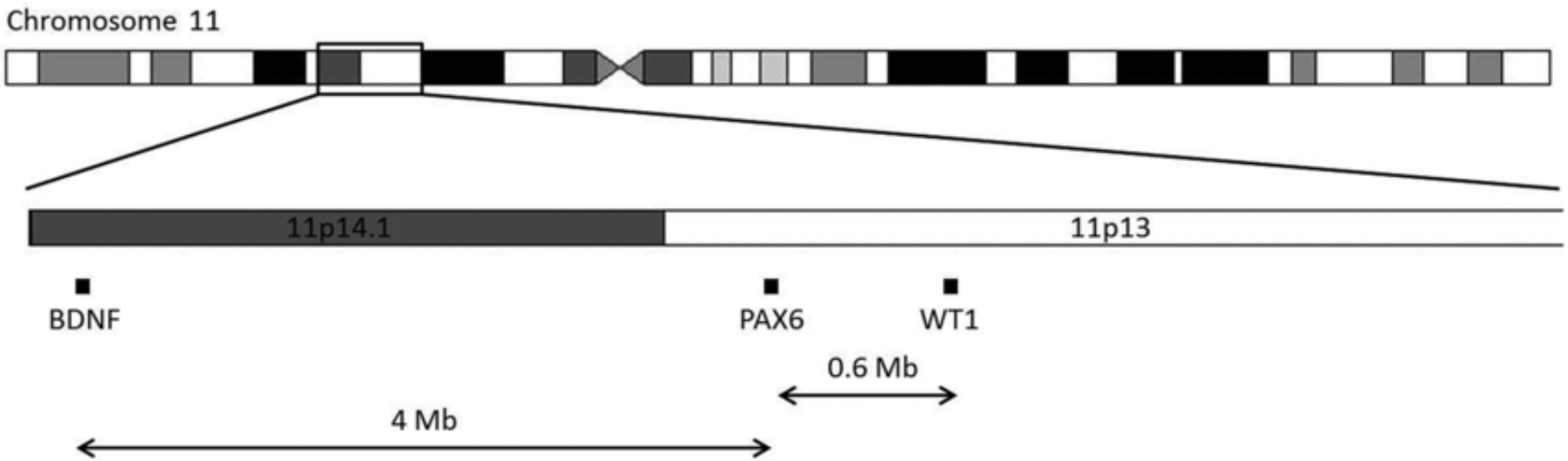
**G**enitourinary anomalies

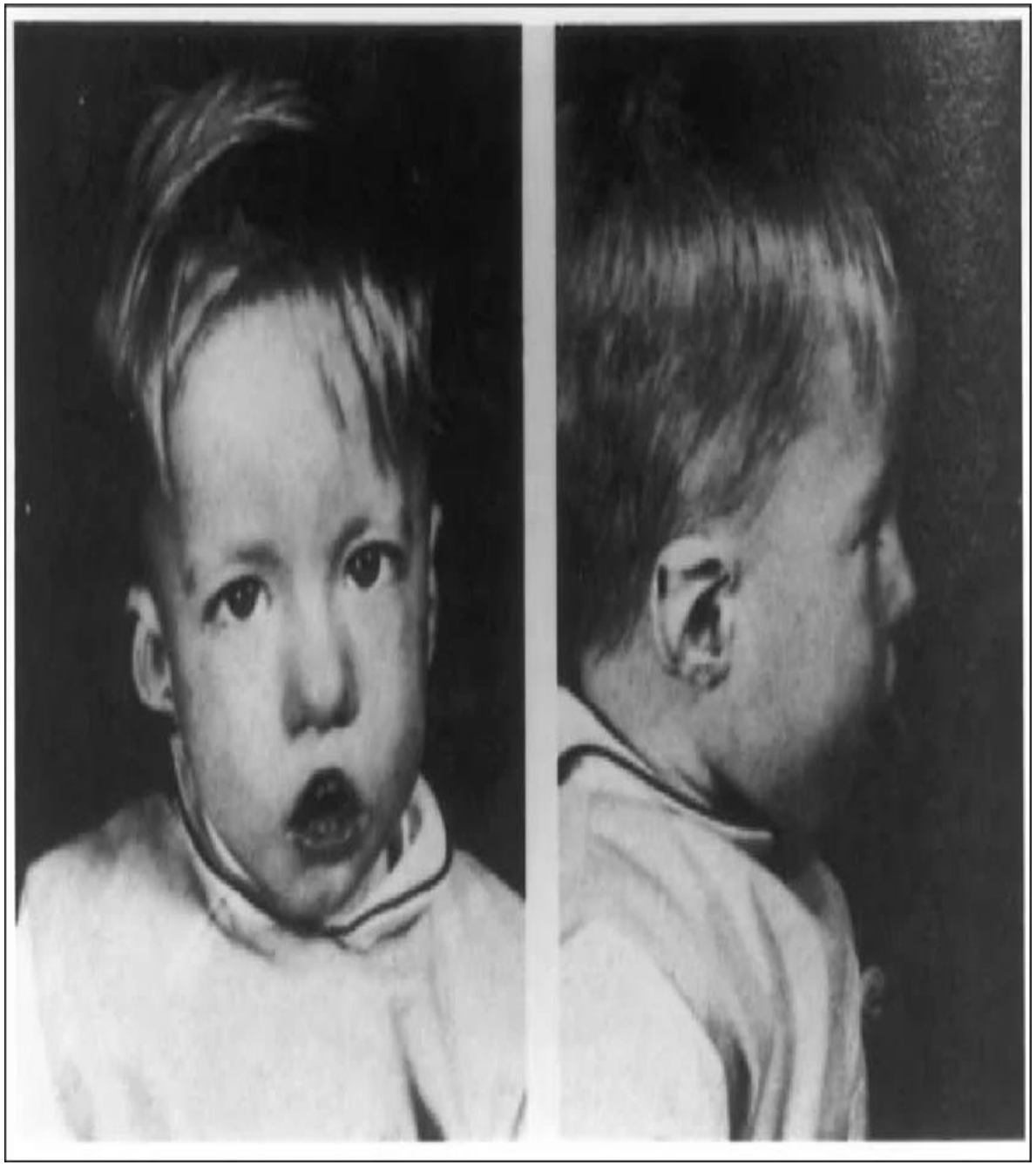
Mental **R**etardation



Normal 11 del(11)(p11.2p13)


Malaise
Hematuria
Hypertension
Palpable
abdominal mass
Fever


Chromosome 11
11p14.1
11p13
BDNF
PAX6
WT1
0.6 Mb
4 Mb



# DiGeorge Syndrome

## Clinical Features Affecting Anesthetic Management

### Airway Manifestations

- Micrognathia
- Retrognathia
- Cleft Palate
- Velopharyngeal insufficiency
- Asymmetric epiglottis
- Irregular vocal cords
- Increase laryngeal angulation
- Tracheal malformations

### Cardiac Manifestations

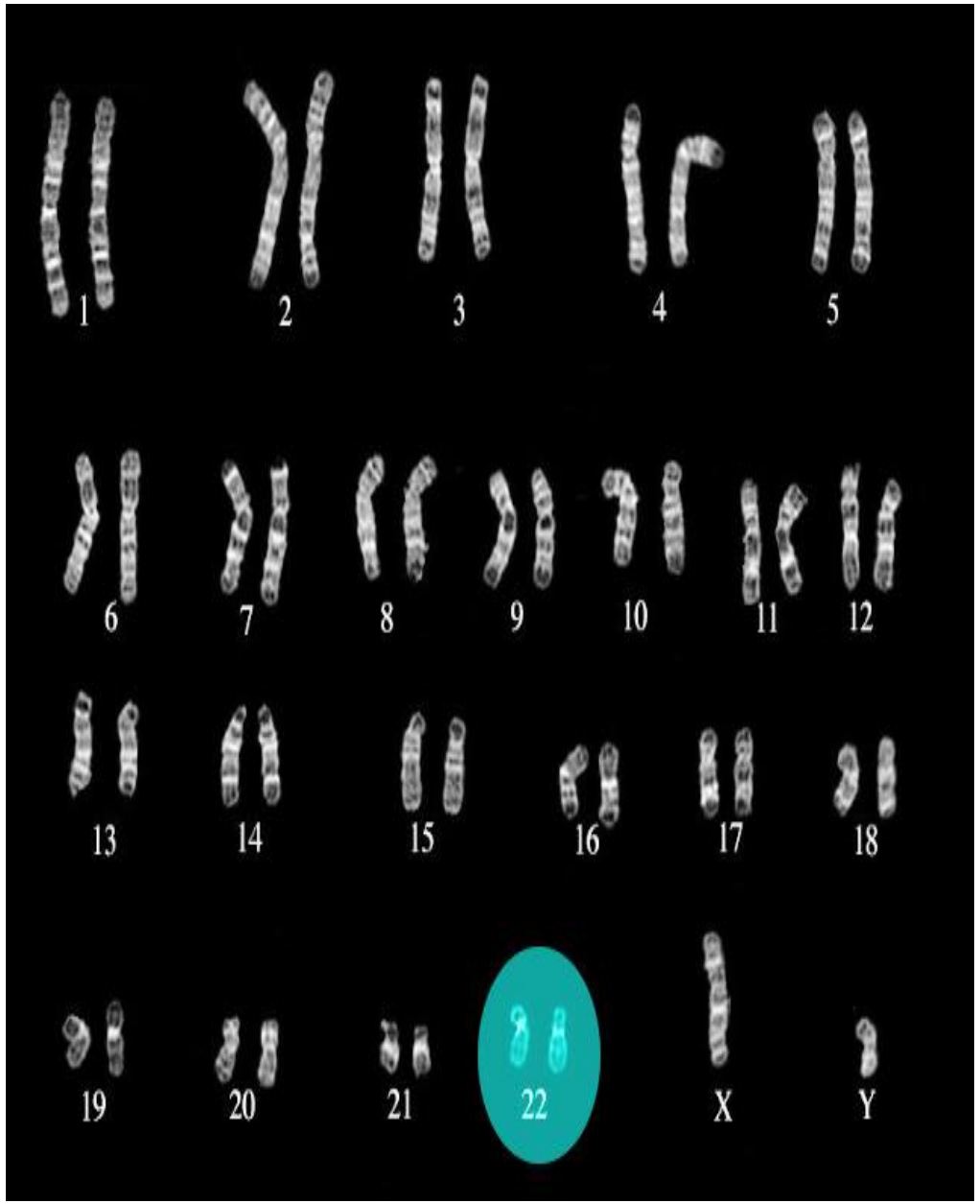
- Tetralogy of Fallot
- Truncus arteriosus
- Aortic arch anomalies
- Septal defects

### Endocrine Manifestations

- Hypoparathyroidism
- Hypocalcemia

### Immunological Manifestations

- Thymic hypoplasia or aplasia
- Cellular and humoral abnormalities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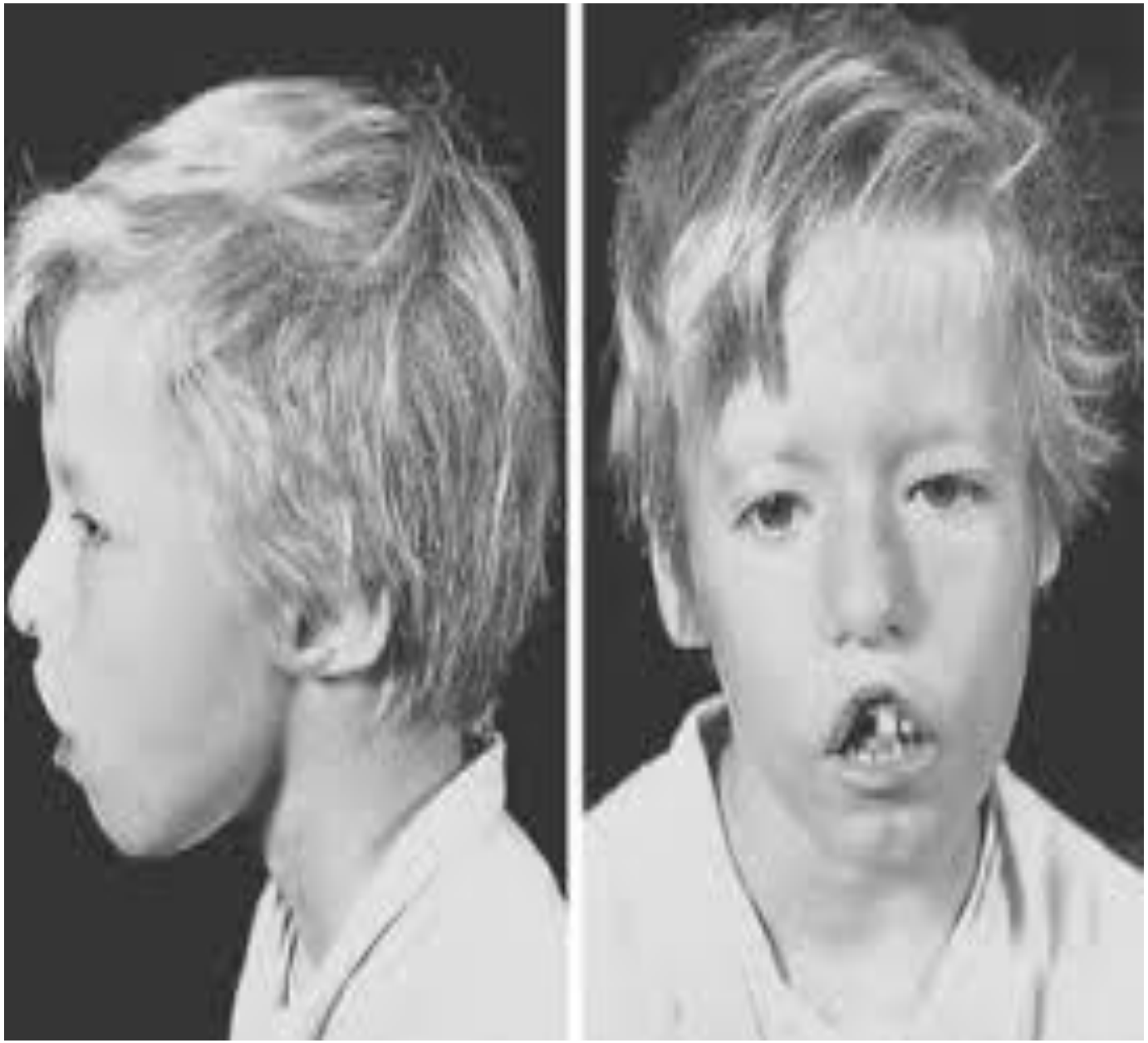
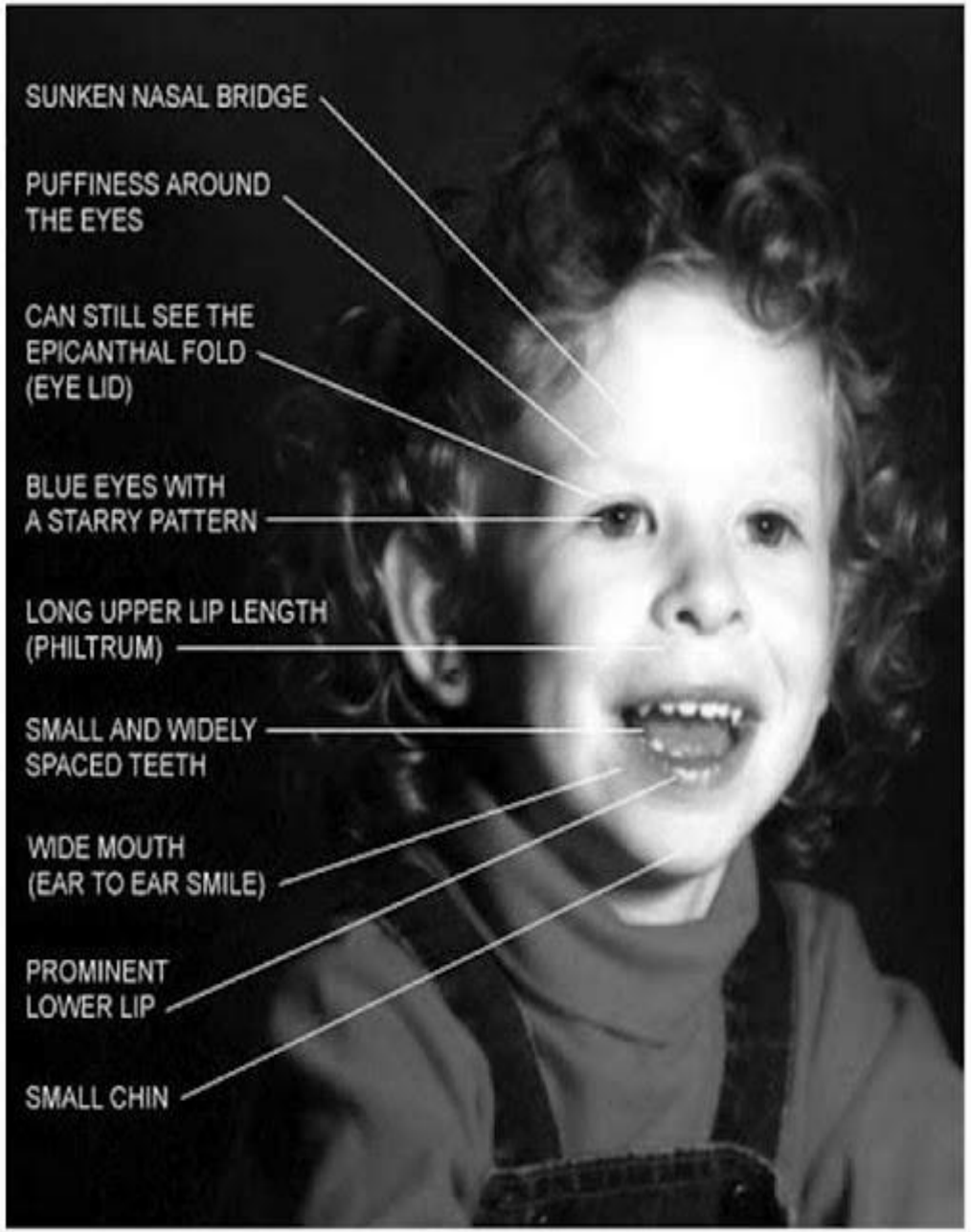
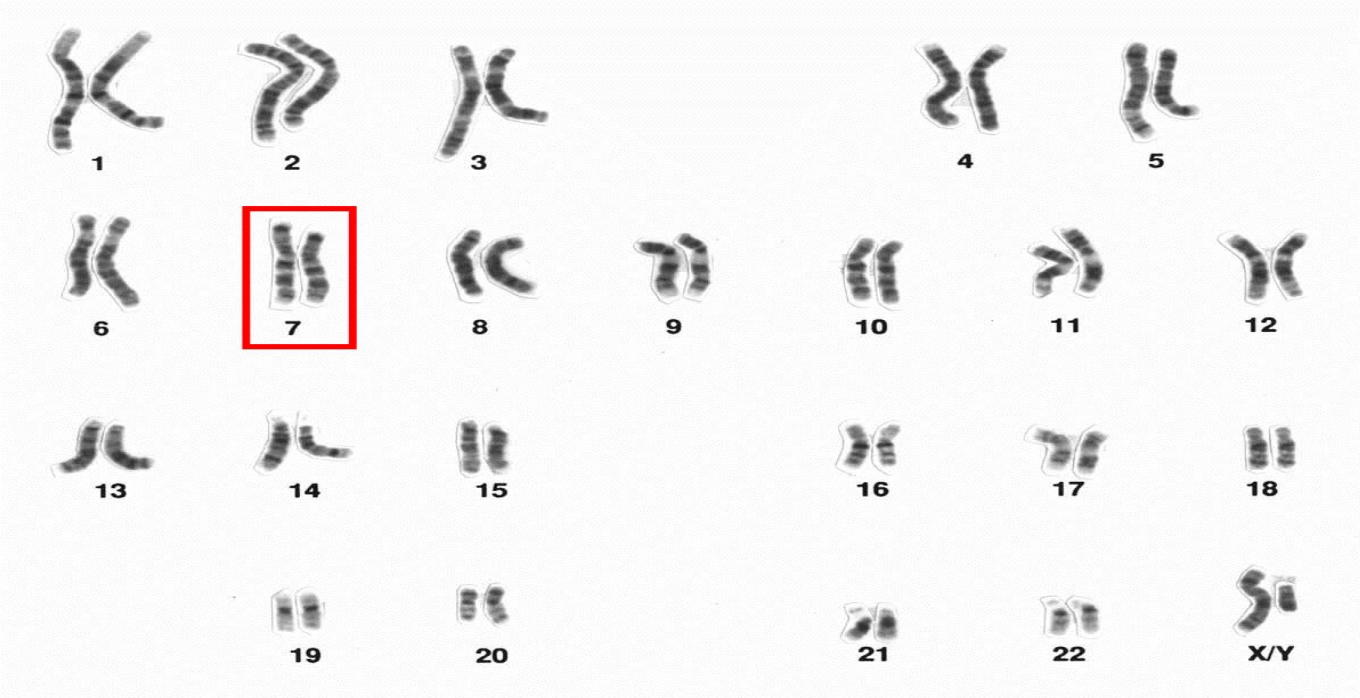
20
21
22
X
Y




SUNKEN NASAL BRIDGE
PUFFINESS AROUND THE EYES
CAN STILL SEE THE EPICANTHAL FOLD (EYE LID)
BLUE EYES WITH A STARRY PATTERN
LONG UPPER LIP LENGTH (PHILTRUM)
SMALL AND WIDELY SPACED TEETH
WIDE MOUTH (EAR TO EAR SMILE)
PROMINENT LOWER LIP
SMALL CHIN


1
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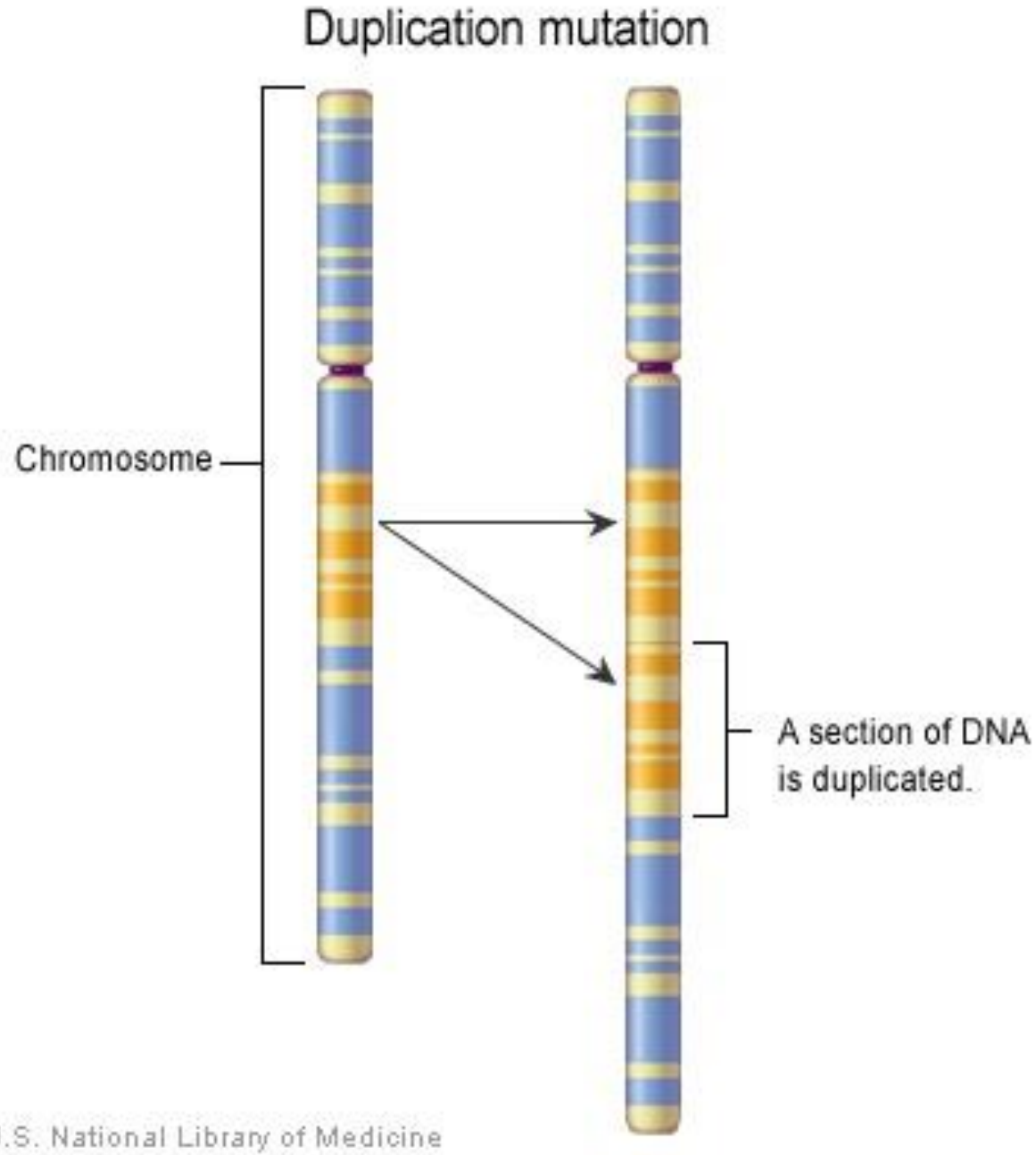
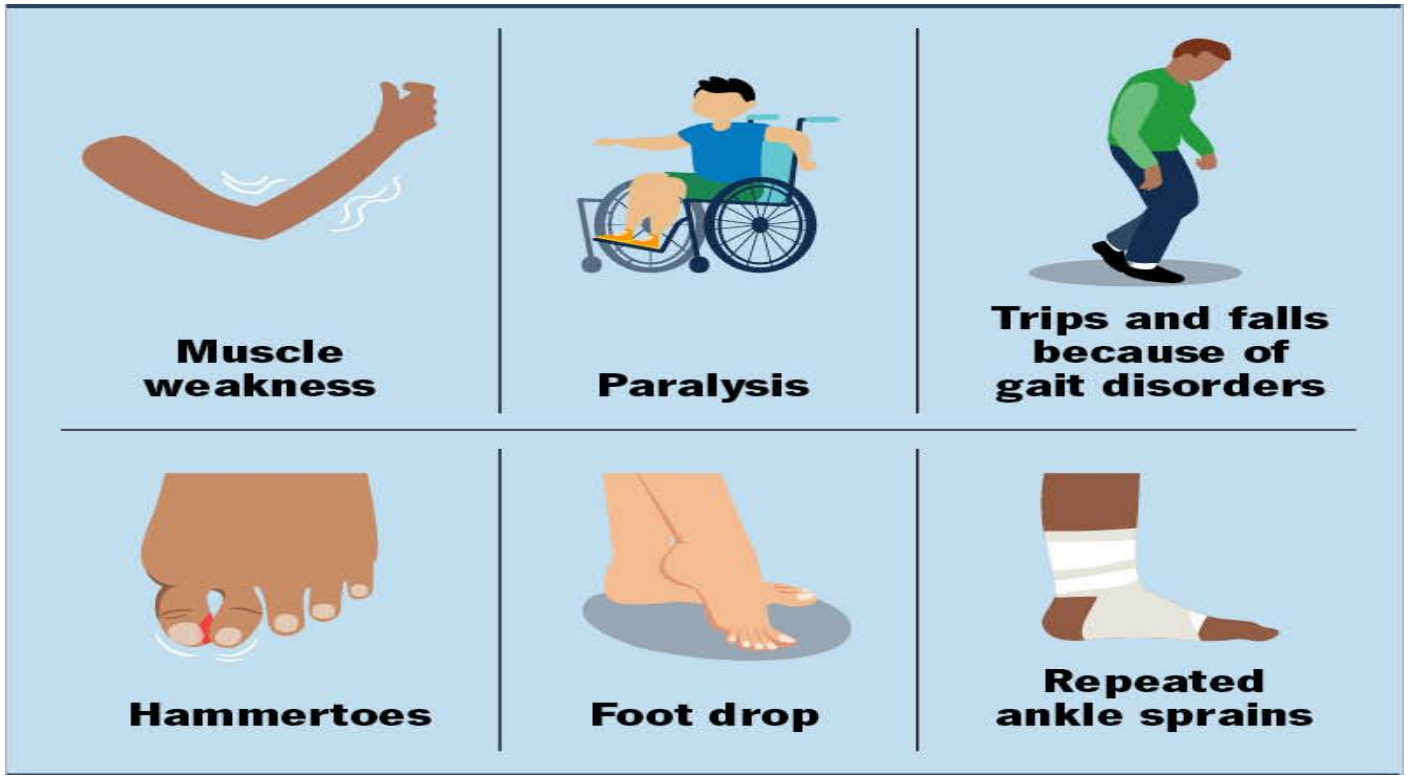
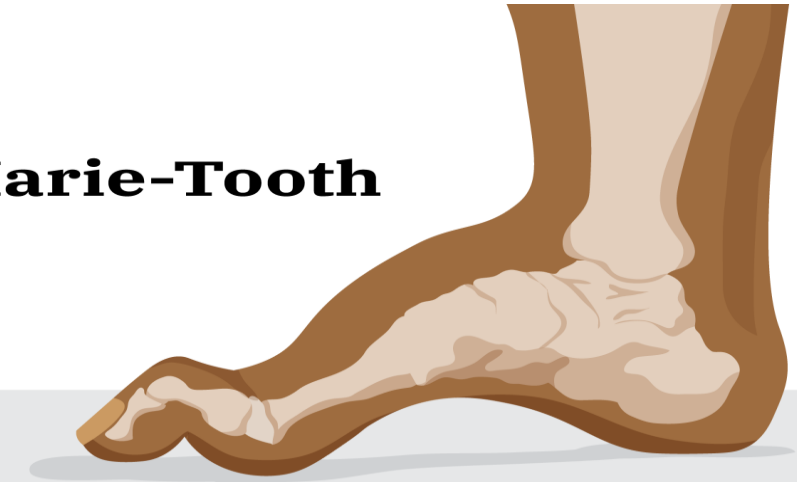
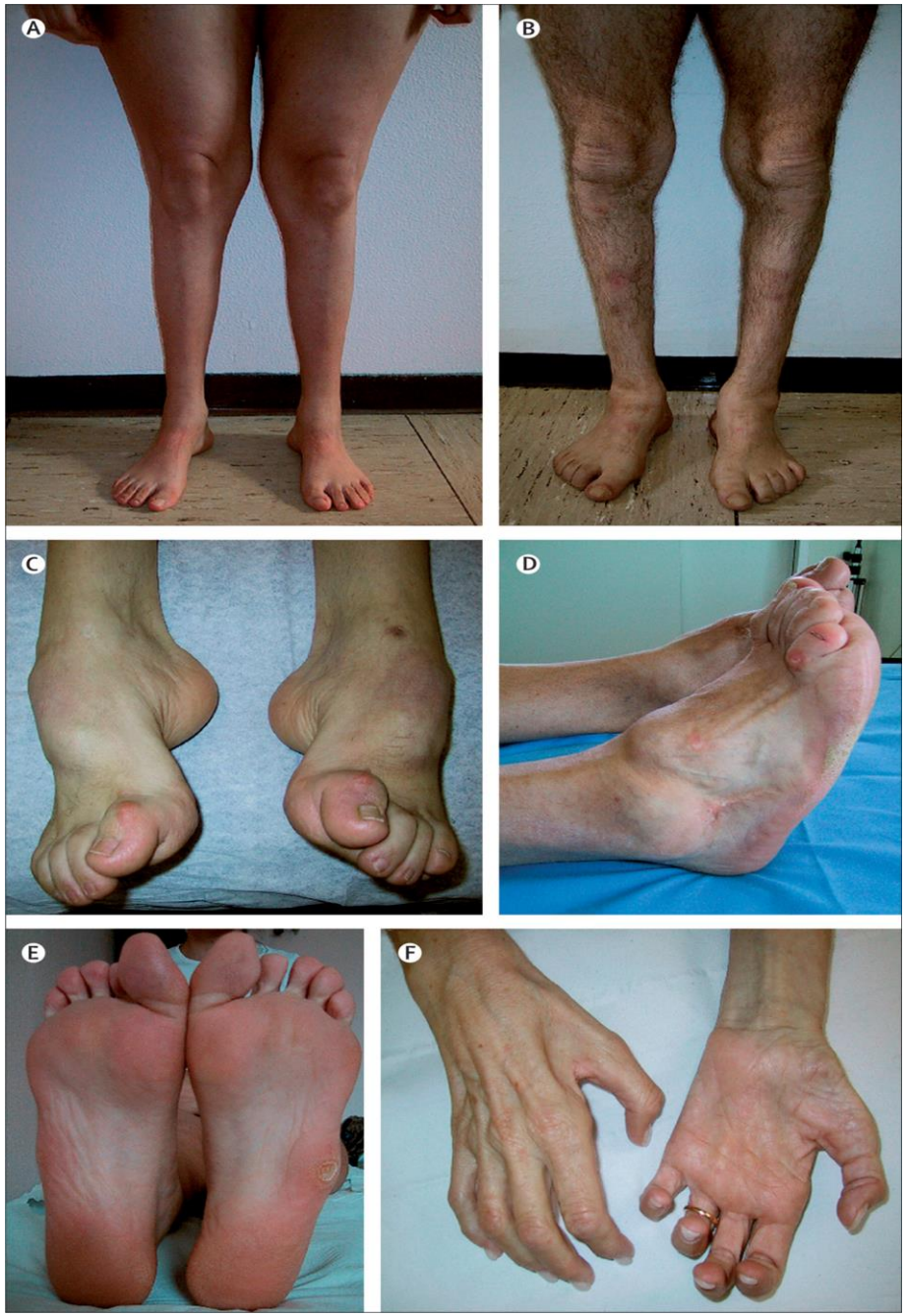
21
22
X/Y


Duplication mutation
Chromosome
A section of DNA
is duplicated.
U.S. National Library of Medicine



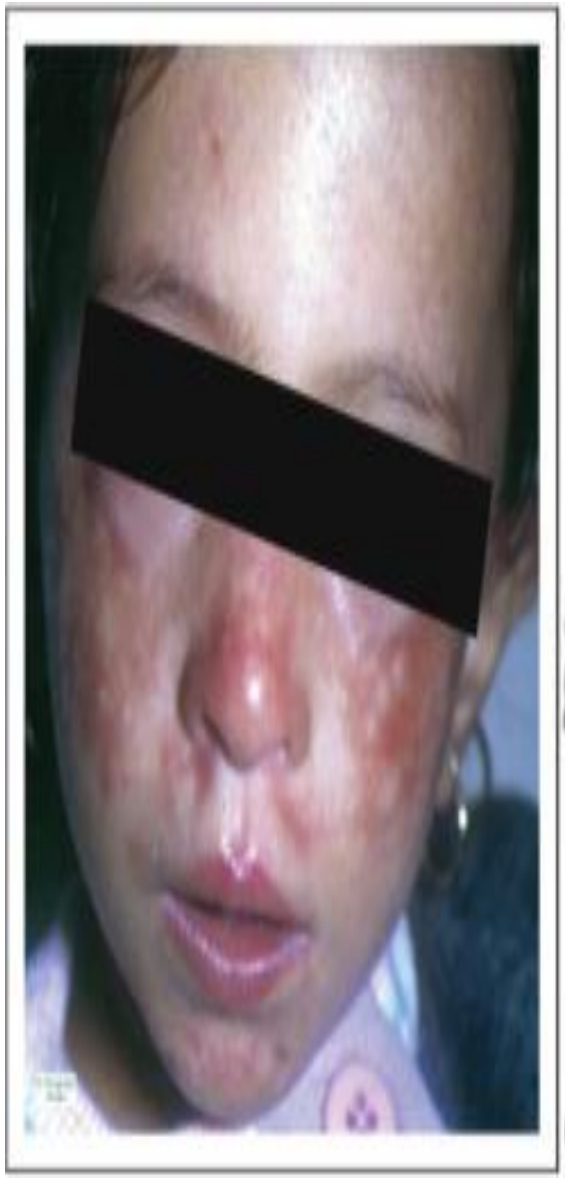

Doença de
**Charcot-Marie-Tooth**

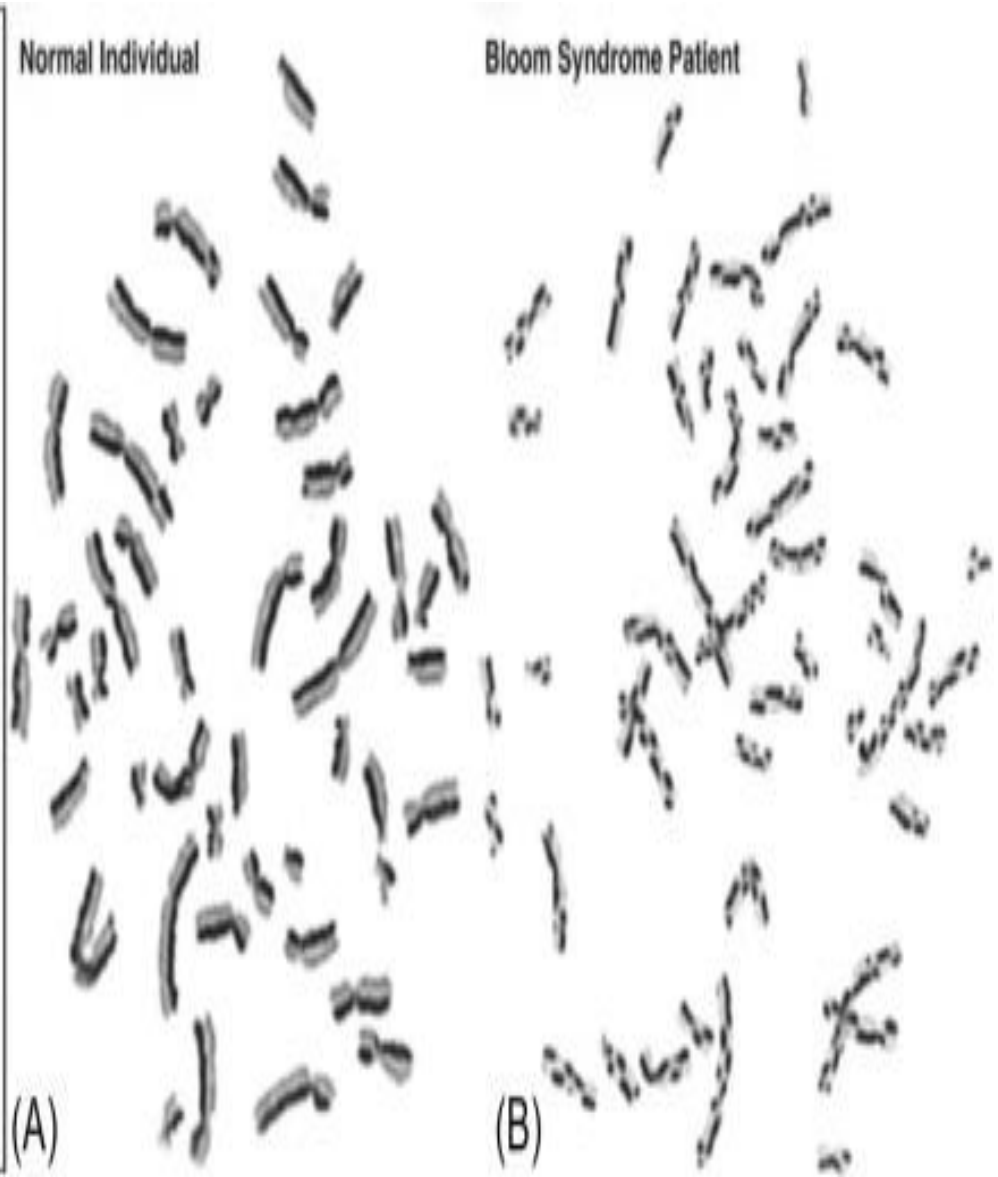


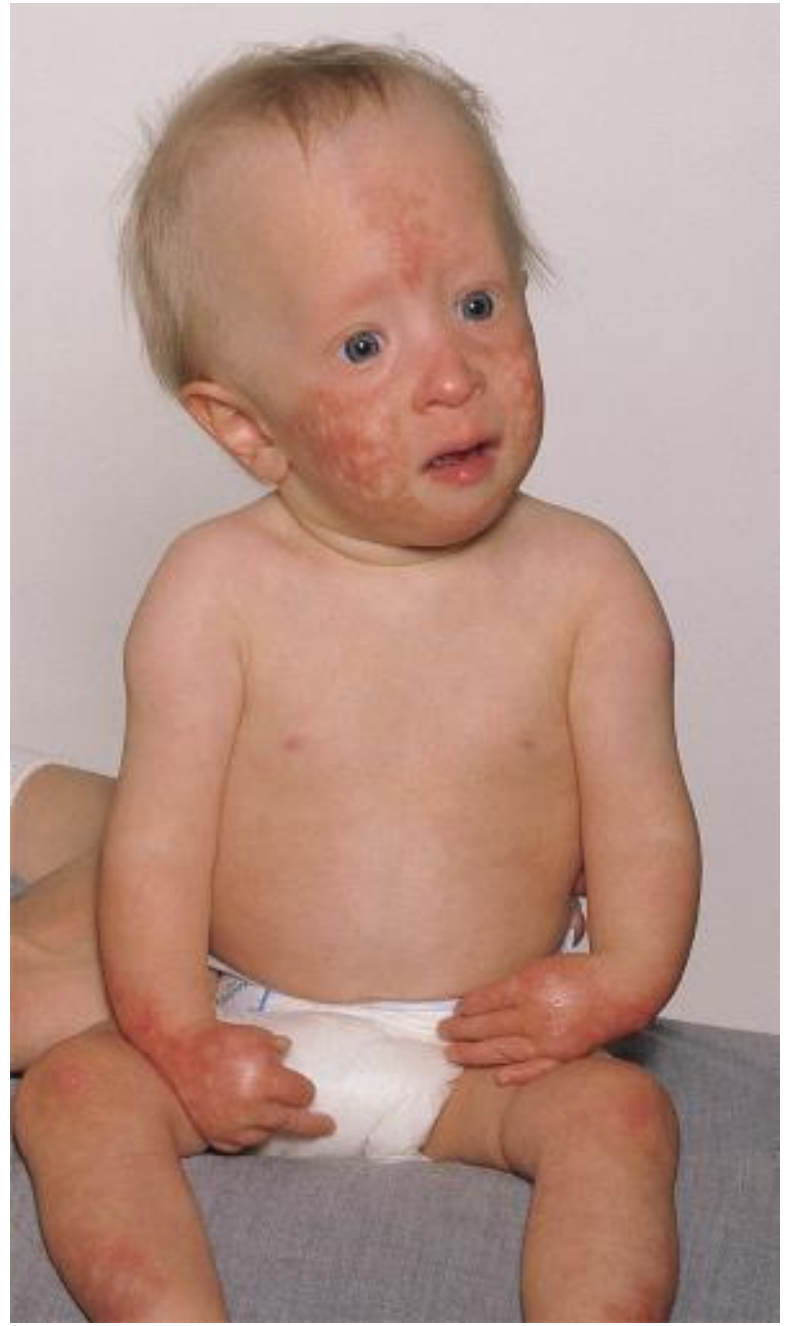


Drived chromosome

- Bloom syndrome
- Fanconi Anemia
- Ataxia-Telangiectasia
- Xeroderma Pigmentosum




Normal Individual
Bloom Syndrome Patient
(A)
(B)



All about

# FANCONI ANEMIA

## What is FA?

Fanconi anemia (FA) is a genetic DNA repair disorder that may lead to bone marrow failure, leukemia, and/or solid tumors (cancer). It is caused by one of at least 23 genes. FA can affect all systems of the body. It is a complex and chronic disease that is psychologically demanding.

**1 in 131,000**

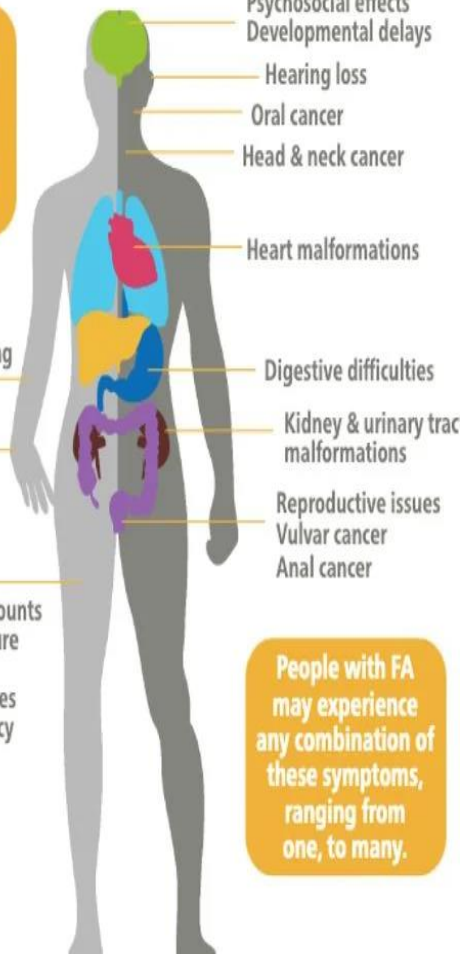
FA occurs almost equally in males and females and is found in all ethnic groups. The likelihood of a child being born with FA is about 1 in 131,000 in the U.S., with approximately 31 babies born each year.


If both parents carry a mutation in the same FA gene, they have a 25% chance of having a child with FA.

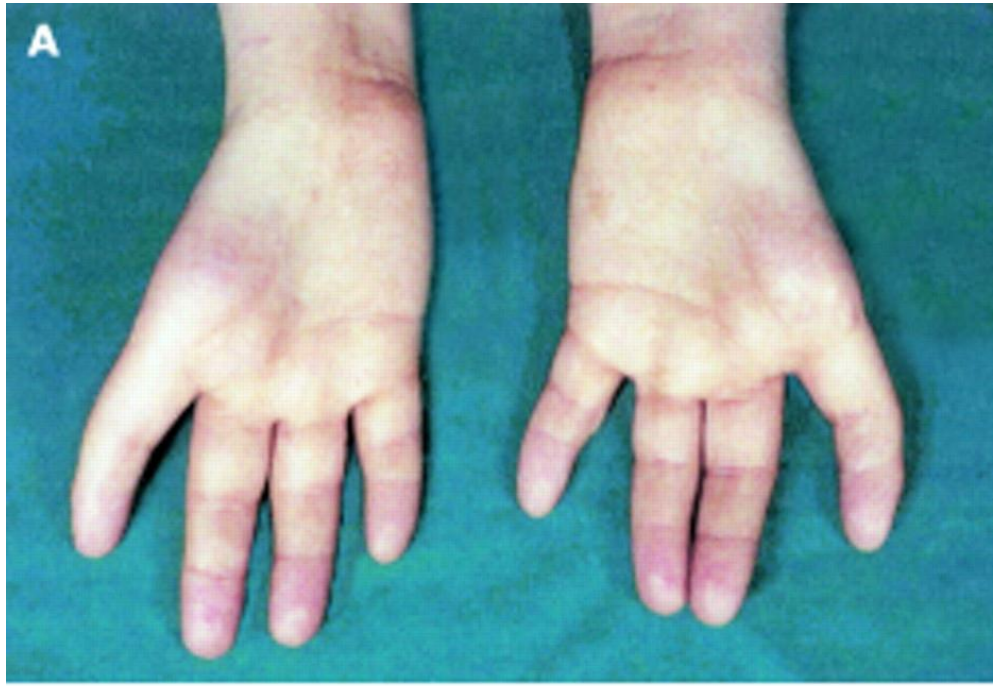
## People are living longer

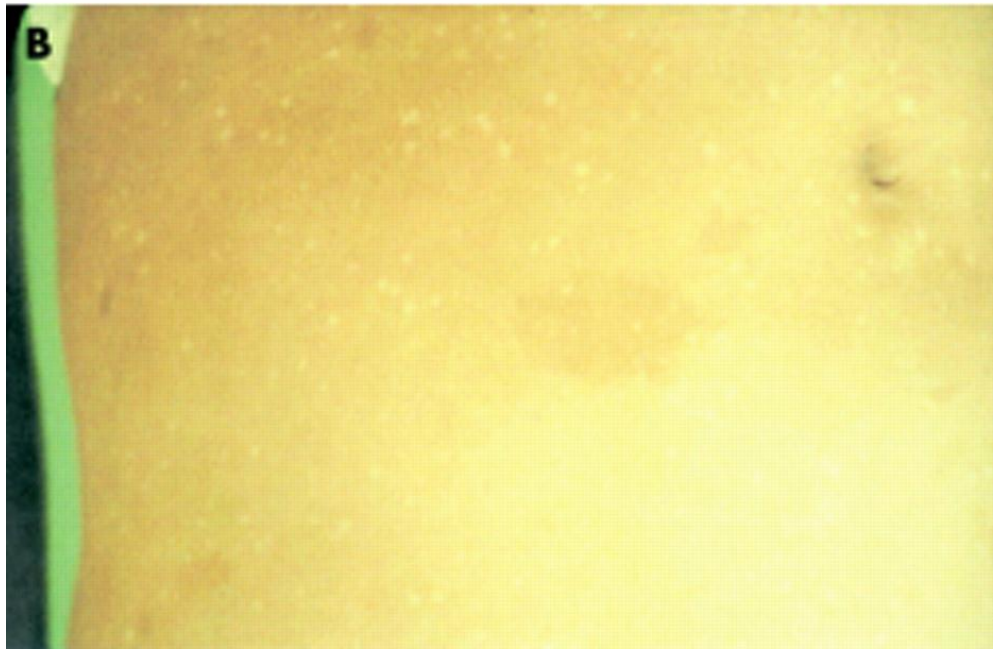
**More than half of the FA population registered with FARF is age 18 or over!**

## How does FA affect the body?



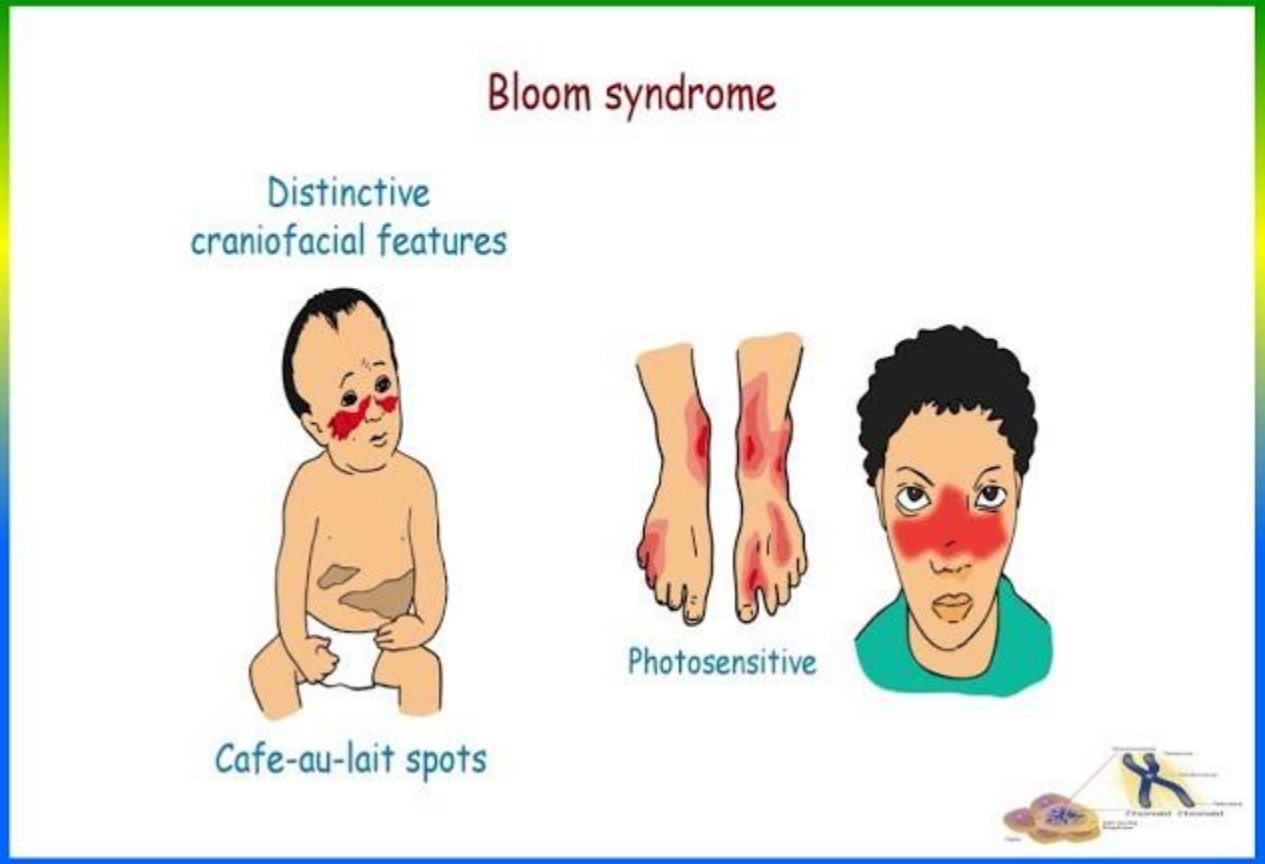

**People with FA may experience any combination of these symptoms, ranging from one, to many.**



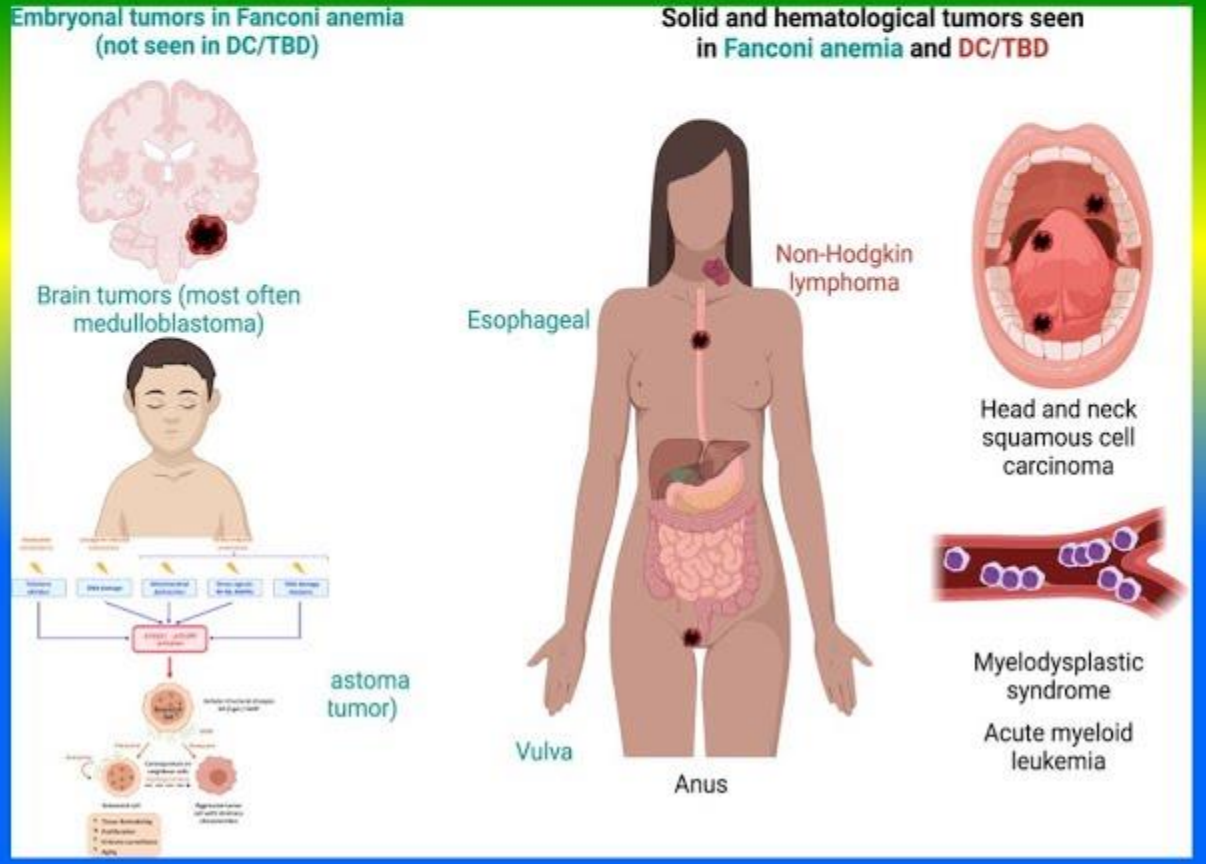



# Difference Between

## Bloom Syndrome




## Fanconi Anemia



# Ataxia-Telangiectasia

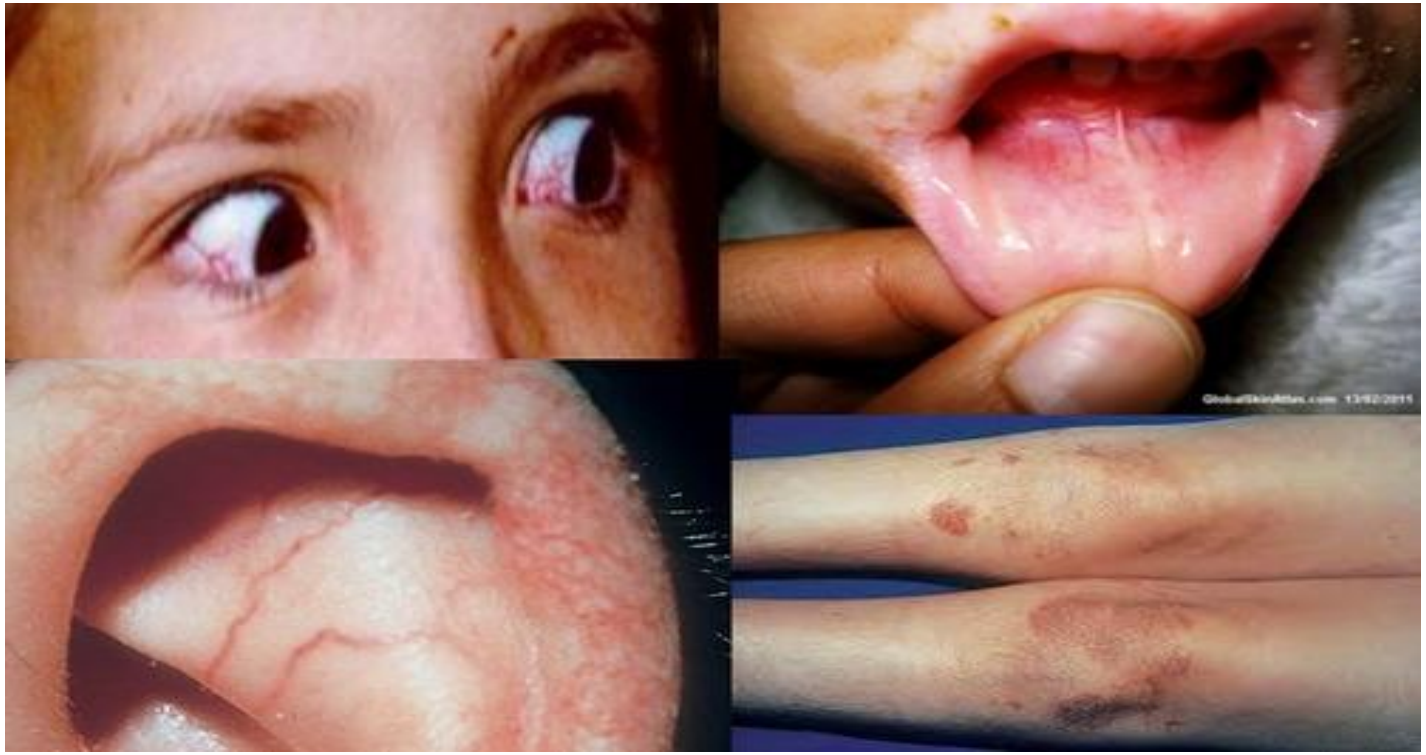
## Symptoms include:

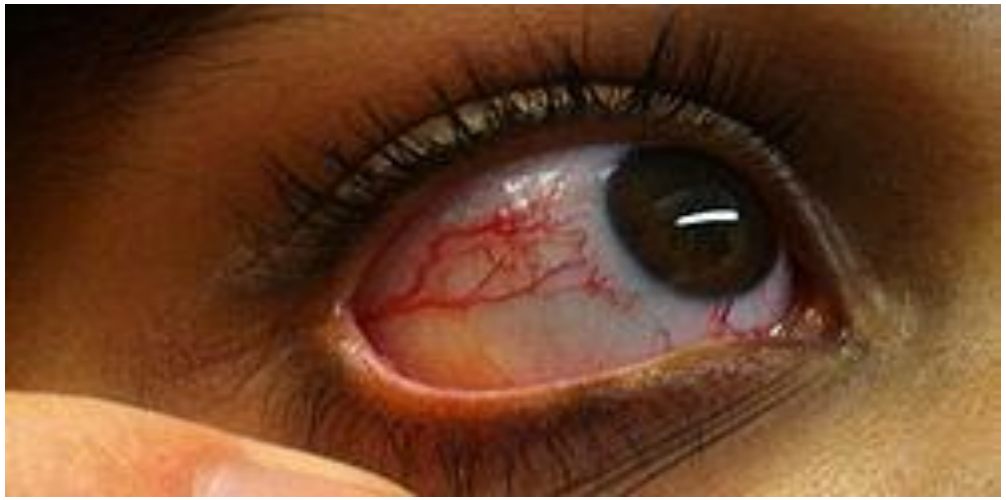
Trouble walking

Muscle twitching

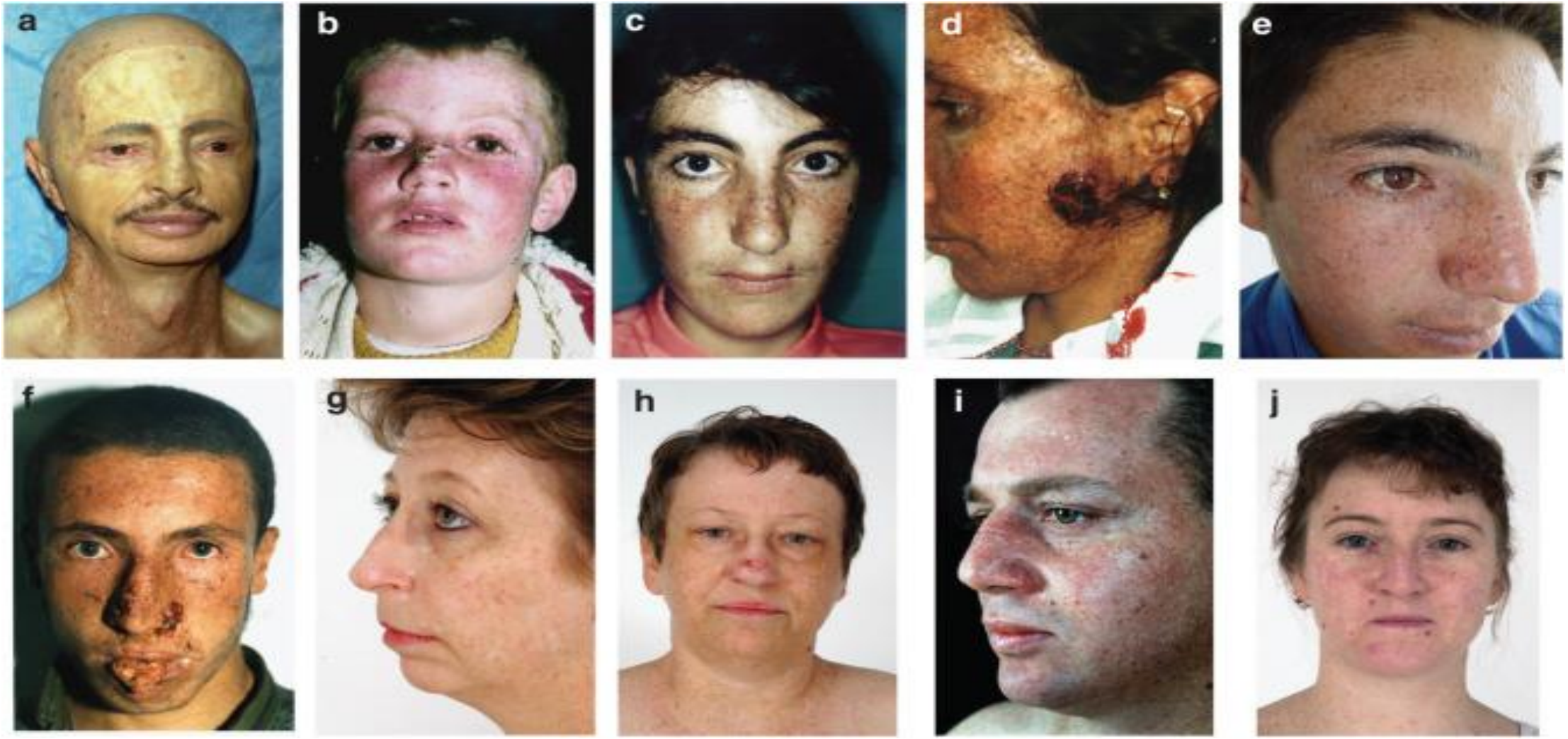
Slurred speech

Frequent infections

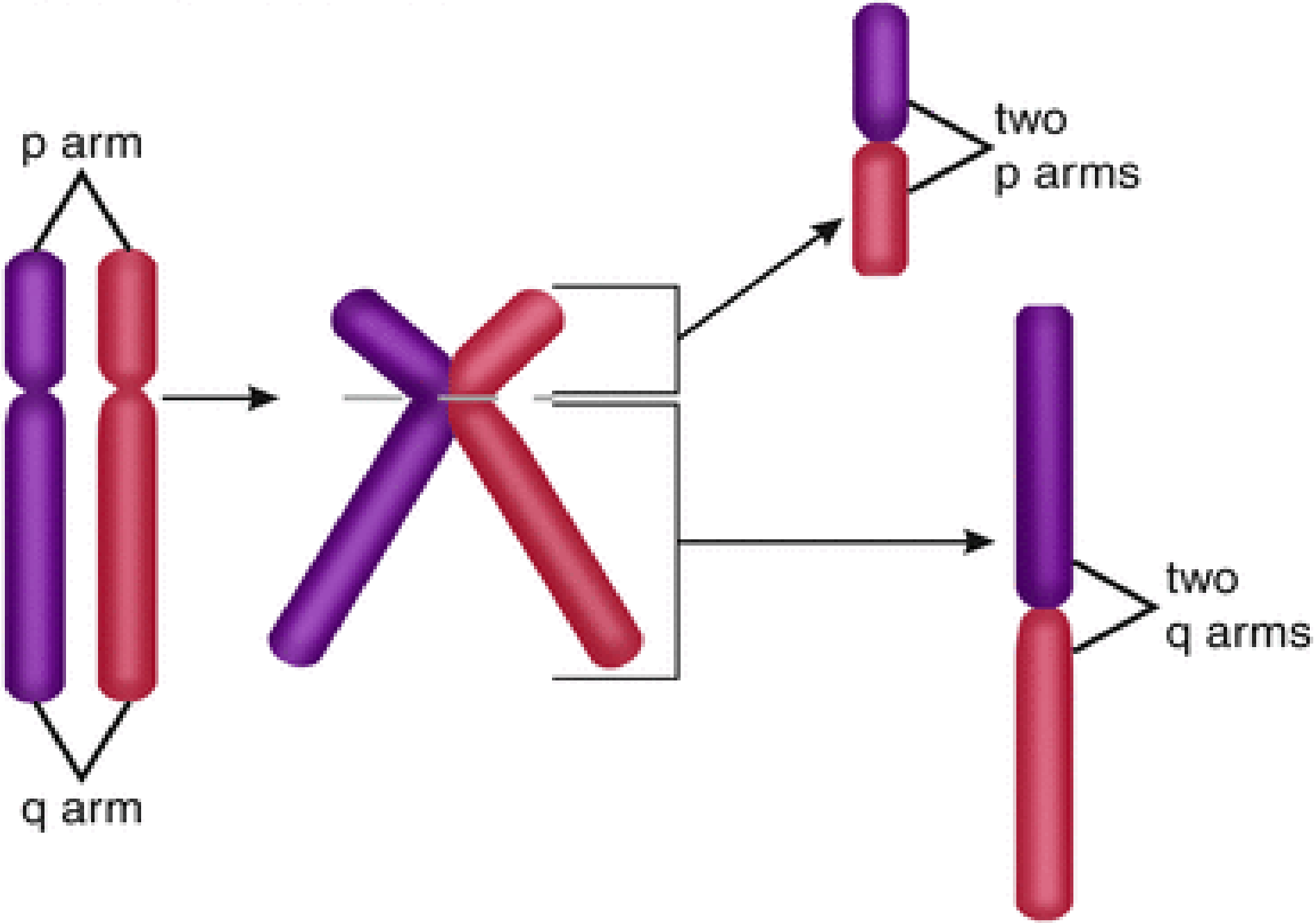


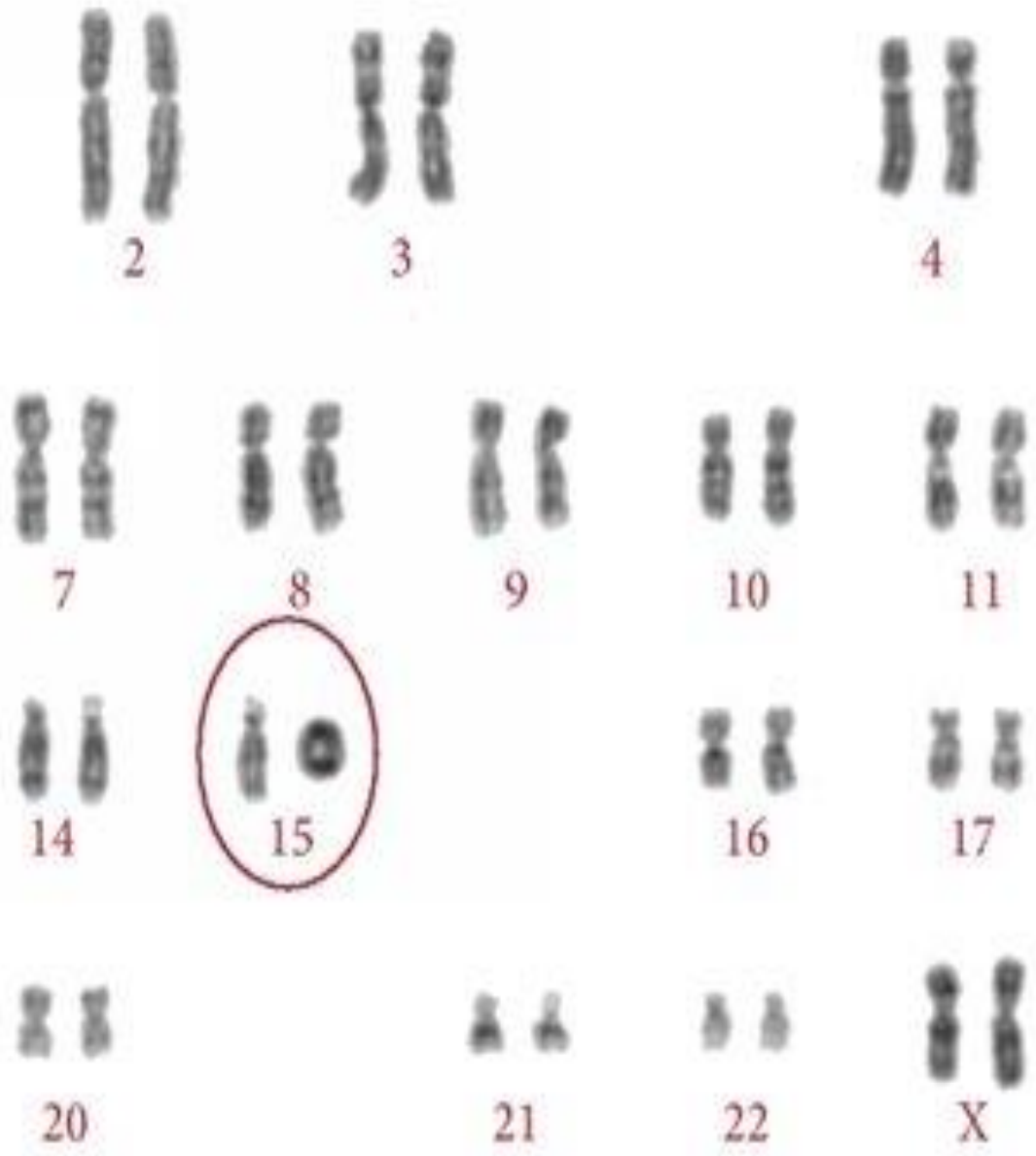


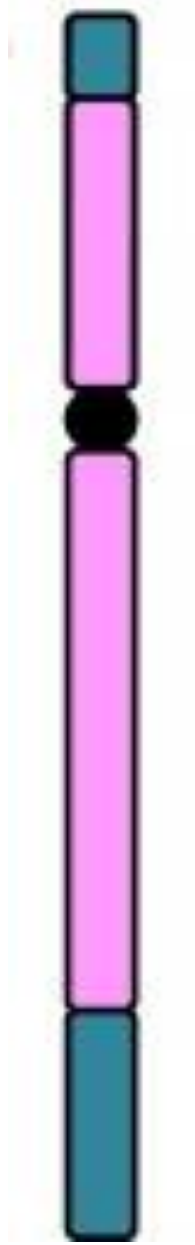
# Xeroderma Pigmentosum



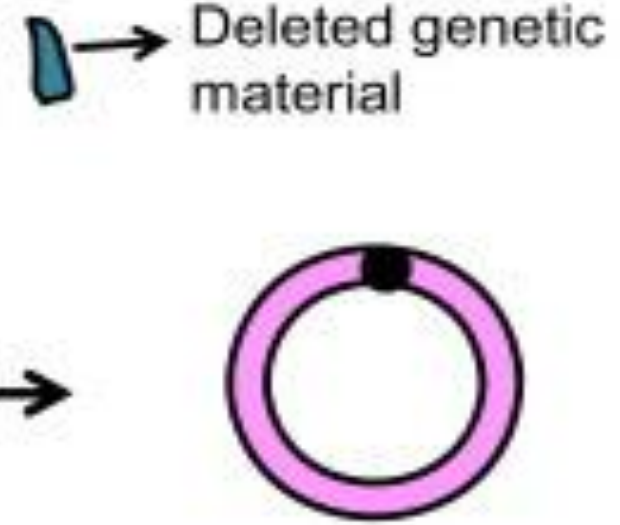
# Isochromosomes

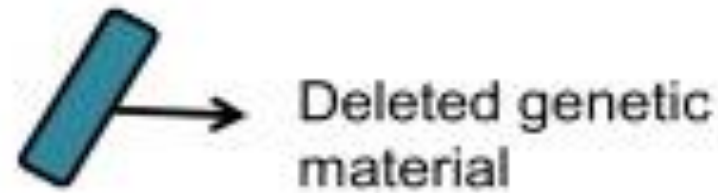




## Ring chromosome



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