Unusual Modes of Inheritance

Wayne Lam

wayne.lam@ed.ac.uk

New Genetics

- Non-Mendelian
  - Genomic Imprinting
  - Digenic Inheritance
  - Triallelic inheritance
- Mitochondrial Inheritance
- Chromosomal
  - Telomeric deletions
  - Contigous gene syndrome
- Trinucleotide repeat expansions
- Somatic and Gonadal/Germ line mosaicism

Disorders of disrupted Genomic imprinting

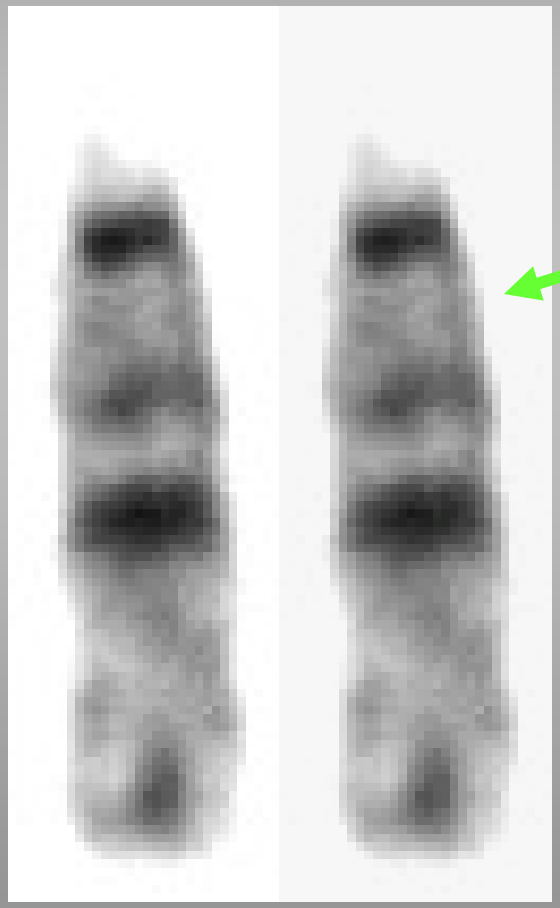
- Severe global developmental delay
- No speech
- Inappropriate laughter
- Drooling
- Seizures
- Cannot walk without help
- No family history

Angelman syndrome

Prader Willi Syndrome

- Floppy at birth, poor feeding
- Short stature, small hands and feet
- Hyperphagia and obesity
- Hyponadism
- Mental retardation (mild to moderate)

Chromosome 15



15q11-13

- Further analysis of these two patients show that the deletion occurred on different chromosomes
- The chromosome that was deleted in Angelman case was derived *from Mother*
- In the Prader-Willi case the chromosome was derived *from Father*

Loss of heterozygosity

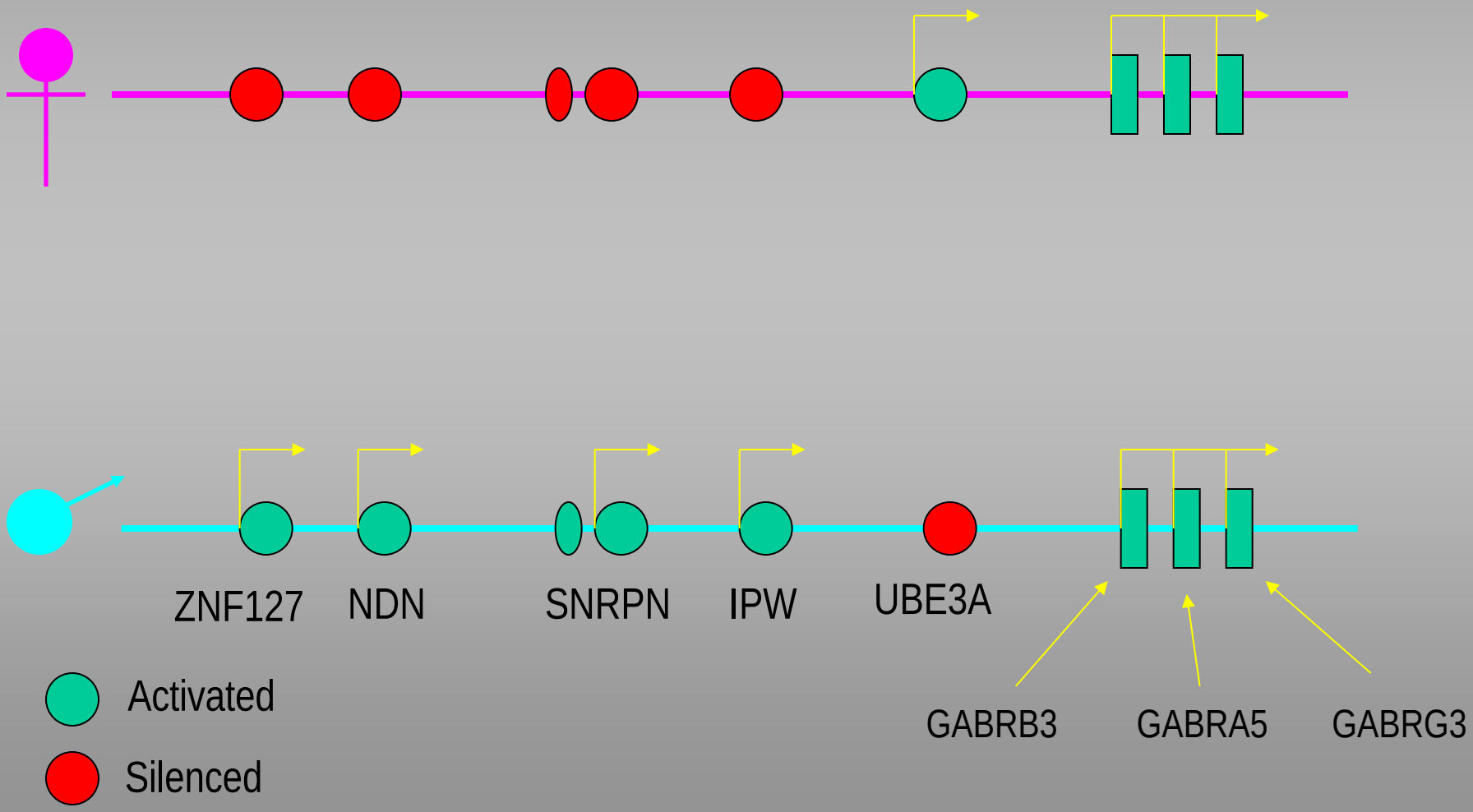
Genomic Imprinting

- Defined as differences in gene expression depending on whether a gene is maternally or paternally inherited
- Specific chromosomal regions contain imprinted genes
- Such regions usually contain both maternally and paternally imprinted genes

Genomic Imprinting

- Leads to functional hemizygosity
- Accounts for only a small number of genes
- Importance?
  - many developmental genes are imprinted
  - disruption of imprinting is implicated in several well known genetic disorders and many cancers

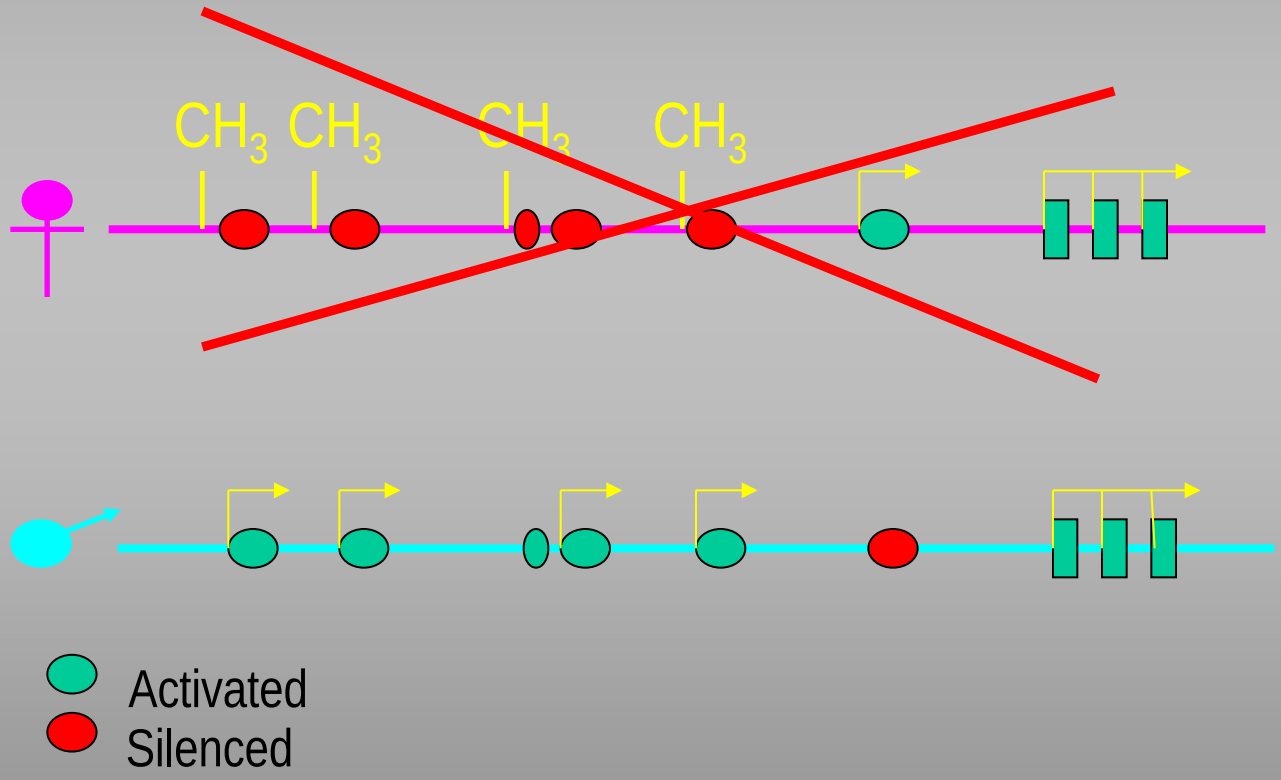
Prader-Willi /Angelman region
Normal expression pattern



Mechanism of loss of imprinting: 1
Chromosome deletion of maternal chromosome

Angelmans syndrome

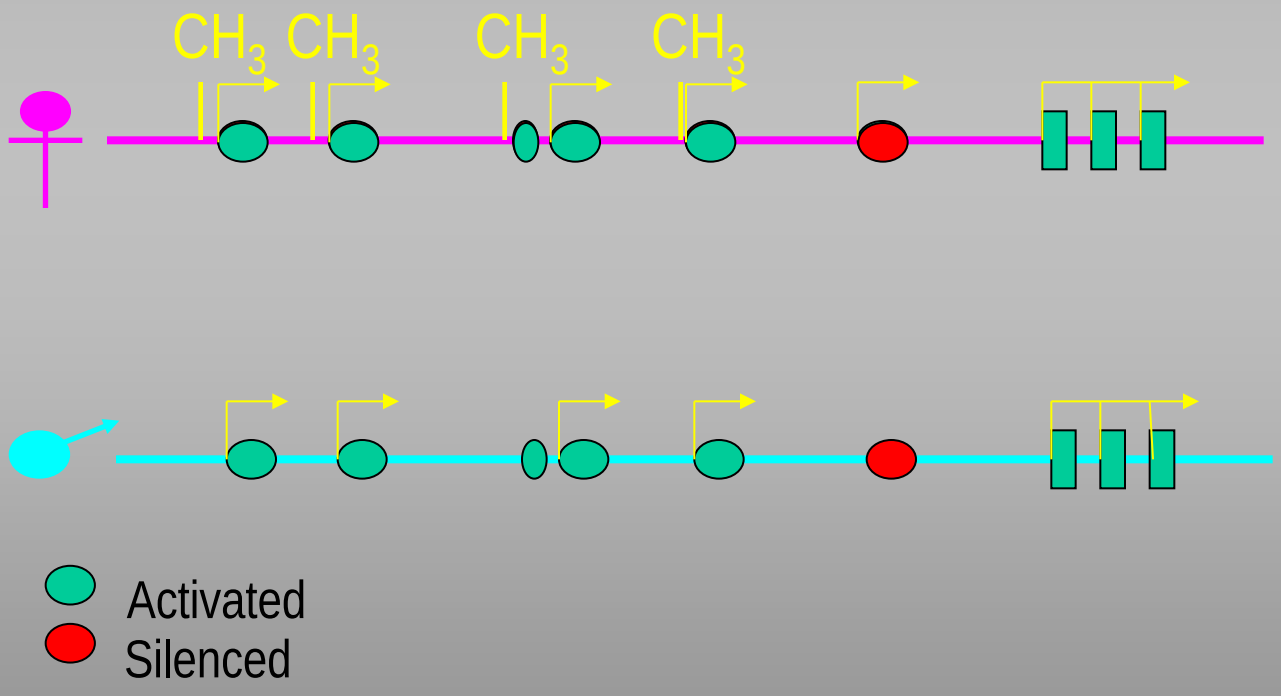
70% of cases



Mechanism of loss of imprinting: 2
Methylation abnormality

Angelmans syndrome

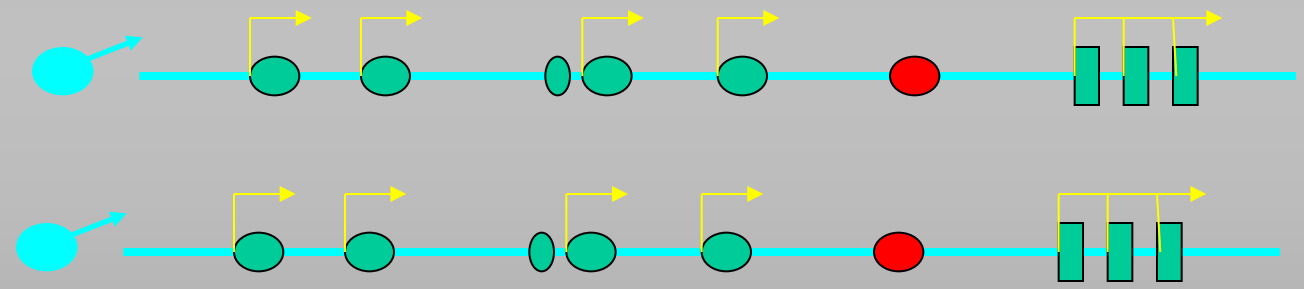
2% of cases



Mechanism of loss of imprinting: 3 Uniparental Disomy

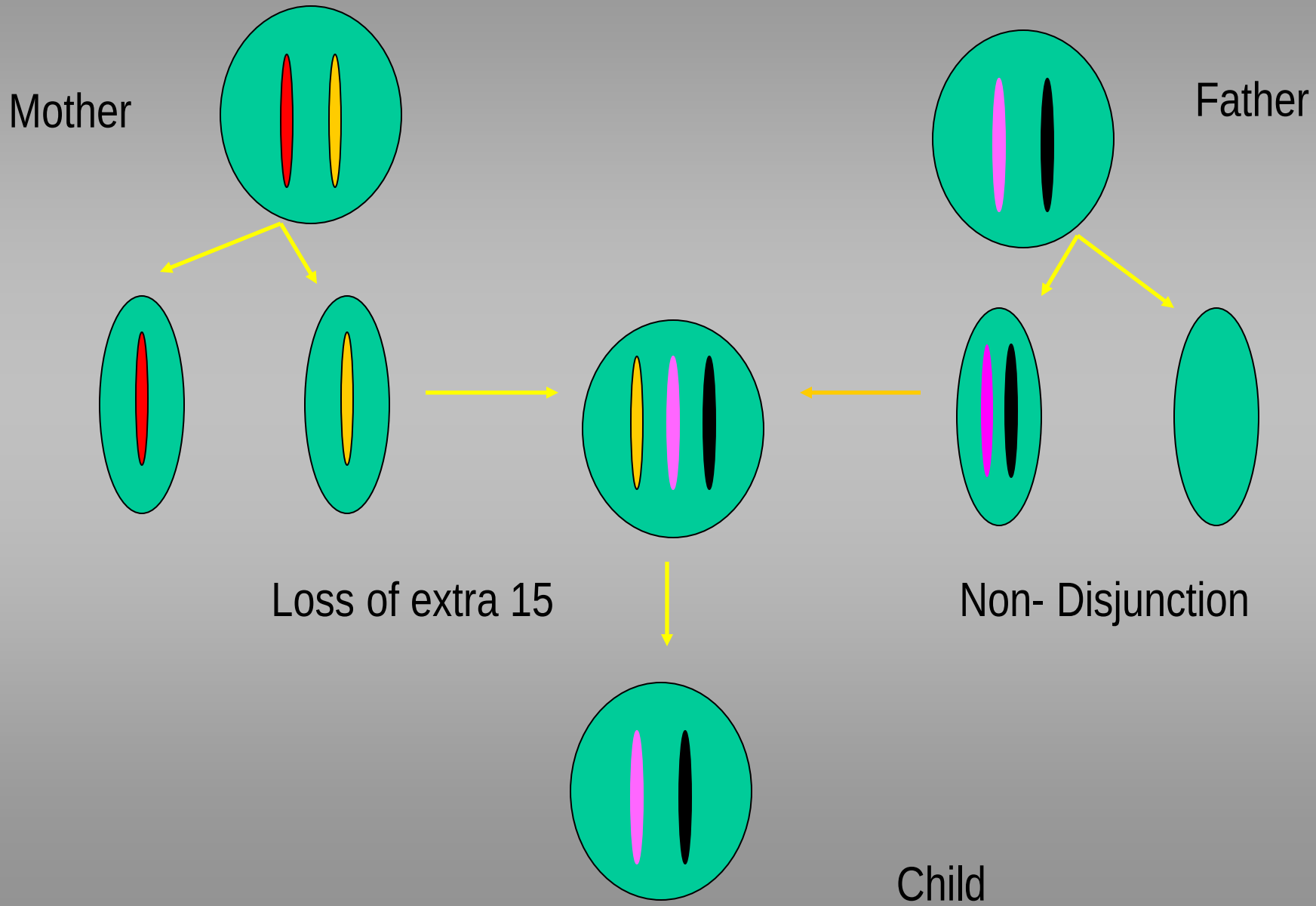
Angelmans syndrome

2% of cases



Activated
Silenced

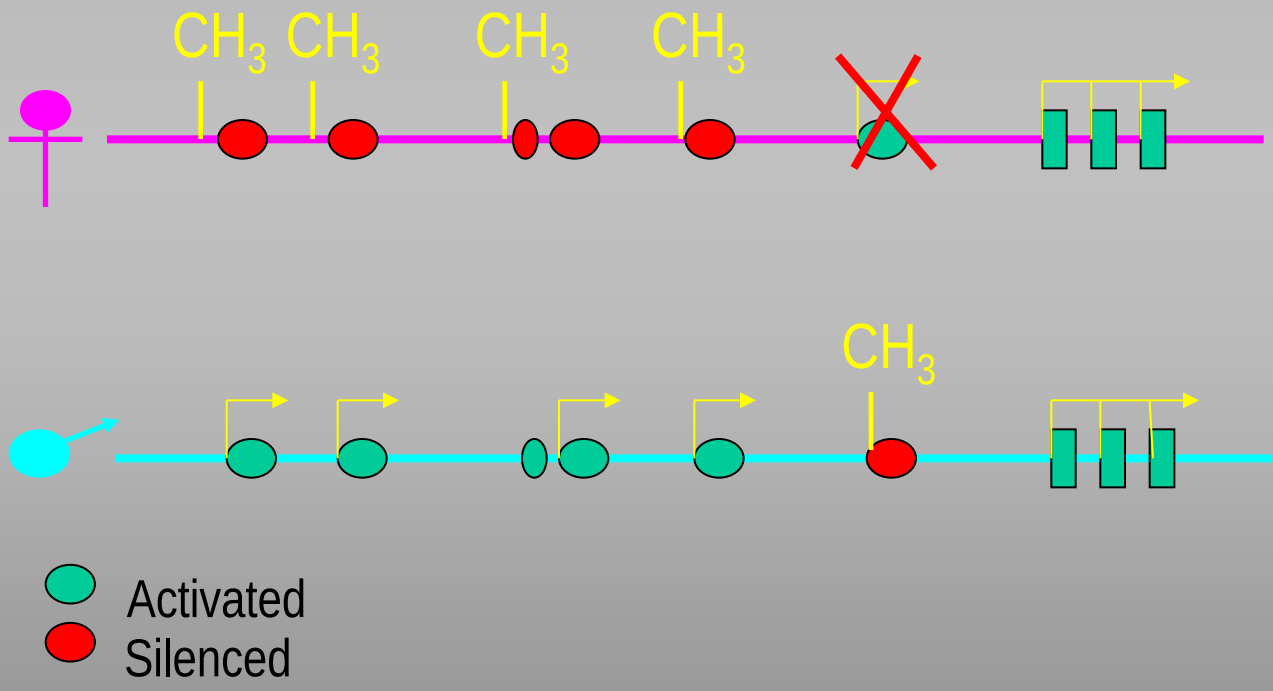
Paternal Uniparental Disomy



Mechanism of loss of imprinting: 4
Mutation in UBE3A gene

Angelmans syndrome

2% of cases

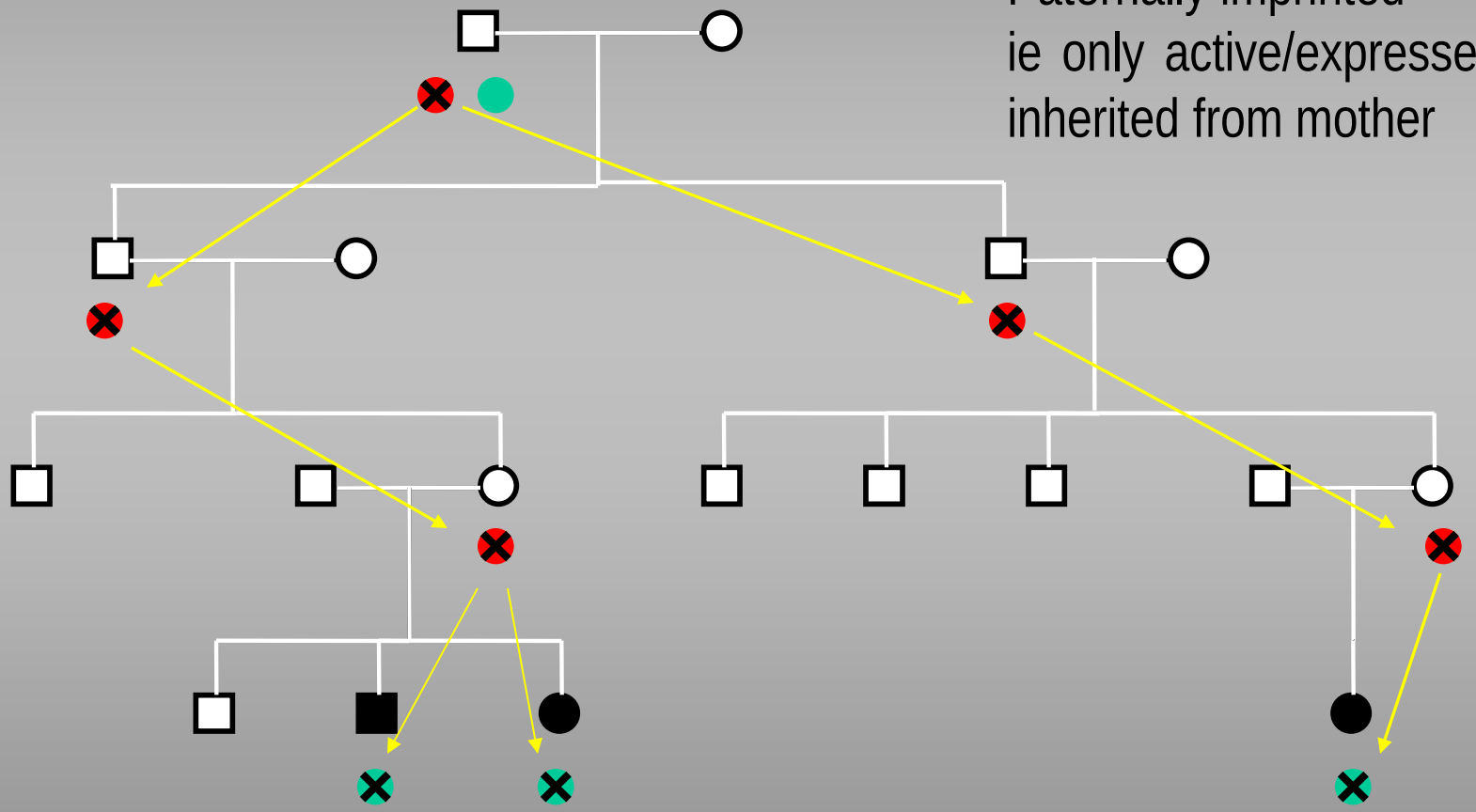


Disruption of Genomic Imprinting

- Parent specific chromosome deletion
- Methylation abnormalities
- Uniparental disomy
- Gene mutations

Family Pedigree of an Imprinting Disorder

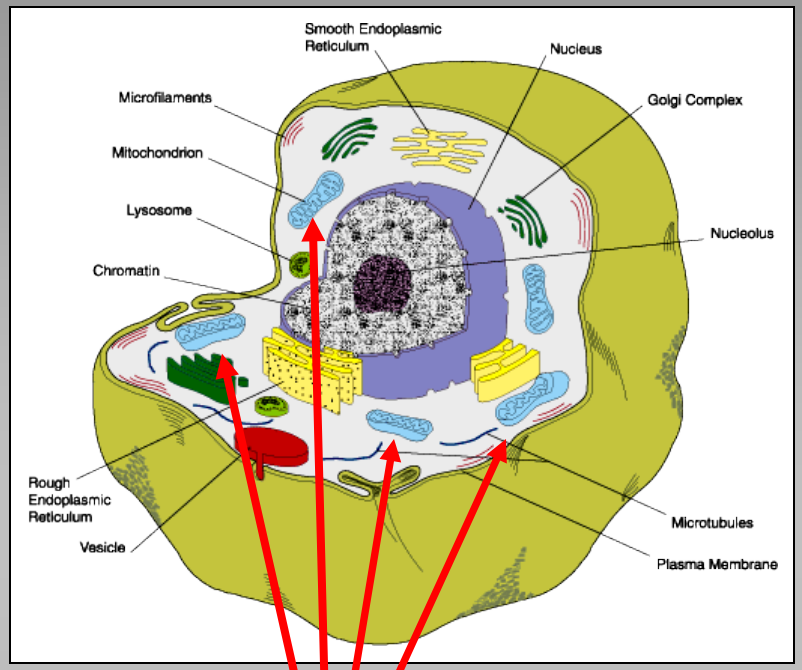
Paternally imprinted
ie only active/expressed if inherited from mother



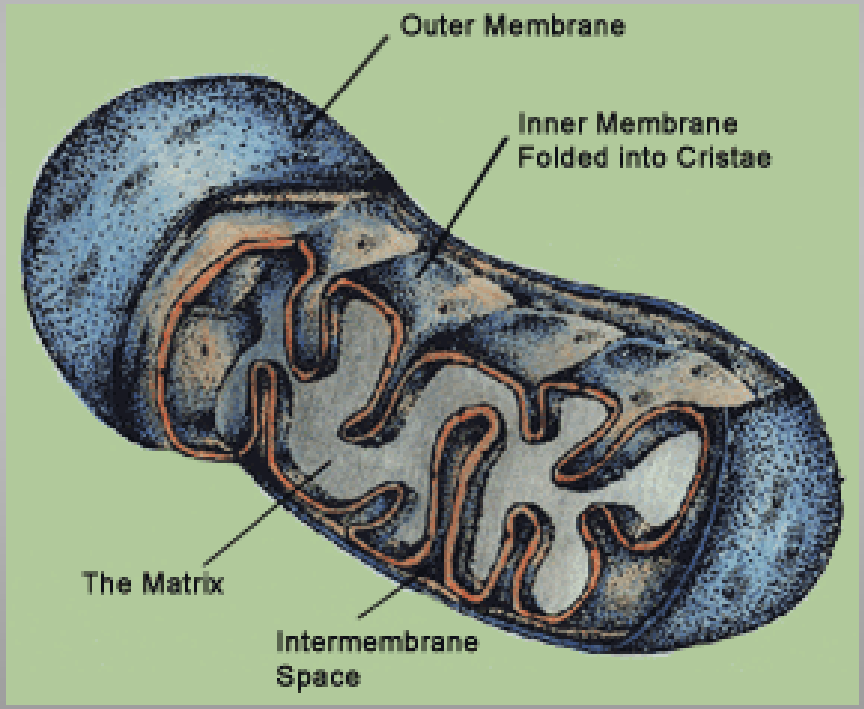
Imprinting and Cancer

- Wilm's tumour – maternal chrom 11p15
- Neuroblastoma – maternal chrom 1p36
  paternal chrom 2
- Acute Myeloblastic Leukaemia – paternal chrom 7
- Rhabdomyosarcoma – maternal chrom 11p15.5
- Osteo-sarcoma – maternal chrom 13

Mitochondrial Inheritance



Mitochondria

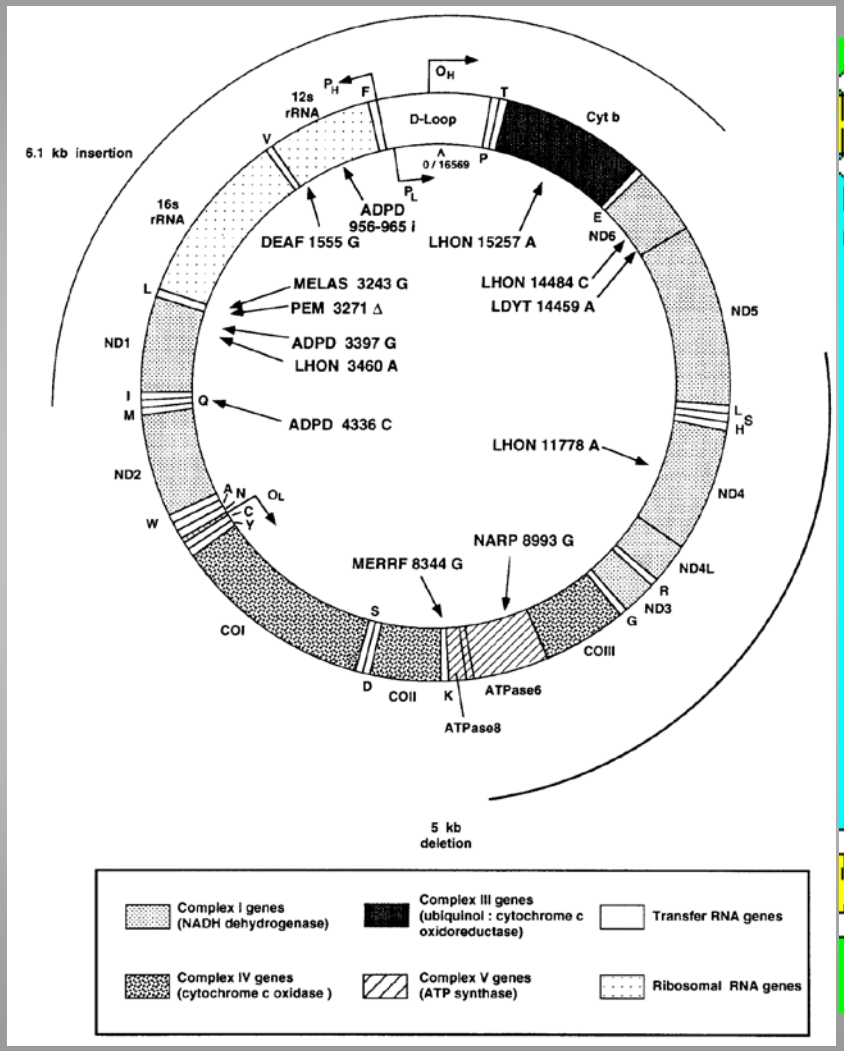


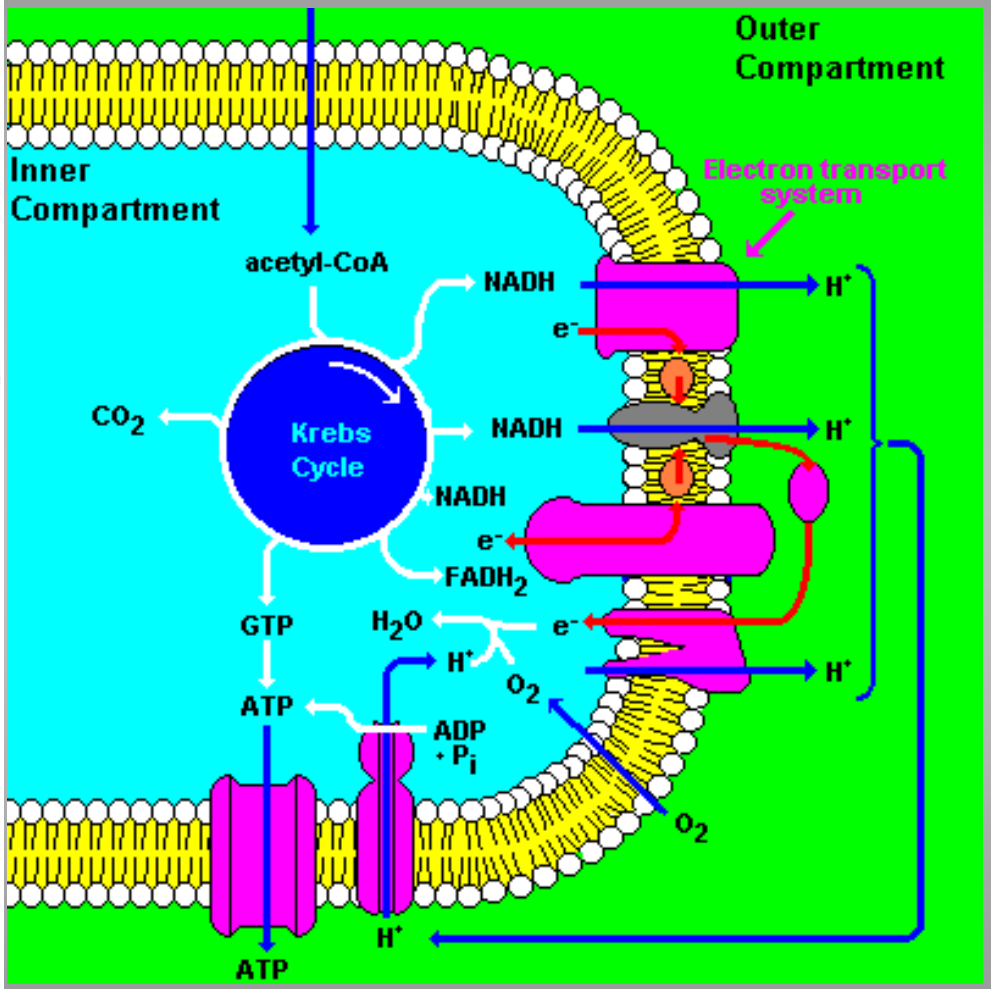
Mitochondrial DNA

- 16,559 base pairs
- Many copies in a cell, dependent on energy requirement of cell/tissue
- Contains important genes for mitochondrial metabolic pathways and ribosomal RNAs
- Inherited almost exclusively maternally
- High rate of mutations
  - Point mutations and deletions occur

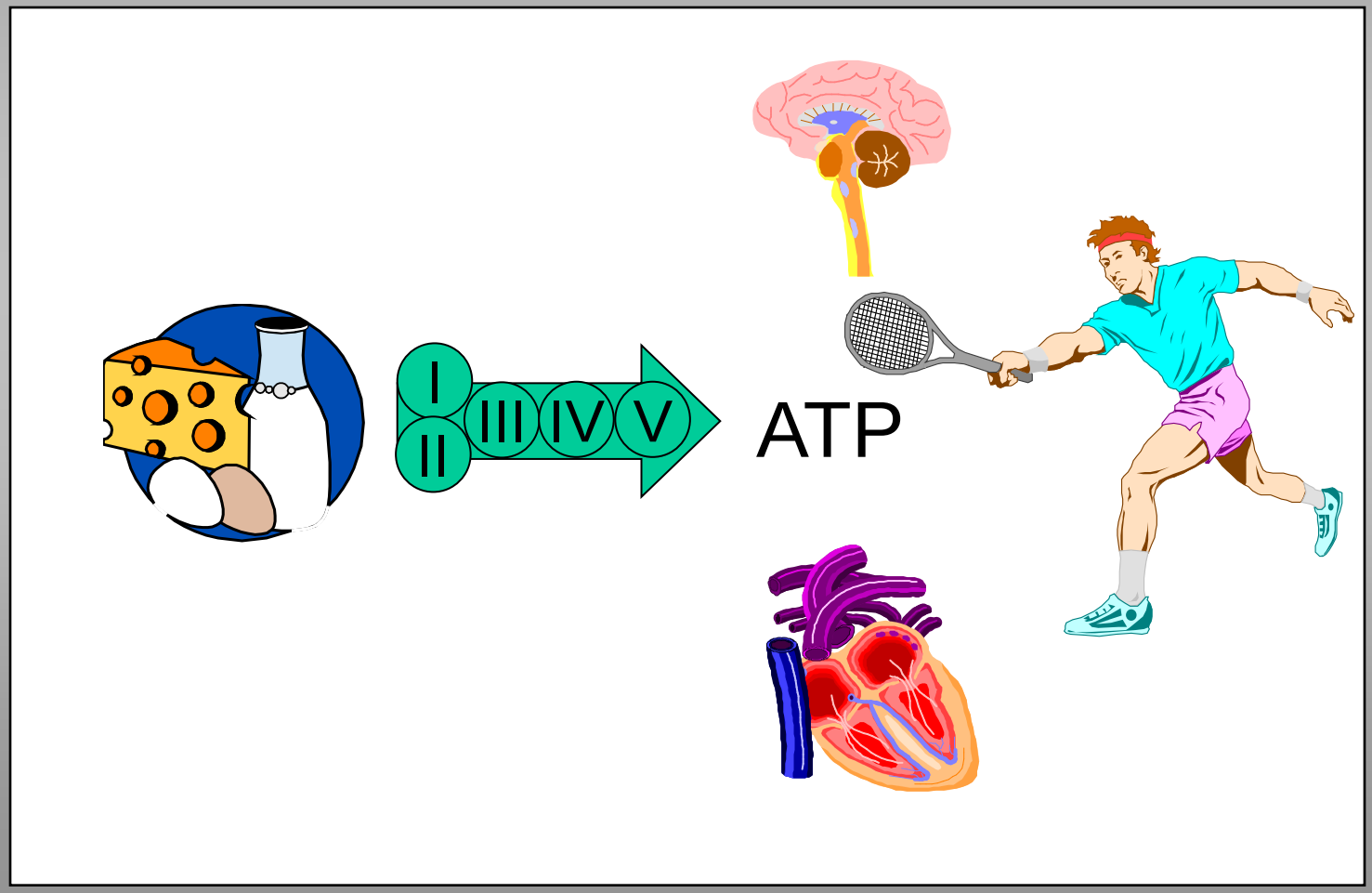
Mitochondrial DNA

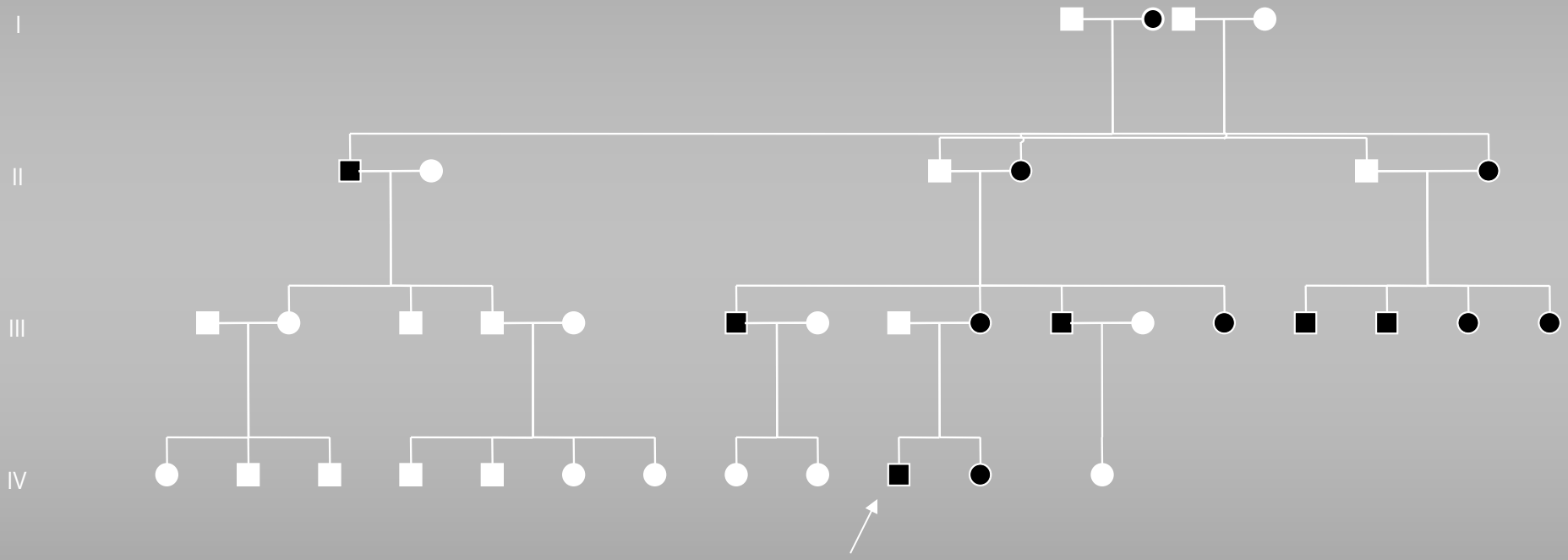
- Double stranded
- Ring structure
- No Introns
- Genes are tightly packed together
- Few or no non-coding nucleotides between genes
- Approx 92% of the mitochondrial genome has coding function.


6.1 kb insertion
12s rRNA
16s rRNA
D-Loop
Cyt b
ADPD 956-965 i
DEAF 1555 G
LHON 15257 A
MELAS 3243 G
PEM 3271 Δ
ADPD 3397 G
LHON 3460 A
LHON 14484 C
LDYT 14459 A
ADPD 4336 C
LHON 11778 A
NARP 8993 G
MERRF 8344 G
ND1
ND2
COI
COII
ATPase8
ATPase6
COIII
ND3
ND4L
ND4
ND5
ND6
5 kb deletion
Complex I genes (NADH dehydrogenase)
Complex III genes (ubiquinol : cytochrome c oxidoreductase)
Transfer RNA genes
Complex IV genes (cytochrome c oxidase)
Complex V genes (ATP synthase)
Ribosomal RNA genes


Outer Compartment
Inner Compartment
Electron transport system
acetyl-CoA
Krebs Cycle
NADH
NADH
NADH
FADH2
CO2
GTP
ATP
H2O
O2
ADP + Pi
H+
e-
ATP

“Mitochondrial Diseases”
= Respiratory Chain Disorders




I
II
III
IV
Affected
Unaffected

Jack H.

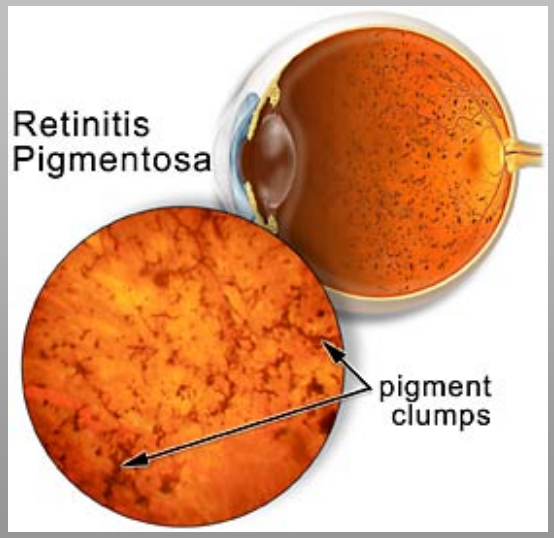
- 21 year old art student
- Presented with diplopia
- Progressive muscle weakness
- Deteriorating vision
- Exertional dyspnoea
  - Echocardiogram: Dilated Cardiomyopathy

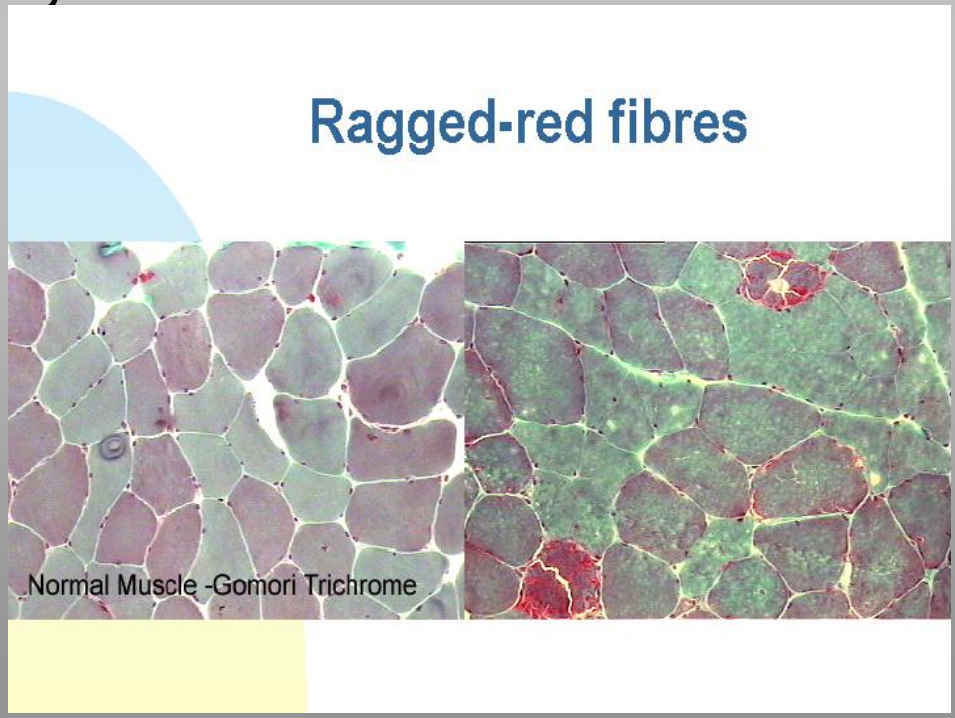
Jack H.

- Serum lactate
  - Raised
- Mitochondrial DNA mutation
  - Blood analysis normal
- Muscle biopsy
  - ragged red fibres
  - 4,977 base pair deletion in muscle mitochondrial DNA

Kearns Sayre Syndrome

- Ophthalmoplegia
- Cardiomyopathy
- Myopathy with ragged red fibres
- Pigmentary retinopathy





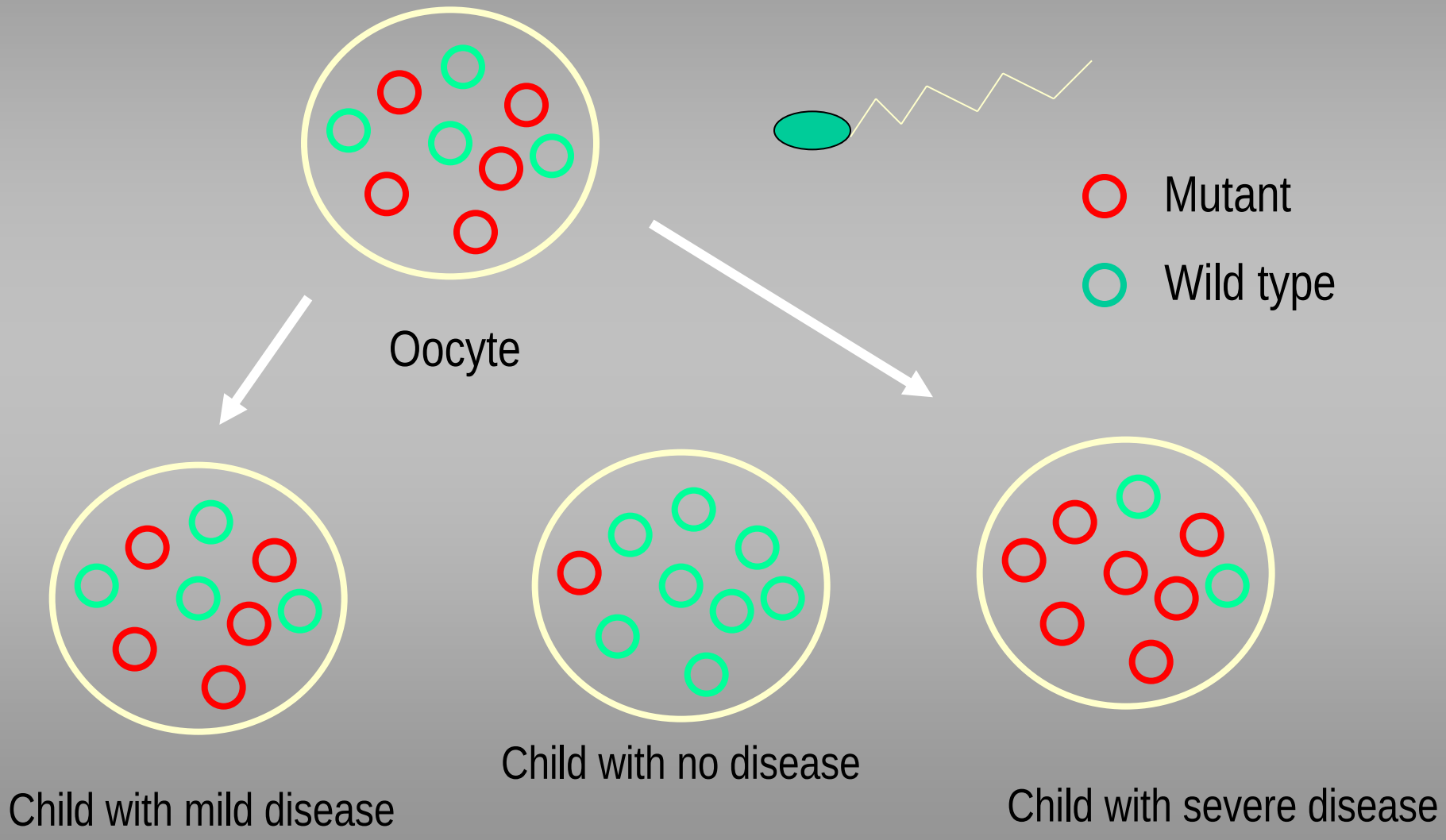
Mitochondrial Mutations

- Multiple phenotypes (clinical heterogeneity)
  - Pearson (Marrow-Pancreas) Syndrome
  - Kearns Sayre Syndrome
  - Myopathy
  - Ataxia
  - Cardiomyopathy
  - Leighs encephalopathy
  - Liebers Hereditary optic neuropathy

Heteroplasmy

- Different daughter cells contain different proportions of mutant mitochondria

Heteroplasmy

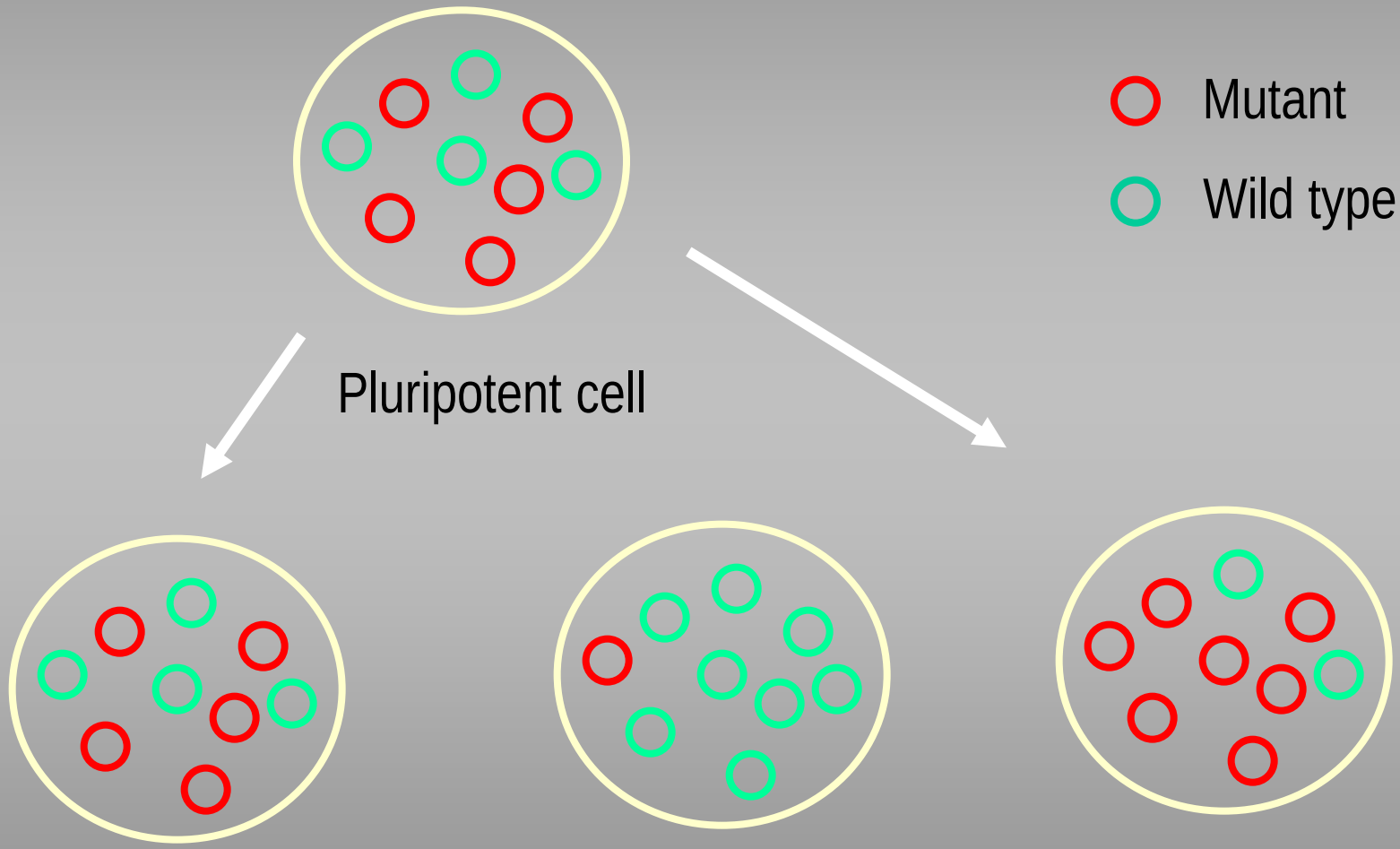


Heteroplasmy

- Different daughter cells contain different proportions of mutant mitochondria
- Severity and nature of phenotype depends on
  - type of tissue involved
  - proportion of mitochondria carrying a mutation
  - type of mutation

Threshold of onset

Heteroplasmy



Manifestation dependent on tissue type

Inheritance patterns in mitochondrial disorder

- Maternal inheritance only if affected gene is from mitochondrial DNA
- Mitochondrial DNA does not code for all mitochondrial protein
- If abnormal mitochondrial protein is coded from genomic DNA then genetic disorders follow mendelian patterns of inheritance

Triplet repeat expansion
Dynamic mutations

Dynamic mutations

- Mutations are evolving
- Not stably inherited
- Mutations are (usually) increasing in size with successive generations
  - But can also contract in size
- Has a threshold effect
- Exhibit a relationship between severity and copy number
  - Explains the clinical phenomenon of Anticipation
    - More severe in succeeding generations

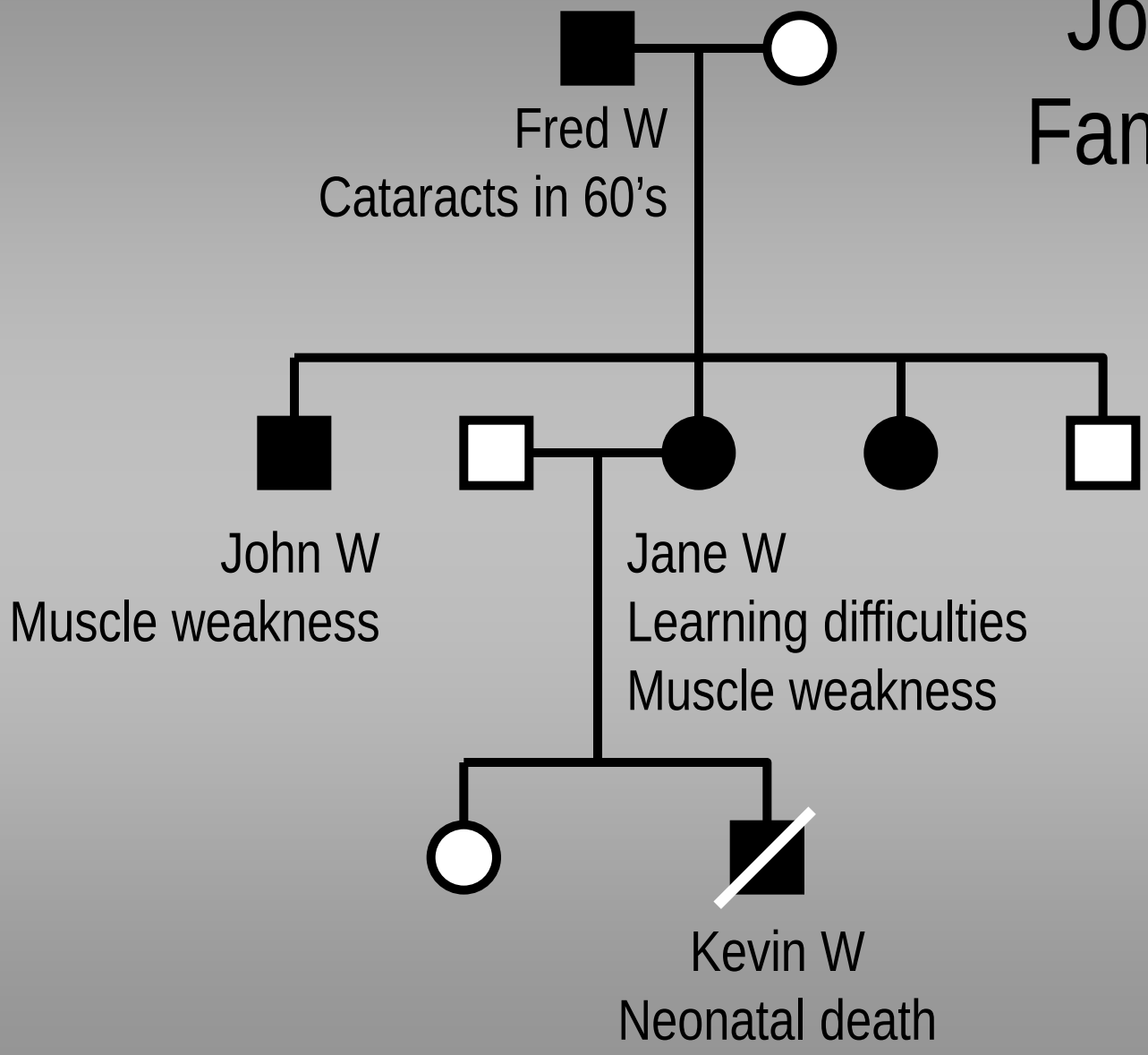
Dynamic mutations

- Most common are triplet repeats
- Expansion of repeats usually has gender bias
  - e.g. HD – expansion when transmitted from paternal line
  - Fragile X – expansion when transmitted from maternal line
- Accounts for over 40 neurological, neuromuscular and neurodegenerative disorder

John W.

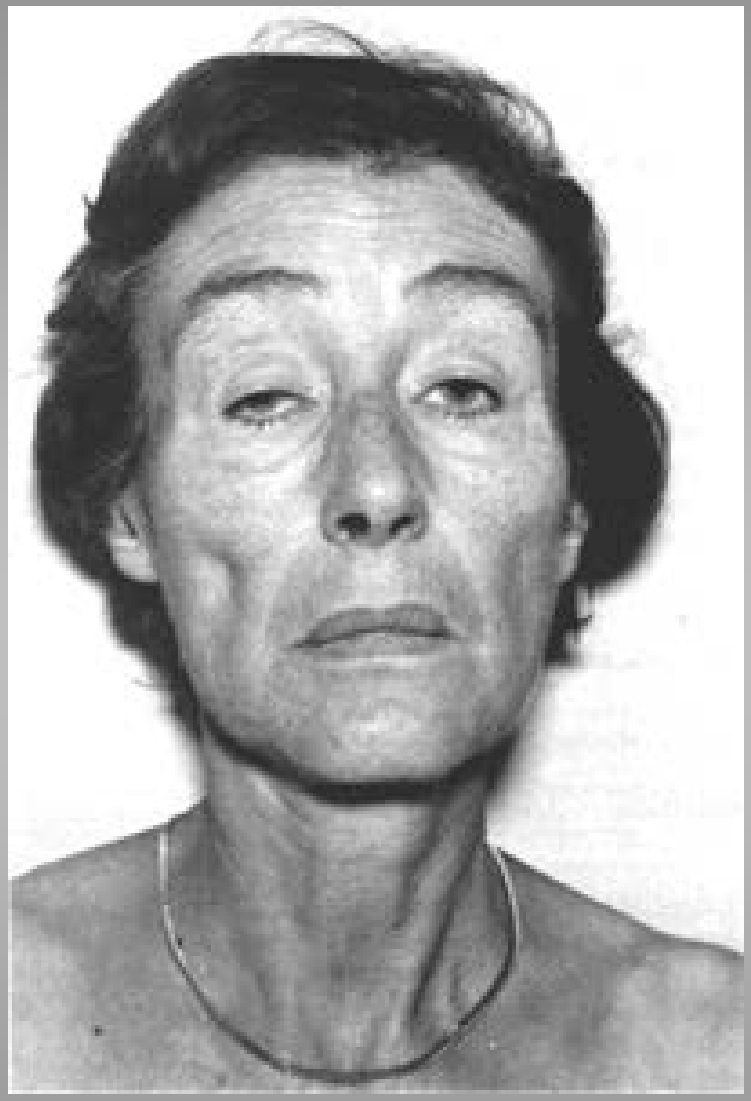
- 32 year old window cleaner
- Adverse reaction to muscle relaxant
- Cataracts
- Difficulty getting up in mornings
- On examination
  - Frontal balding
  - Expressionless face
  - Grip myotonia

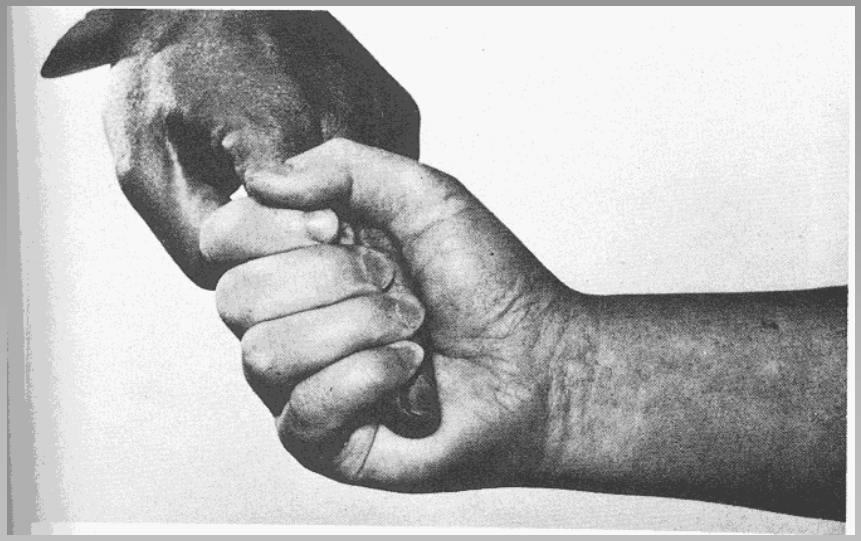
John W Family Hx

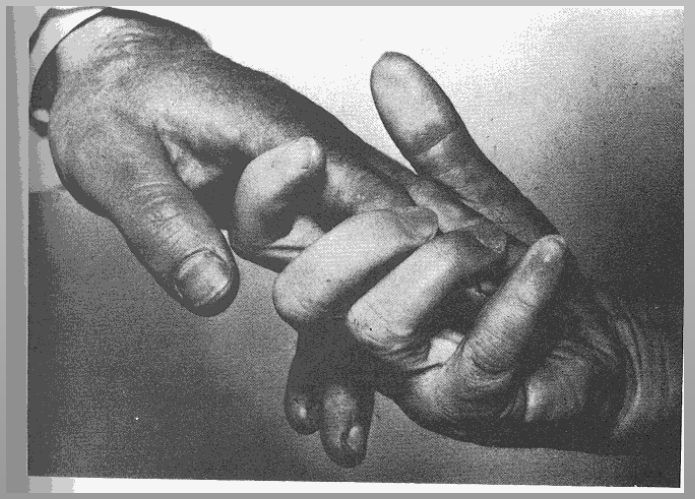


Myotonic Dystrophy

- Frontal balding
- Cataracts
- Muscle weakness
- Myopathic facies
- Myotonia
- Dysphagia
- Intellectual deterioration

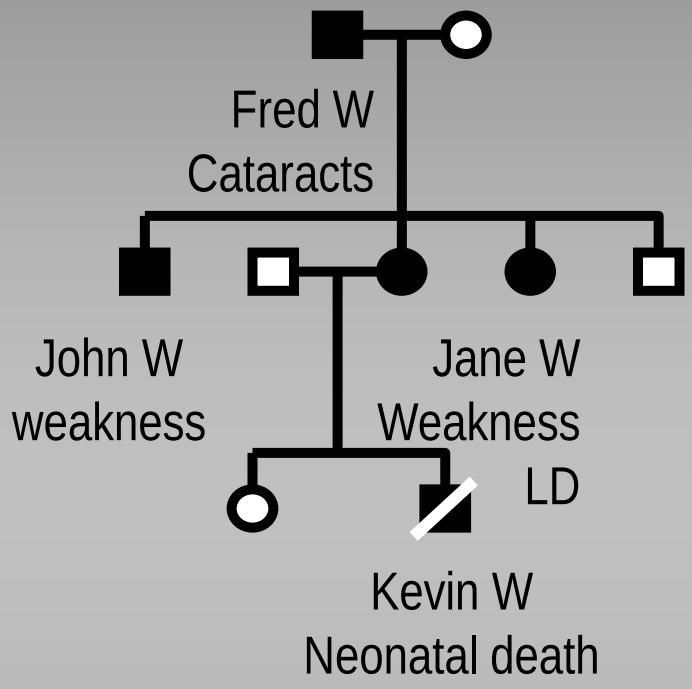


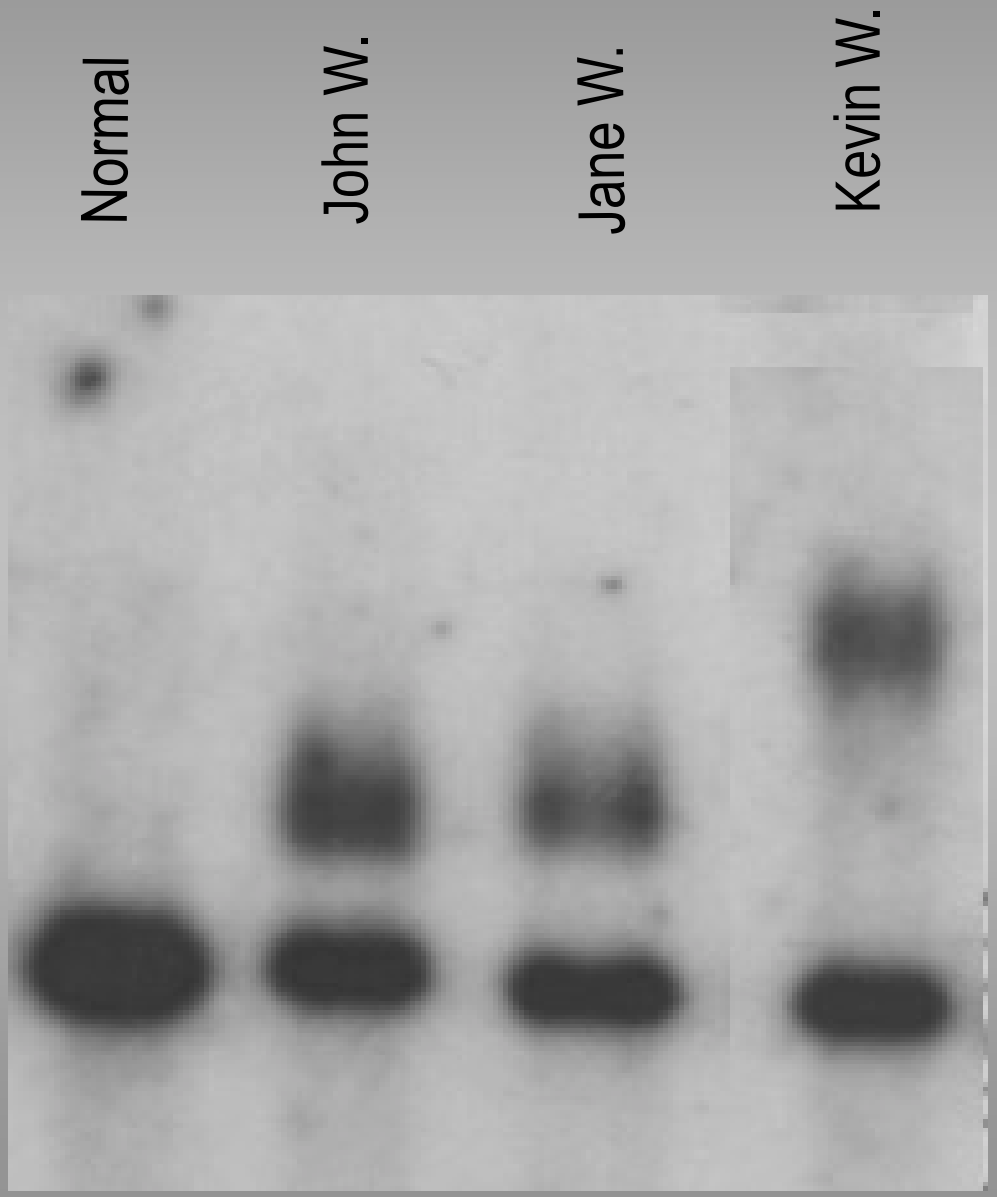




Myotonic Dystrophy

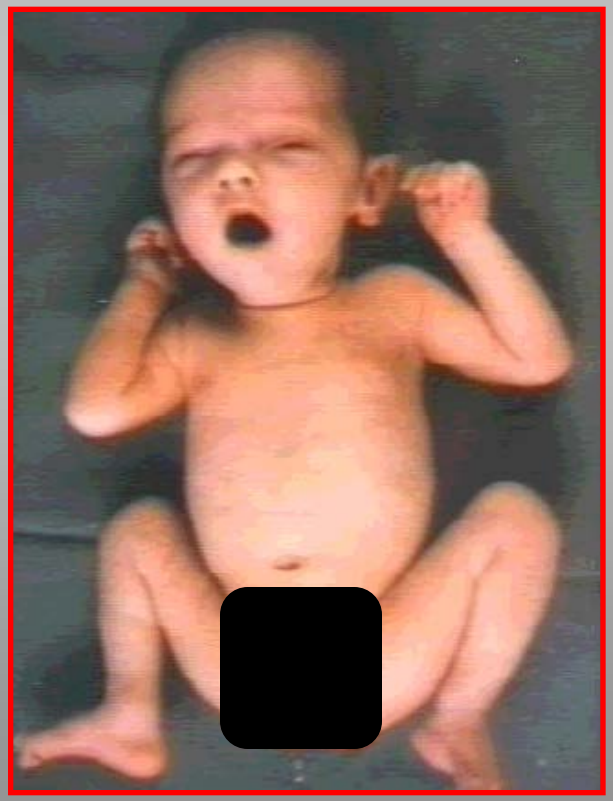
- CTG trinucleotide repeat in 3’ UTR of Myotonic dystrophy gene.
- Normally 5-27 copies of repeat
- Disease alleles 50-2000 repeats
- Repeat expands on male or female transmission
- Disease shows anticipation
  - More severe in succeeding generations


Fred W
Cataracts
John W
weakness
Jane W
Weakness
LD
Kevin W
Neonatal death


Normal
John W.
Jane W.
Kevin W.

Congenital Myotonic Dystrophy

- Severe neonatal muscle weakness
- Neonatal death from respiratory failure
- Usually > 500 repeats
- Almost invariably mother is affected



Trinucleotide Repeat Disease

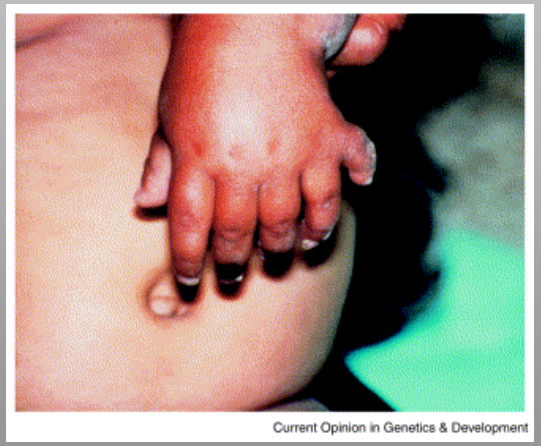
• Myotonic Dystrophy $(CTG)_n$	Affects RNA Processing
• Fragile X $(CCG)_n$	Causes Methylation silencing of gene
• Huntingtons Disease $(CAG)_n$	Expression of mutant protein (gain of function)
• Friedreich Ataxia $(GAA)_n$	Affects RNA Processing
• Spinocerebellar Ataxias (polyglutamine tract)	Expression of mutant protein (gain of function)

Digenic Inheritance

- First came to light in patients with Sensorineural deafness
- >100 genes involved
- Usually conform to mendelian patterns of inheritance
- However a proportion of patients with deafness, were double heterozygotes for know deafness genes
  - ie no hearing deficit were found in patients who were only carriers of a mutation in a single locus but deafness occurred where patients were carriers of mutations in 2 gene loci

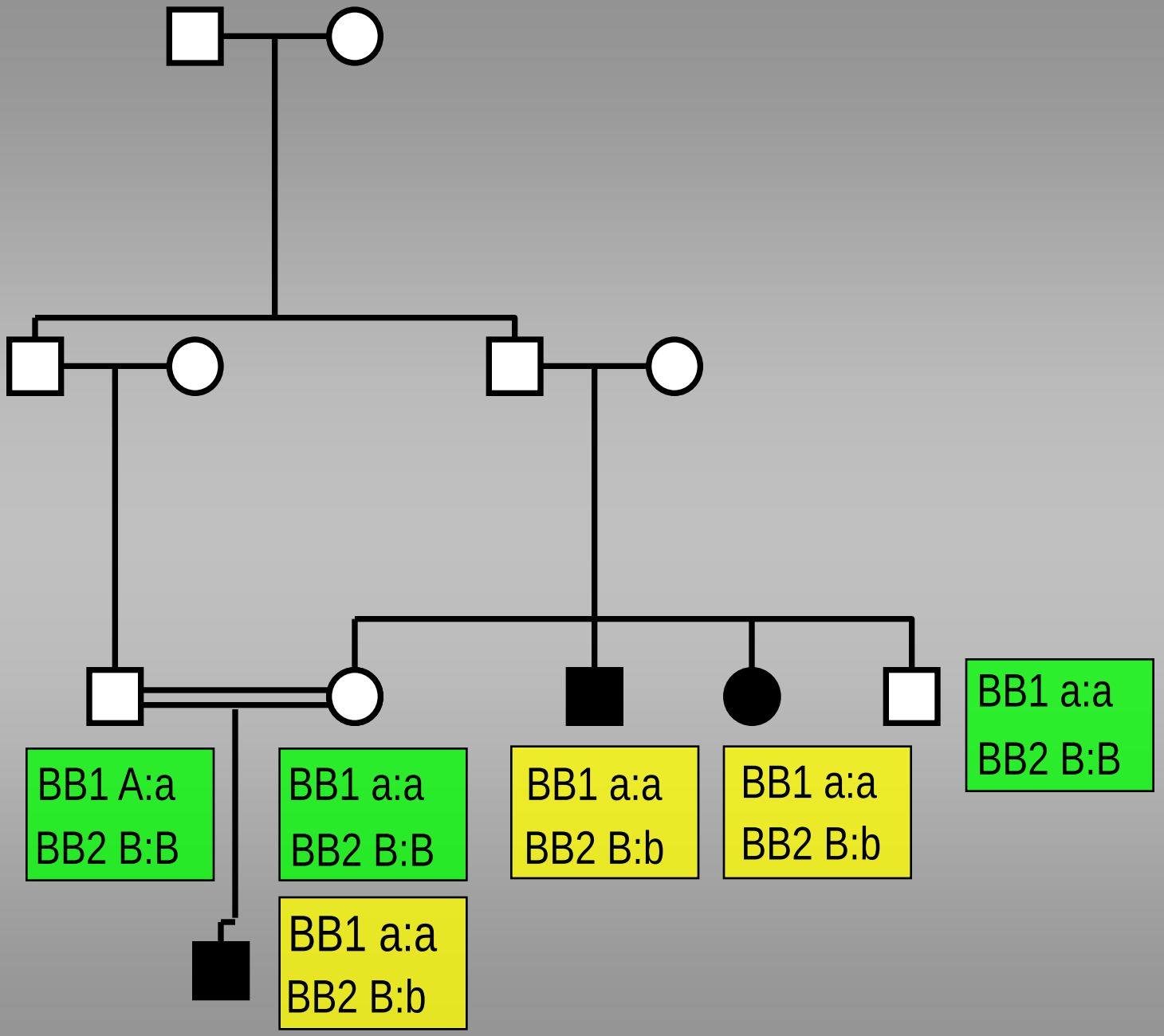
Tri-allelic Inheritance

- Only found in 1 syndrome so far
- Bardet Biedl syndrome
  - multisystem disorder characterized by
    - obesity
    - retinal degeneraton
    - polydactyly
    - gonadal and renal malformations,
    - behavioural and developmental problems



Tri-allelic Inheritance

- 15 loci and 6 genes identified
- Family studies the pattern of inheritance would fit with an autosomal recessive condition
- Found discrepancy in mutation data
- A proportion of patients did not conform to mendelian inheritance pattern
- Found that in some families the condition only manifested if there were 3 mutant genes in 2 locus


BB1 A:a
BB2 B:B
BB1 a:a
BB2 B:B
BB1 a:a
BB2 B:b
BB1 a:a
BB2 B:b
BB1 a:a
BB2 B:B
BB1 a:a
BB2 B:b

Contigous gene deletion syndromes

What is a contiguous gene deletion syndrome?

What is a contiguous gene deletion syndrome?

“A syndrome caused by a microdeletion that spans two or more genes tandemly positioned along a chromosome”

Well known contiguous gene deletion syndromes:

- Williams-Beuren syndrome 7q11.23
- DiGeorge syndrome 22q11.2
- Wolf-Hirschhorn syndrome 4p16.3
- Smith-Magenis syndrome 17p11.2

Genotype-Phenotype correlations

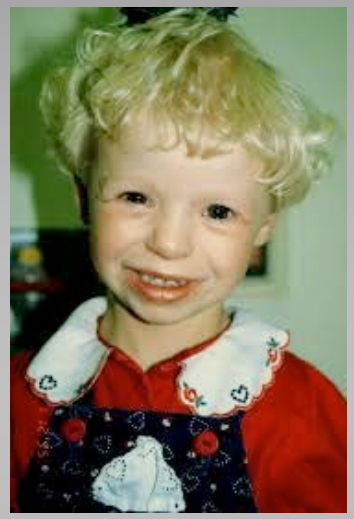
- Is the clinical manifestations due to the genes which have been deleted
- If so can we attribute particular phenotype to the particular genes which has been deleted
- Or is the syndrome due to just one of the genes that has been deleted

Williams Beuren syndrome 7q11.23

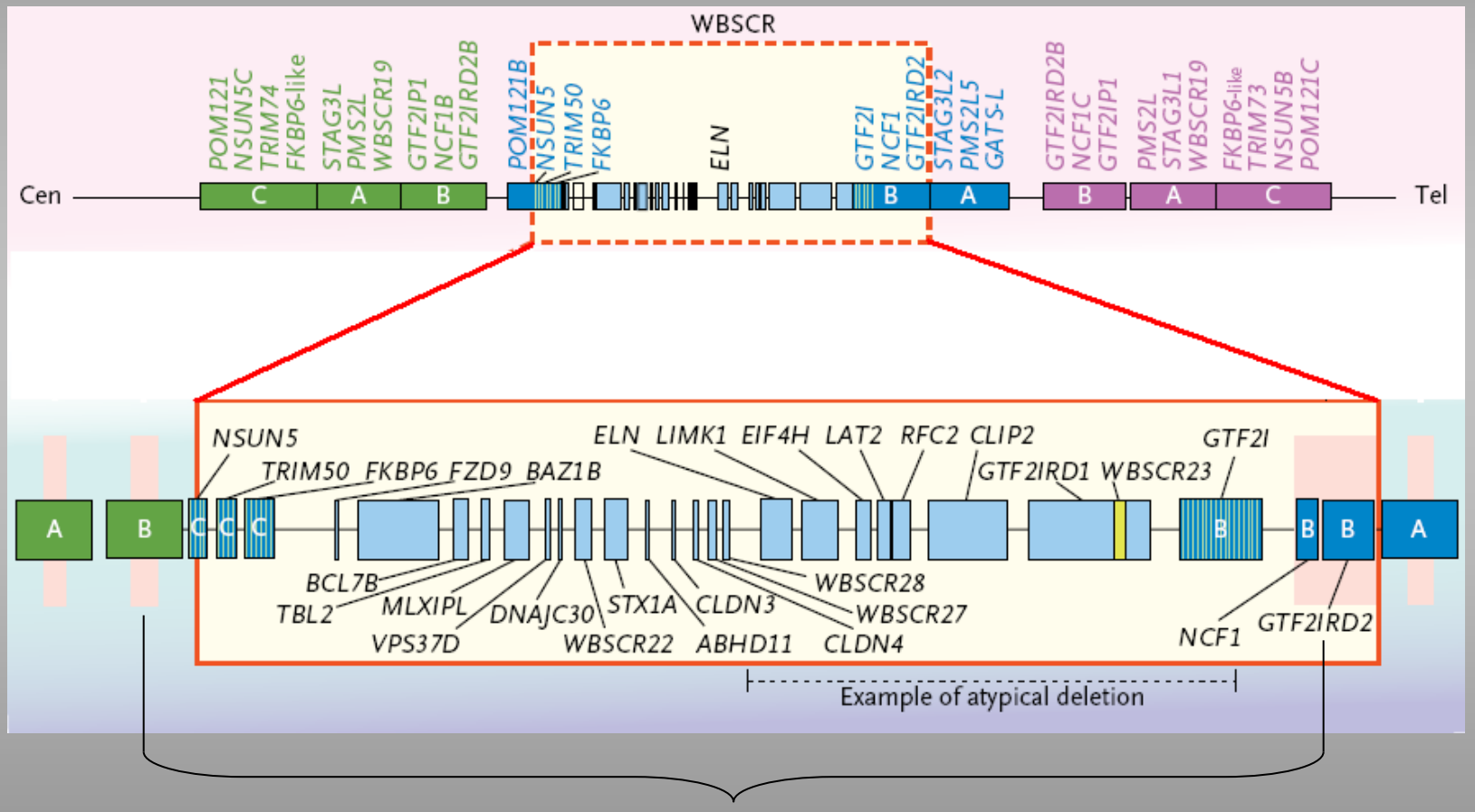
- Common 1.5Mb deletion spanning 24-28 genes
- 320-500Kb highly repetitive sequence flanking the Williams critical region
- Due to defective homologous non-allelic recombination

Williams Beuren syndrome 7q11.23

- Dysmorphic facial features
- “Cocktail party” demeanour
- Excessive non-social anxiety
- Preserved vocabulary
- Cardiovascular problems
- Supravalvular aortic & renal stenosis
- Transient hypercalcaemia (paediatric)



Williams Beuren syndrome 7q11.23



Genes involved in common 1.5Mb deletion (95% cases)

Dissecting the roles of particular genes in WBS

- *ELN*: Elastin gene. 90-100 % of the WBS patients have hemizygous deletion of *ELN*

  => Cause of supravalvular aortic stenosis (SVAS)

  => ? Cause of facial features

- *CLIP2*: Encodes cytoplasmic linker protein subunit 2 / 115 (CLIP115); implicated in membranous organelles / microtubules interaction

  => ? A cause of neurological features of Williams syndrome

- *LIMK1*: Encodes LIM Kinase; strongly expressed in brain

  => some neurological features of WBS

Subtelomeric deletions

del(22)(q13->pter)

- First described as a possible syndrome in 1994 (but first reported case in 1985)
- Submicroscopic deletions detected when looking for deletions at DiGeorge locus
- Characteristic phenotype
  - Global developmental delay
  - Autistic behaviour
  - Absent/severely delayed speech
  - ?Angelman like

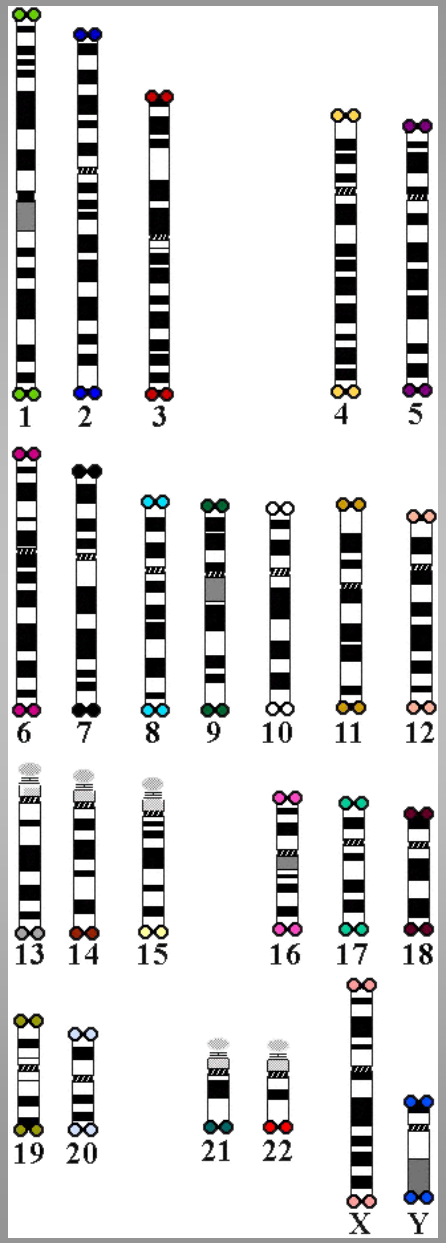
Subtelomeric chromosomal rearrangements

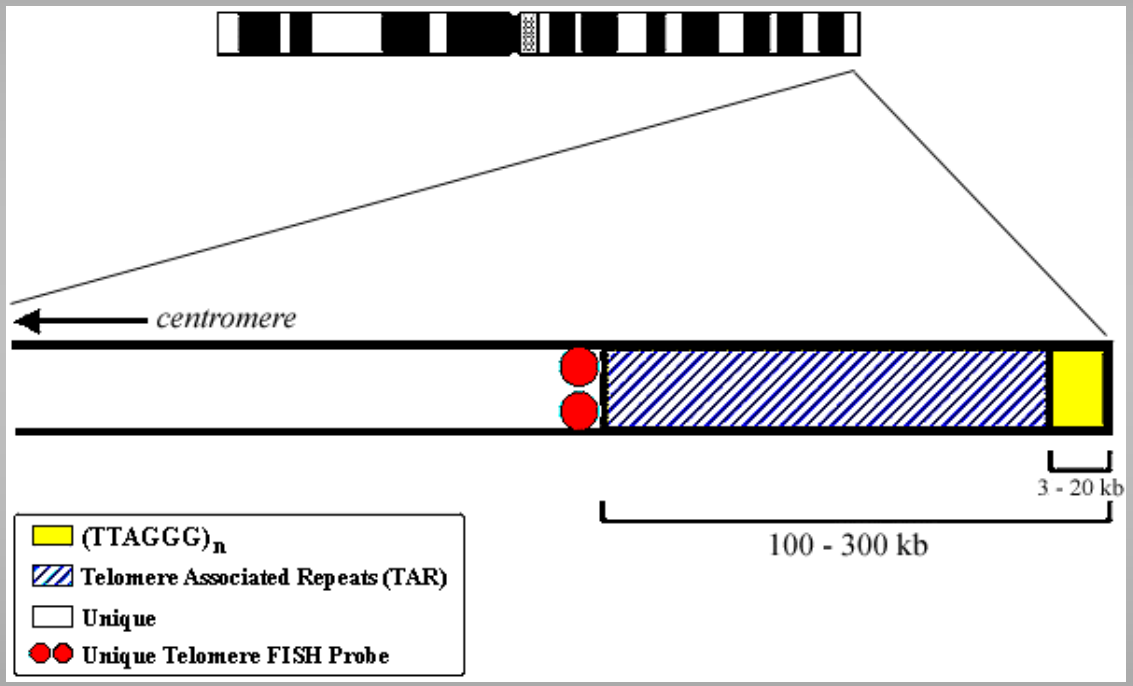
- Mental retardation affects 3% of population, but diagnosis is obtained in less than half of all cases
- Cause remains unknown in 34% of moderate-severe and 80% of mild cases

Subtelomeric chromosomal rearrangements

- Why focus on telomeres?
  - Majority of translocations involve chromosome ends (shared telomere-associated repeats)
  - Gene rich adjacent regions (rearrangements likely to have phenotypic consequences)
- Moderate-severe MR
  - for sporadic cases (7%)
  - for familial cases (25%)

Telomeres


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


centromere
3 - 20 kb
100 - 300 kb
(TTAGGG)n
Telomere Associated Repeats (TAR)
Unique
Unique Telomere FISH Probe

Cellular Mosaicism

Mosaicism

- When an individual is made up of populations of cells with different genetic constitutions.

Can be mosaic for

- Chromosomal Aneuploidy
- Molecular Mutations

Somatic Mosaicism

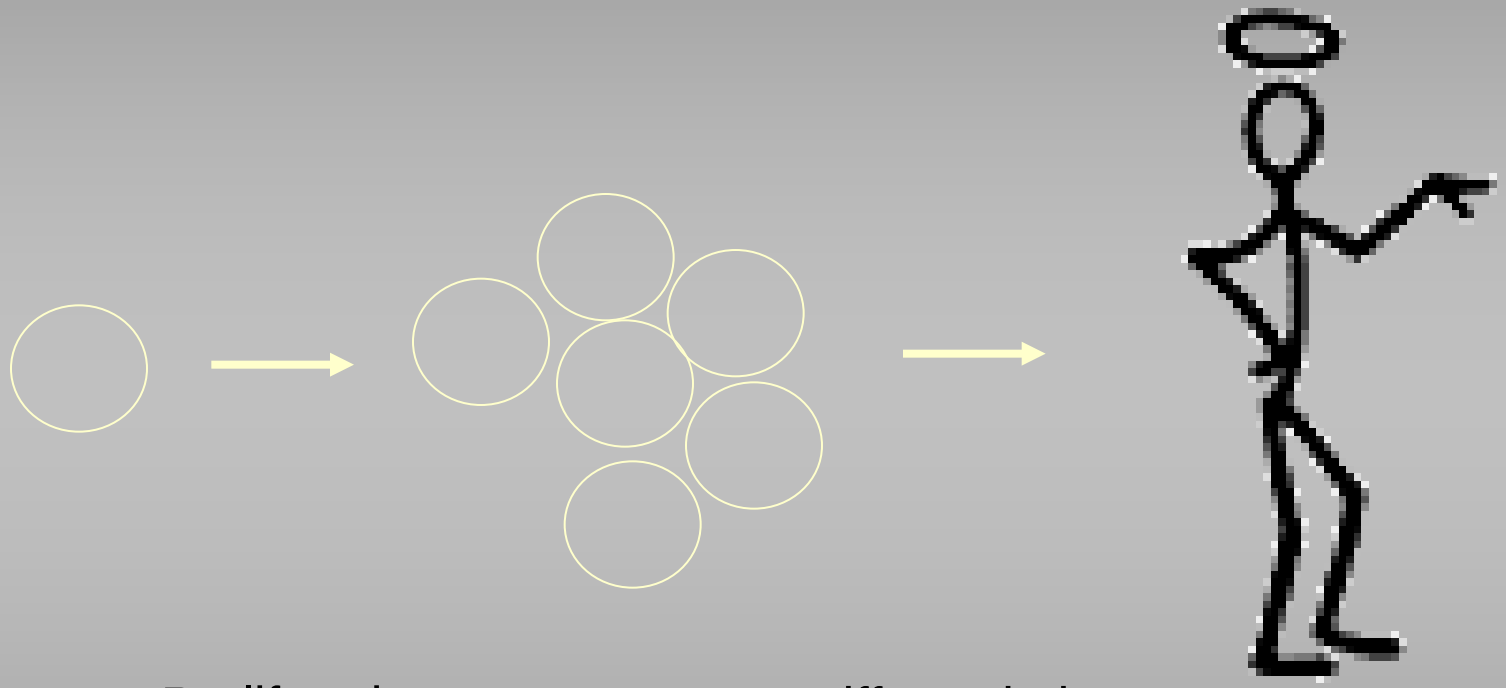
- All cells suffer mutations as they divide
  - At meiosis and at mitosis
  - Approximately 10^{-6} per gene per cell division
- Repair Mechanisms Exist
  - Can give rise to reversion
- Given the numbers of cells in the body
  - everybody will have some cells which has a mutation of some sort

Mosaicism

May become clinical important

- If mutant cells has tendency to grow and replace normal cells (cancer cells)
- If the mutation arose early in embryonic development, so becomes a large proportion of the whole body
- If the mutation occurred in the germ line

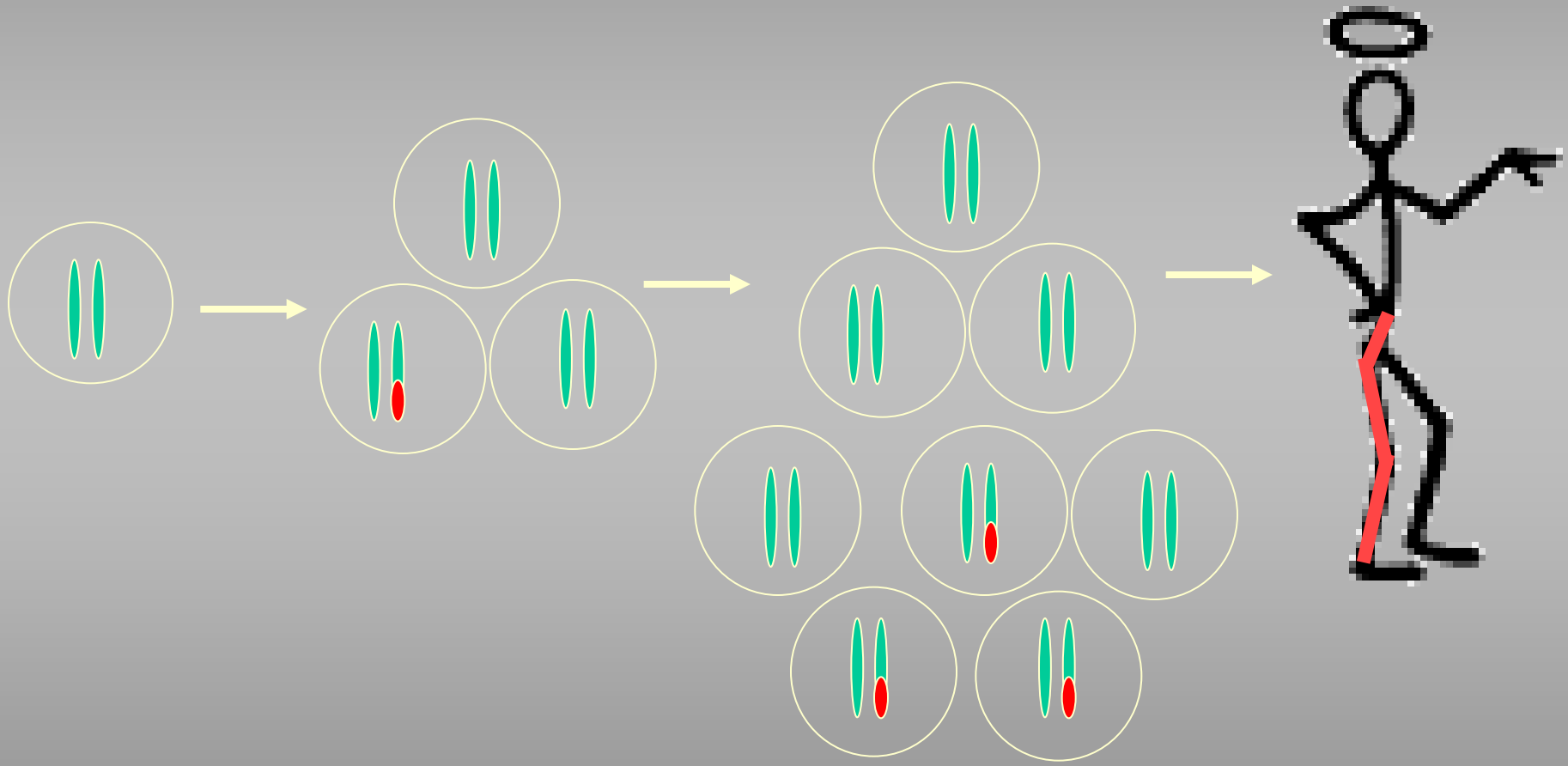
Somatic Mosaicism

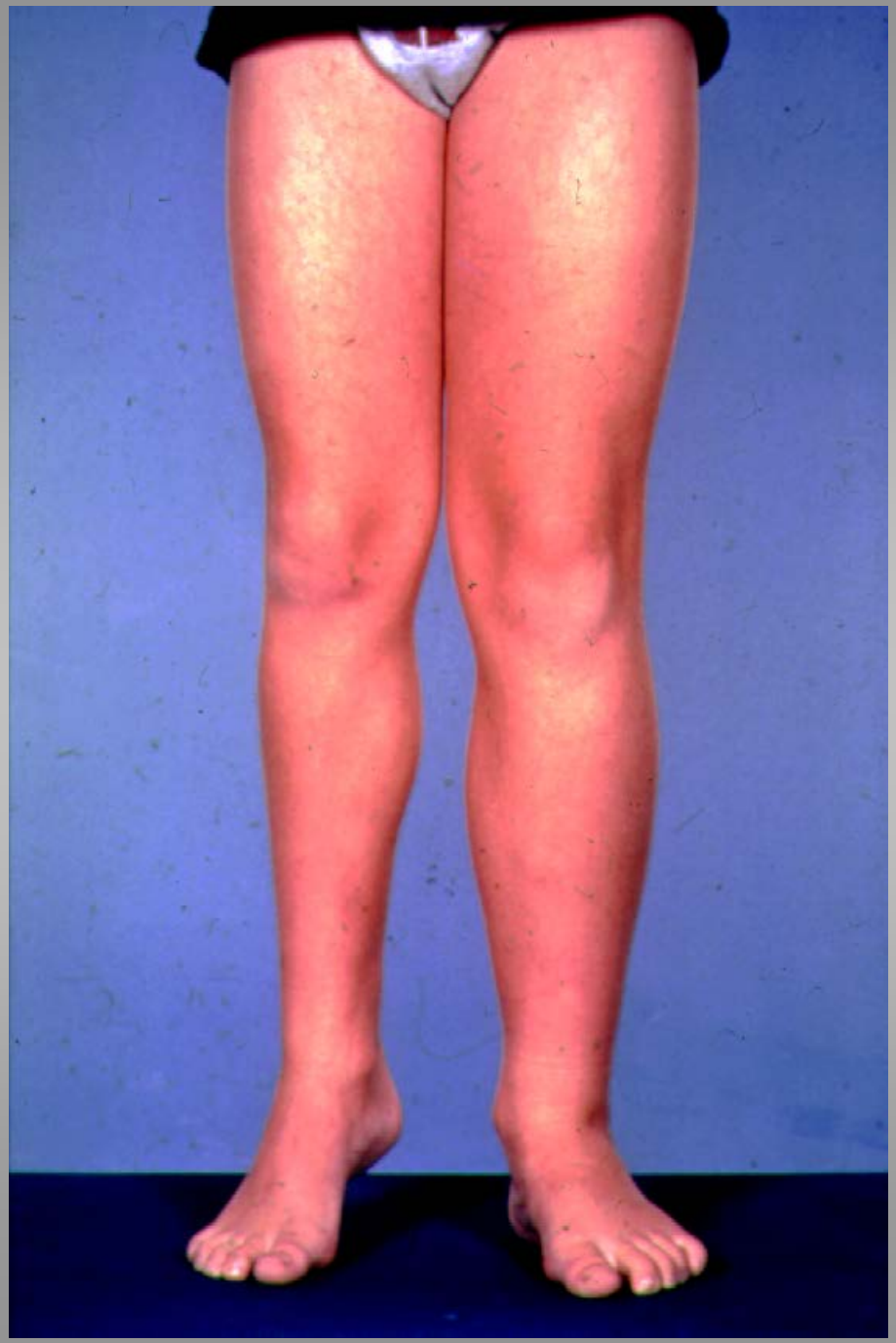


Proliferation

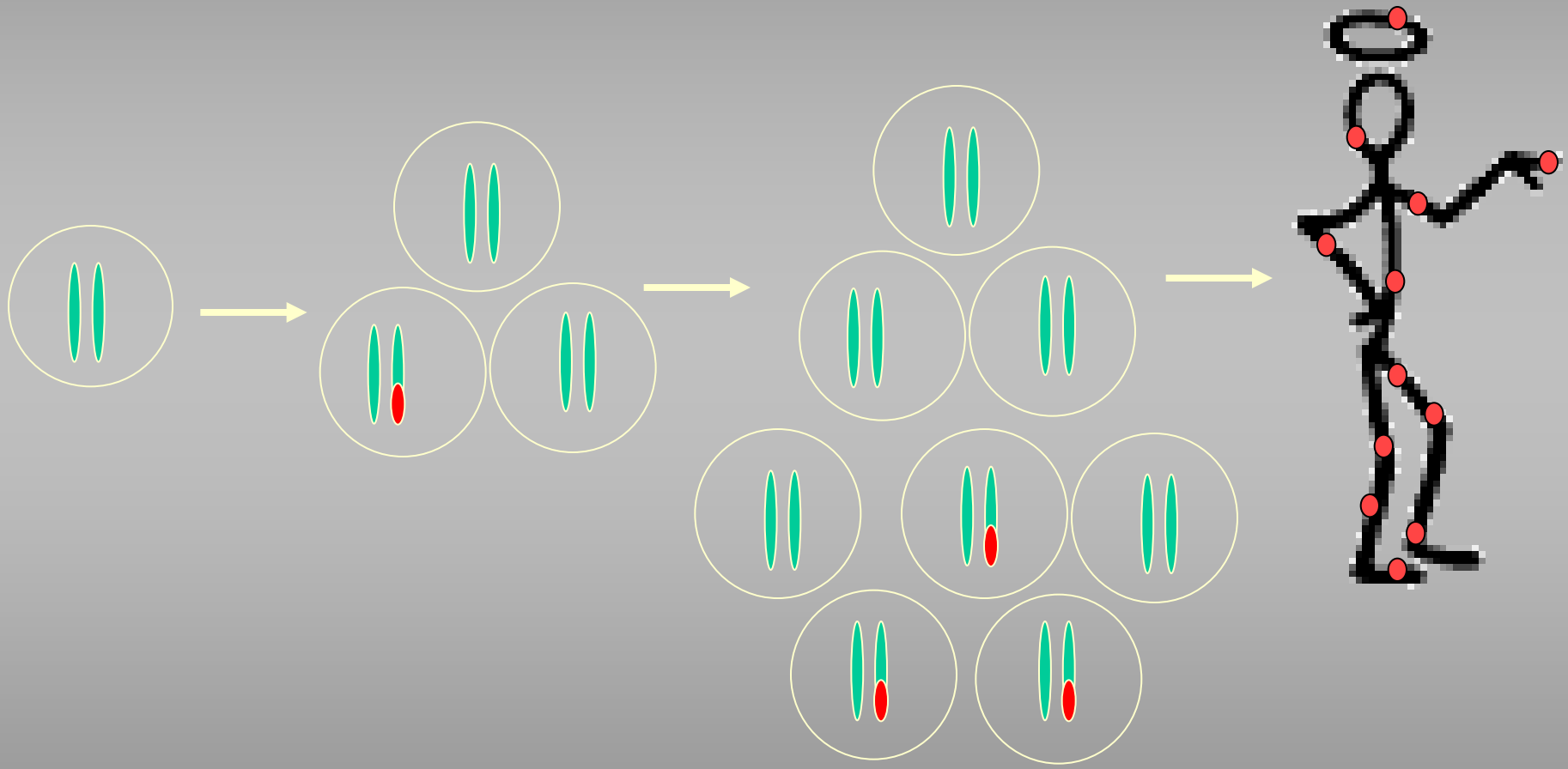
Differentiation

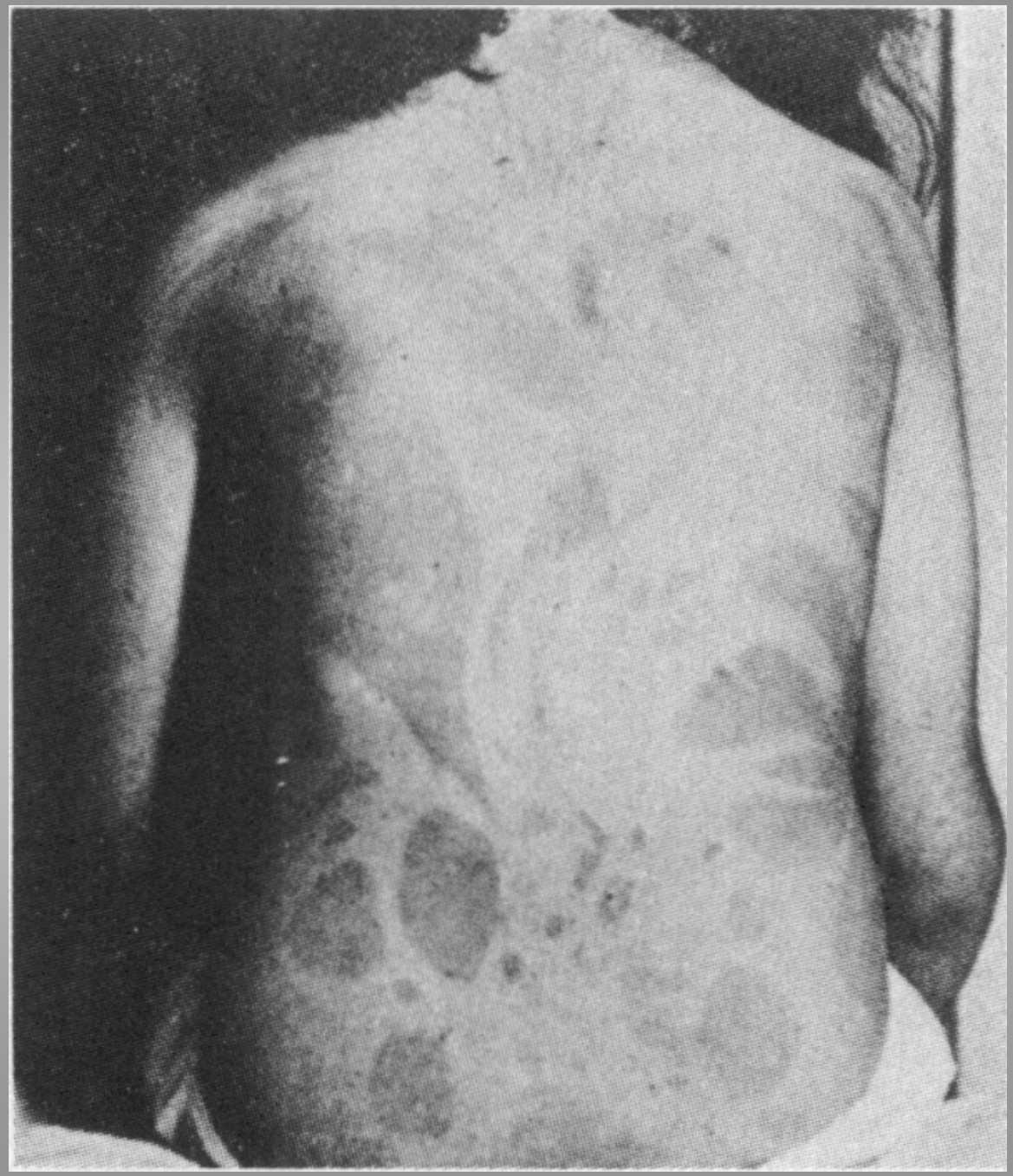
Somatic Mosaicism



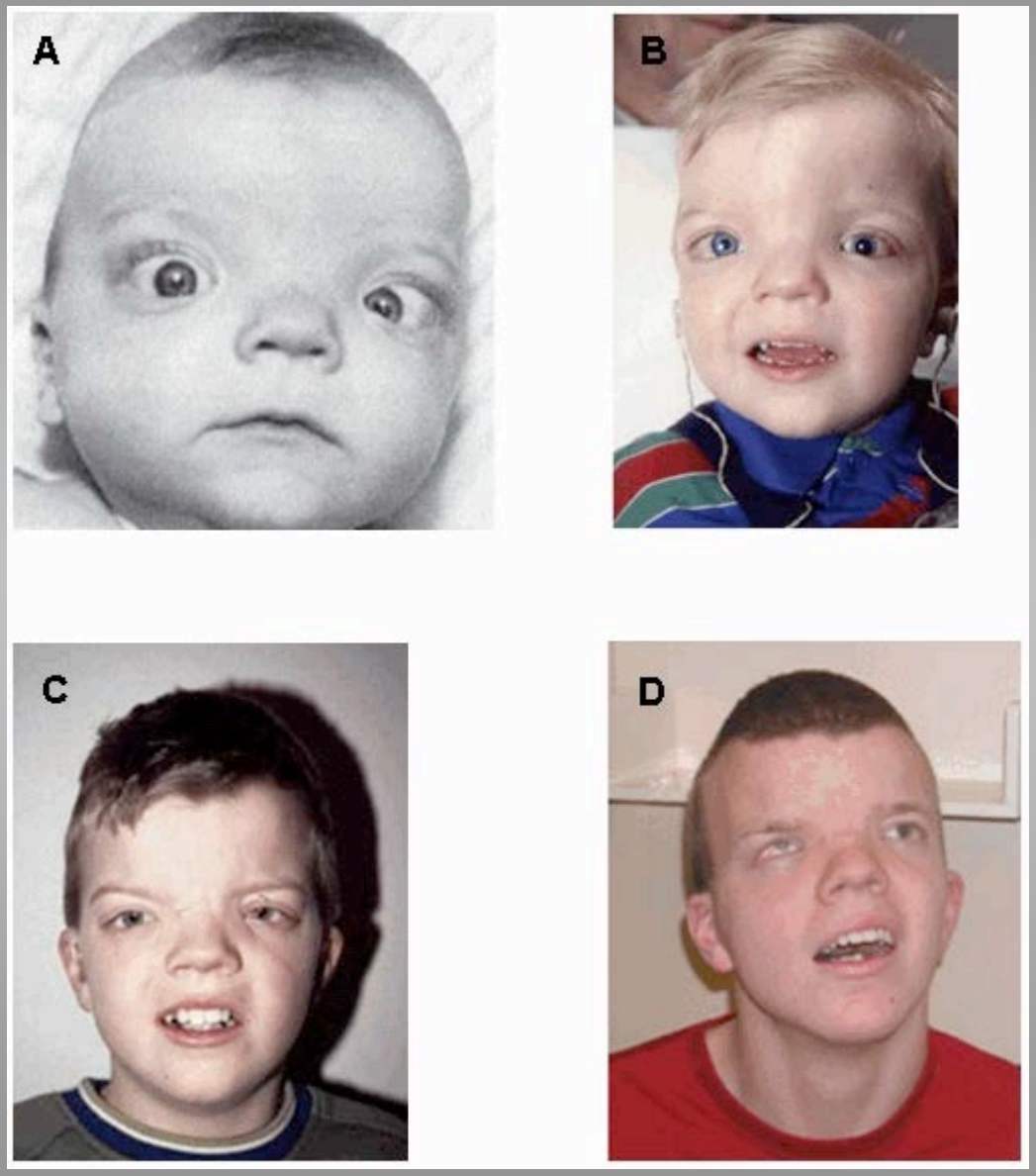


Somatic Mosaicism





Pallister Killian syndrome mosaic tetrasomy 12p



Gonadal Mosaicism

- Commoner in some diseases
  - Duchenne Muscular Dystrophy
  - Osteogenesis Imperfecta
- Can offer pre-natal diagnosis for a second child, even when parents are unaffected (if a mutation is identified)
- Causes recurrence risk for fatal dominant conditions

New Genetics

- Non-Mendelian
  - Genomic Imprinting
  - Digenic Inheritance
  - Triallelic inheritance
  - Mitochondrial Inheritance
- Chromosomal
  - Micro/telomeric deletions
  - Contigous gene syndrome
- Trinucleotide repeat expansions
- Somatic and gonadal mosaicism

- Multifactorial inheritance