MENDELIAN INHERITANCE

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July 2nd . 2014

MGL- 8

Classification of genetic disorders

- Chromosomal
- Single gene
  - Autosomal recessive
  - Autosomal dominant
  - X-linked recessive
  - X-linked dominant
- Nontraditional type GD
- Multifactorial
- Somatic mutations (cancer)

Non-Traditional Types of Gene Disorders (NTGD)

Non-Traditional Types of Gene Disorders (NTGD)

- Mosaciasm
- Imprinting
- Trinucleotide expansion
- Uniparental Disomy
- Mitochondrial
- Fragile X Syndrome

Mosaciasm

Mosaicism

Gonadal Mosaicism :

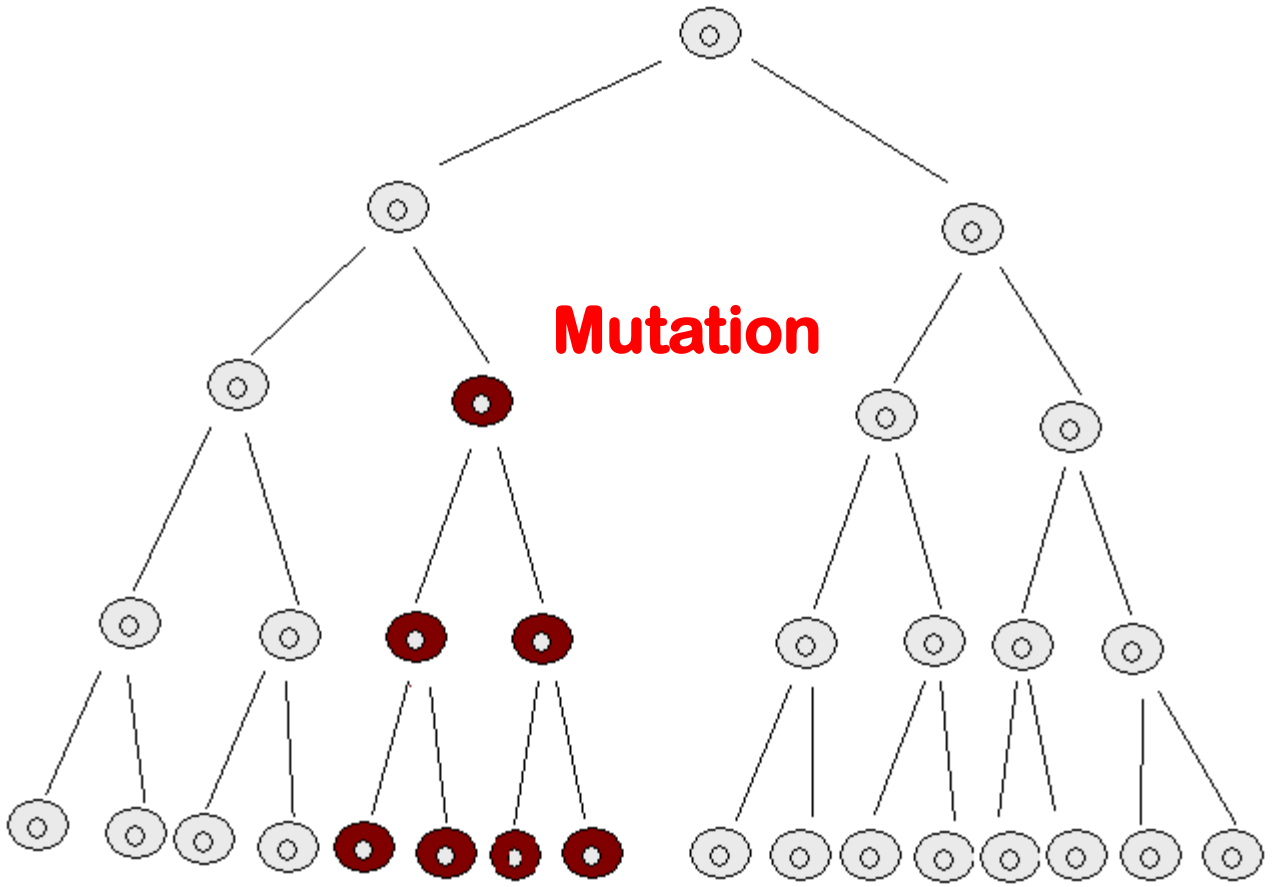
- The presence of a mutation in all or part of the germ line but not in the rest of the body.
- This implies that a mutation occurred in a precursor sperm or egg cell.
- Gonadal mosaicism has been observed in humans:

  - Osteogenesis imperfecta,
  - Duchenne muscular dystrophy,
  - Achondroplasia,
  - Hemophilia A.

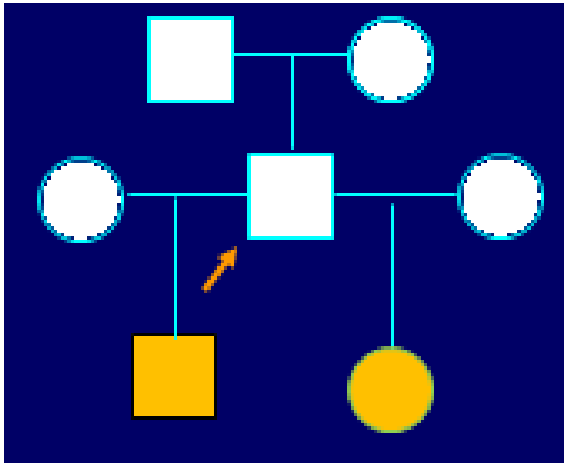
Germ line Mosaicism (rather than a new mutation)

- When an individual presents with an autosomal dominant disorder for the first time in a family.

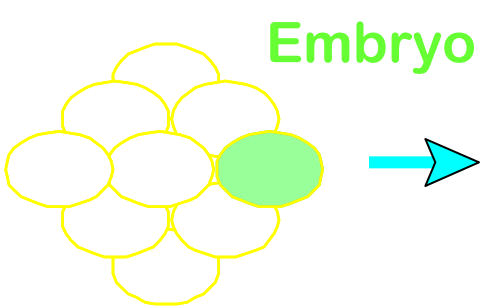
Mosaicism

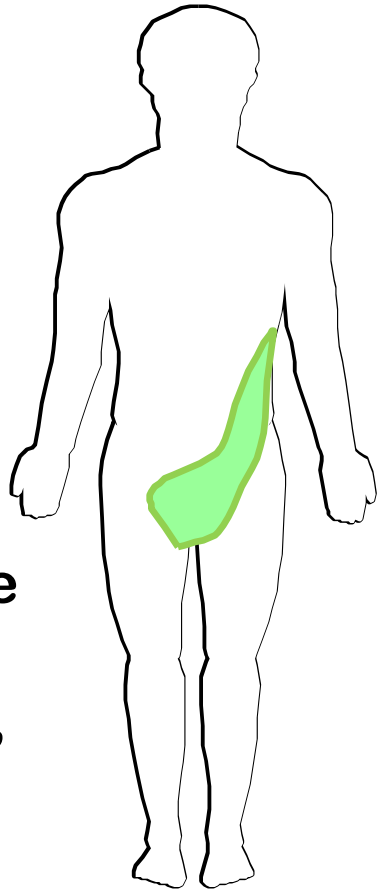


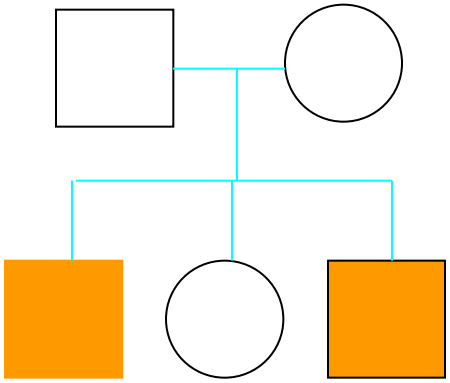
A mutation occurring during cell proliferation, in either somatic or during gametogenesis, leads to a proportion of cells carrying the mutation



Germline Mosaicism







No previous family history of this disorder

All or part of a parent's germ line is affected by a disease mutation, but the somatic cells are not

Imprinting

Genomic Imprinting

Mechanism of Imprinting

- Must occur before fertilization
- Must be able to confer transcriptional silencing
- Must be stably transmitted through mitosis in somatic cells
- Must be reversible on passage through the opposite parental germline (*i.e., if an allele is maternally imprinted, this must be removed in the gametes of a male offspring*)
- Methylation

Genomic Imprinting

- Transient Neonatal Diabetes
  Uniparental Disomy Chro. 6
  * Insulin Absent in Newborn
  * Spontaneous correction at Age 3

- Insulin - Chromosome 11p

* Biparental Expression
* Uniparental Expression at Yolk Sac

Trinucleotide expansion

Triplet Repeat Disorders

- The biologic basis of this phenomenon is now known to be due to specific areas of instability in the human genome.
- In normal individuals, the triplet repeat sequences are stable during meiosis and mitosis and the sequence copy number is transmitted as a polymorphism from parent to child.
- In families affected by these disorders, the area is unstable, leading to progressive amplification of the gene sequence with each succeeding generation.
- This molecular finding has two important clinical correlations:
  1. A direct relationship between the severity of the phenotype and repeat copy number,
  2. Identification of the "premutation" in a clinically asymptomatic individual

Repeat location

Coding disorders

Diseases with a CAG expansion within the coding region, produces an enlarged polyglutamine tract Huntigngton disease and Spinocerebellar ataxia type 1…) .

Non coding disorders

1. Untranslated 5' (Fragile X,syndrome, Spinocerebellar Ataxia type 2..)
2. Untranslated 3' (myotonic dystrophy)
3. Intron (Friedreich ataxia,)

Examples of disorders caused by STR expansions

Disorder	Gene	Unit	Location
Huntington disease	HD	CAG	Coding sequence
Spinobulbar atropy	AR	CAG	Coding sequence
Spinocerebellar ataxia 1	SCA1	CAG	Coding sequence
Spinocerebellar ataxia 2	SCA2	CAG	Coding sequence
….			
Spinocerebellar ataxia 7	SCA7	CAG	Coding sequence
Myotonic dystrophy	ZFN9	CCTG	Intron
Fredreich ataxia	X25	AAG	Intron
DMI-associated cataract	SIX5	CTG	Promoter
Progressive myoclonus epilepsy	Cys b	12 bp	Promoter
Fragile X	FRAXA	CTG	5’ UTR
Fragile XE	FRAXE	CCG	5’ UTR
Spinocerebellar ataxia 12	SCA12	CAG	5’UTR

Uniparental Disomy

Uniparental Disomy

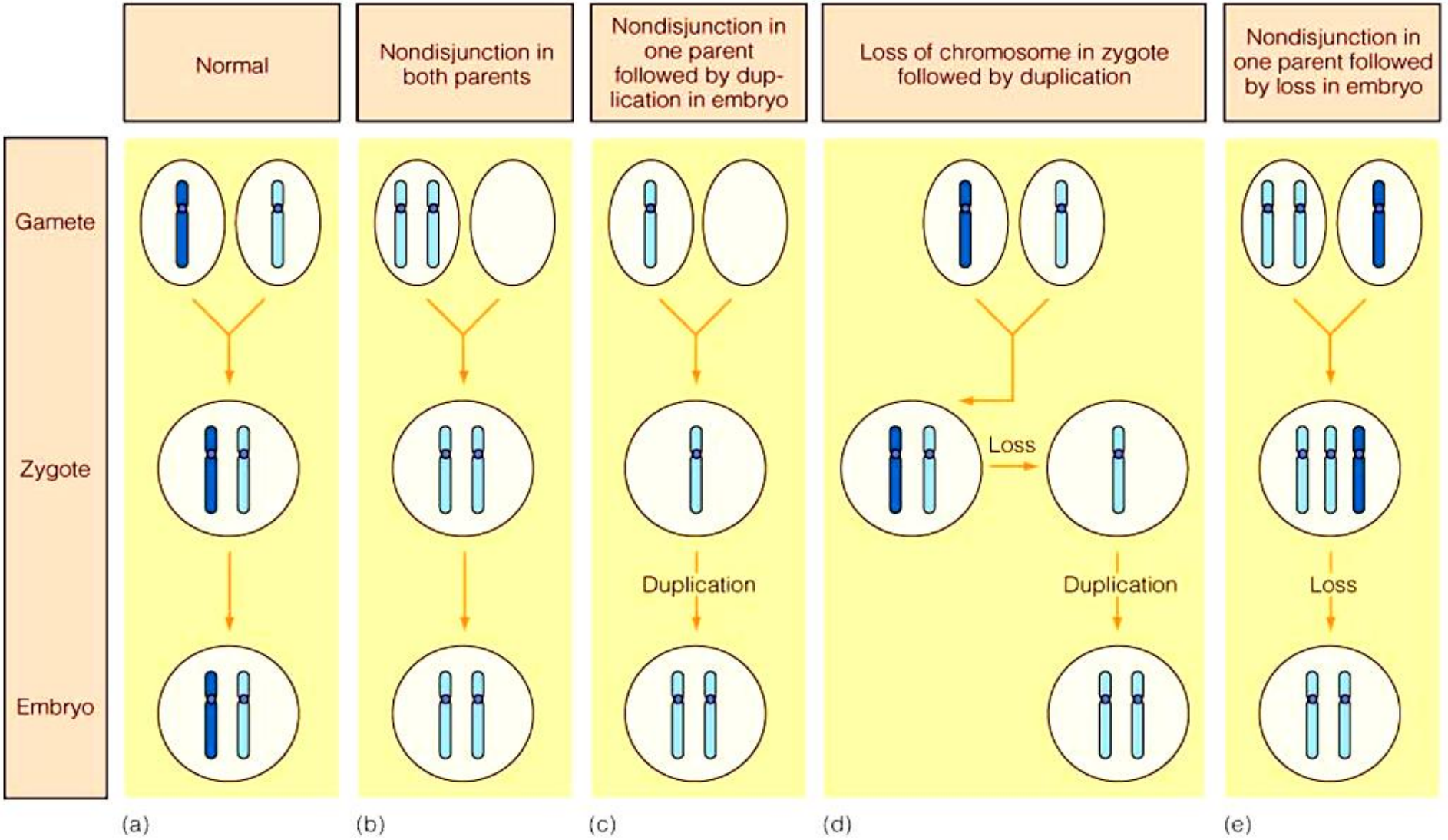
- **Uniparental disomy** (UPD) is defined as the presence of two homologous chromosomes inherited in part or in total from only one parent.
- This means that one parent has contributed two copies of a chromosome and the other parent has contributed no copies.
- The incidence of UPD is estimated to be as high as 2.8 to 16.5 per 10,000 conceptions.

Uniparental Disomy

- **Isodisomy:** If the parent passed on two copies of the same chromosome (as results from non-disjunction in meiosis II).

- **Heterodisomy**. If the parent provides one copy of each homolog (as results from non-disjunction in meiosis I),

Uniparental Disomy

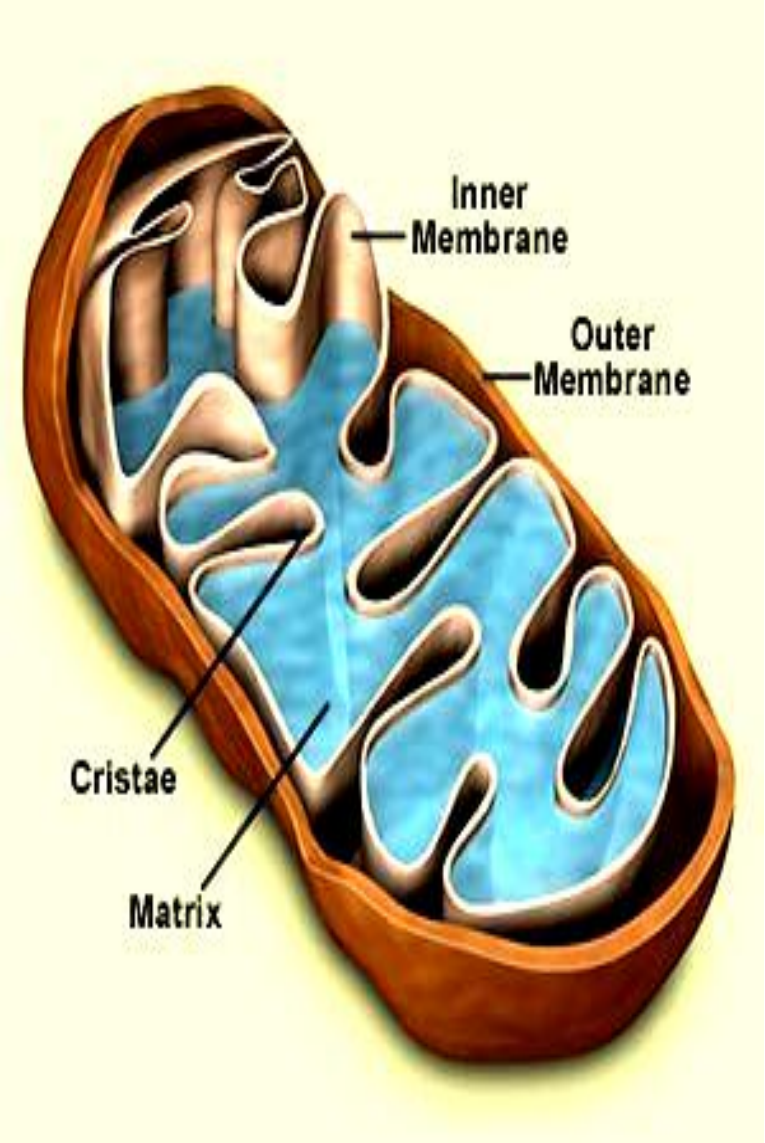


Examples of Uniparental Disomy

- Cases of PWS & AS
- Two CF patients with short stature, inherited two identical copies of most all of their maternal chr. 7. In both cases, the mother happened to be a carrier for CF
- Father-to-son transmission of hemophilia, affected by inherited both X & Y from father
- Expression of X-linked in homozygous form in a female offspring of a carrier mother and a normal father

UNIPARENTAL ISODISOMY REDUCTION TO HOMOZYGOSITY LEADING TO RECESSIVE DISORDERS

Recessive Disorders	UDP type
Pycnodysostosis	1 pat
Junctional epidermolysis bullosa, Herlitz type	1 mat
Spinal muscular atrophy III (juvenil type)	5 pat
Complement deficiency of C4A+C4B	6 pat
Methylmalonic acidemia	6 pat
Cystic fibrosis	7 mat
Osteogenesis imperfecta (COL1A2 mutation)	7 mat
Cystic fibrosis and Kartagener syndrome	7 pat
Congenital chloride diarrhea	7 pat
Chylomicronemia, familial	8 pat
Cartilage / hair hypoplasia	9 mat
Beta-thalassemia major	11 pat
Complete congenital achromatopsia (rod monochr.)	14 mat
Bloom syndrome (with Prader-Willi syndrome)	15 mat
Hydrops fetalis alpha-thalassemia	16 pat
Duchenne muscular dystrophy	X mat
Hemophilia A	XY



MITOCHONDRIAL GENETICS

Mitochondria

- A mitochondrion (singular of mitochondria) is part of every cell in the body that contains genetic material.
- Mitochondria are responsible for processing oxygen and converting substances from the foods we eat into energy for essential cell functions.
- Mitochondria produce energy in the form of ATP, which is then transported to the cytoplasm of a cell for use in numerous cell functions.

Mitochondrial Inheritance

- Mitochondrial DNA = 16.5 Kb circular DNA molecule.
- The entire human mitochondrial chro. has been cloned and sequenced.
- Oxidative Phosphorolation to produce ATP
- Most proteins are:
  - Nuclear genes,
  - Mitochondrial genes,
  - Combination of both

Mitochondrial Enzymes

- Mitochondria perform cellular respiration after the cytosolic glycolysis step.

- The enzymes needed for respiration, include:

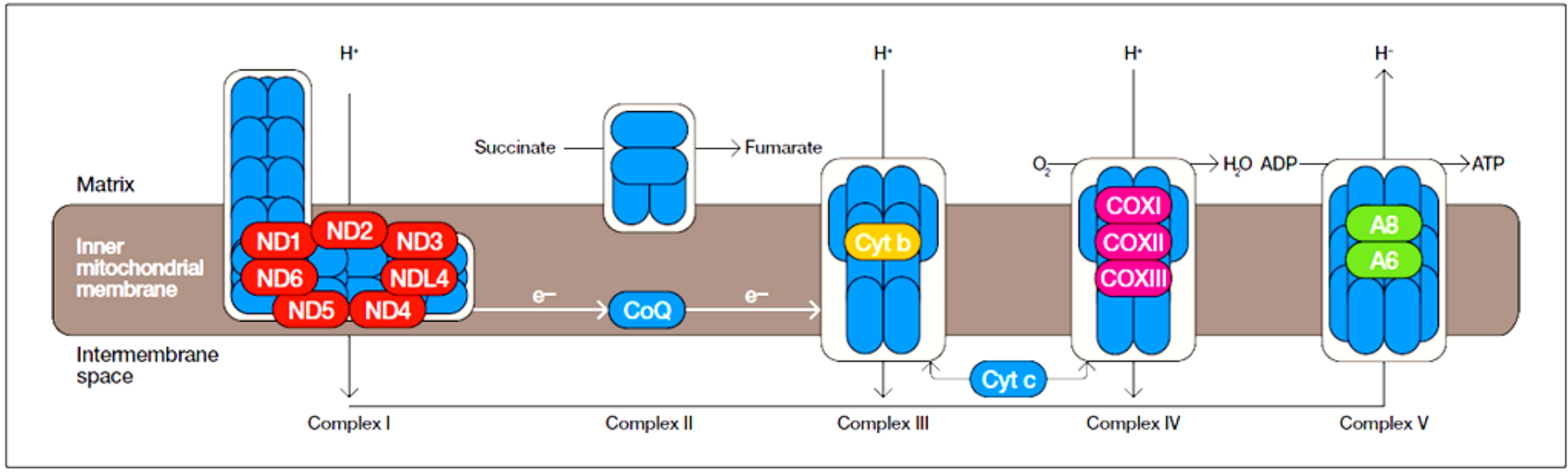
  a. Pyruvate dehydrogenase.
  b. Electron transport and OP enzymes.
  c. Citric acid cycle enzymes.
  d. Fatty acid oxidation enzymes

Respiratory Chain System.

Subunits encoded by mtDNA are shown in red and subunits encoded by nuclear DNA are shown in blue.

Electrons (e-) flow along the electron transport chain, and protons (H+) are pumped from the matrix to the inter membrane space through complexes I, III, and IV, then back into the matrix through complex V, producing ATP.

Coenzyme and cytochrome c are electron carriers.



Genetic Characteristics

1. Semi-independent
2. Non-universality of the genetic code
3. Matrilineal inheritance
5. Threshold value
6. High mutation rate
7. Degenerative diseases
8. Aging

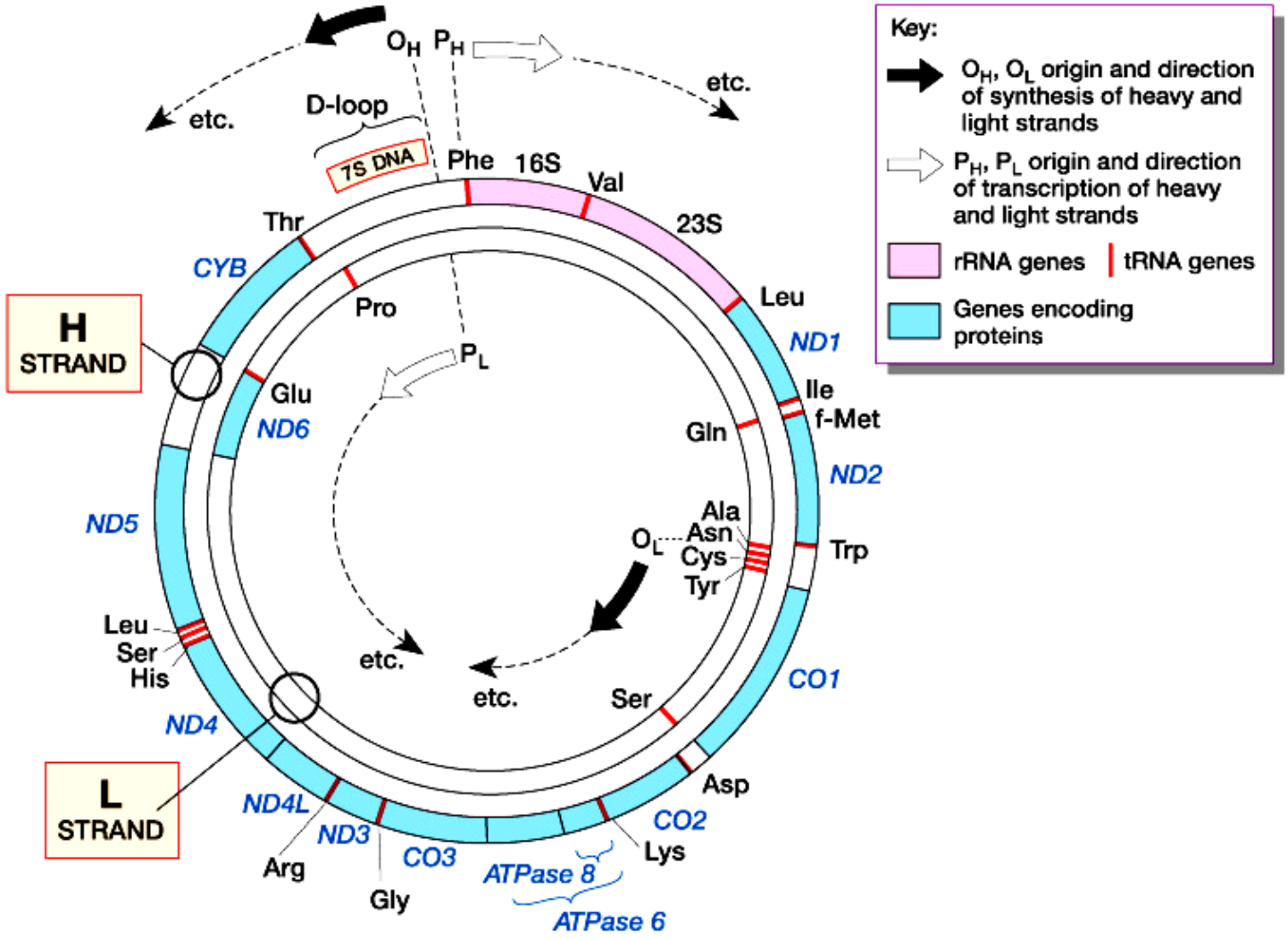
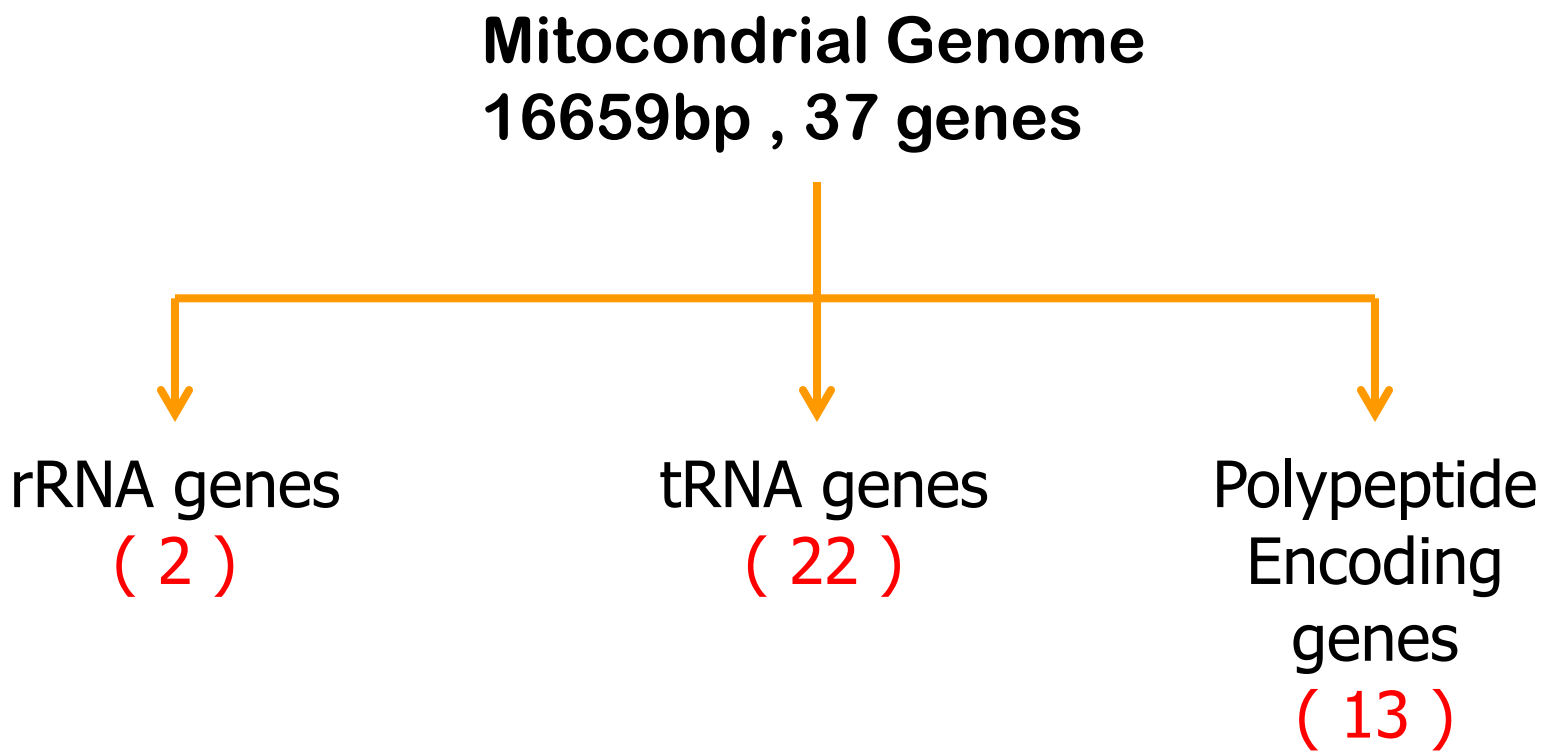


Figure 9-2 Human Molecular Genetics, 3/e. (© Garland Science 2004)

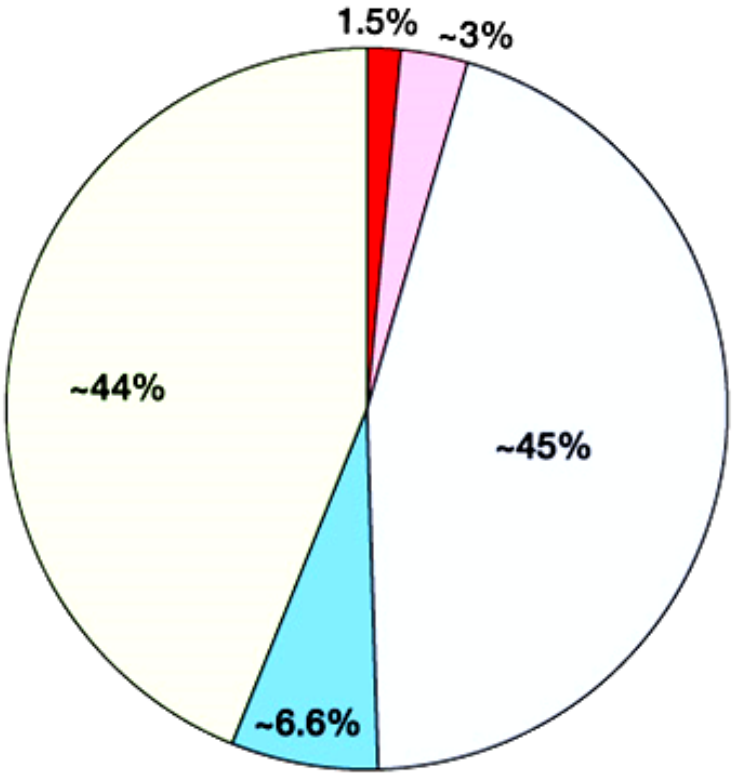
Mitocondrial Genome



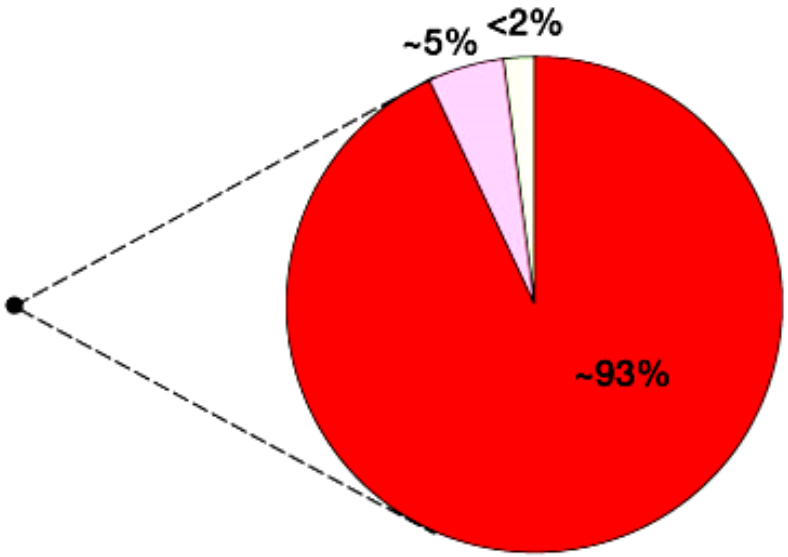
Varition in Genetic Code

Codon	Universal code	mtDNA
UGG	Trp	Trp
UGA	Stop	Trp
AGG	Arg	Stop
AGA	Arg	Stop
AUG	Met	Met
AUA	Ile	Met

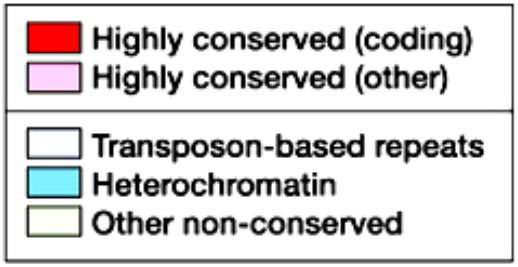
Comparison of Nuclear and Mitocondrial DNA



Nuclear genome
(24 linear double-stranded DNA molecules – 3200 Mb; ~30 000 genes)



Mitochondrial genome
(1 circular double-stranded DNA 16.6 kb; 37 genes)



The human nuclear and mitochondrial genomes

	Nuclear Genome	Mitochondrial Genome
Size	3200 Mb	16.6 kb
No. of different DNA molecules	23 (in XX cells) or 24 (in XY cells); all linear	One circular DNA molecule
Total no. of DNA molecules per cell	46 in diploid cells, but varies according to ploidy	Often several thousands (but variable)
Associated protein	Several classes of histone & nonhistone protein	Largely free of protein
No. of genes	~ 30 000 ~35-000	37
Gene density	~ 1/100 kb	1/0.45 kb

Repetitive DNA	Over 50% of genome	Very little
Transcription	The great bulk of genes are transcribed individually	Co-transcription of multiple genes from both the heavy and light strands
Introns	Found in most genes	Absent
% of coding DNA	~ 1.5%	~ 93%
Codon usage	Slightly different see slide	
Recombination	At least once for each pair of homologs at meiosis	No evidence for this occurring naturally
Inheritance	Mendelian for sequence on X and autosomes; paternal for sequence on Y	Exclusively maternal

Mitochondrial Inheritance

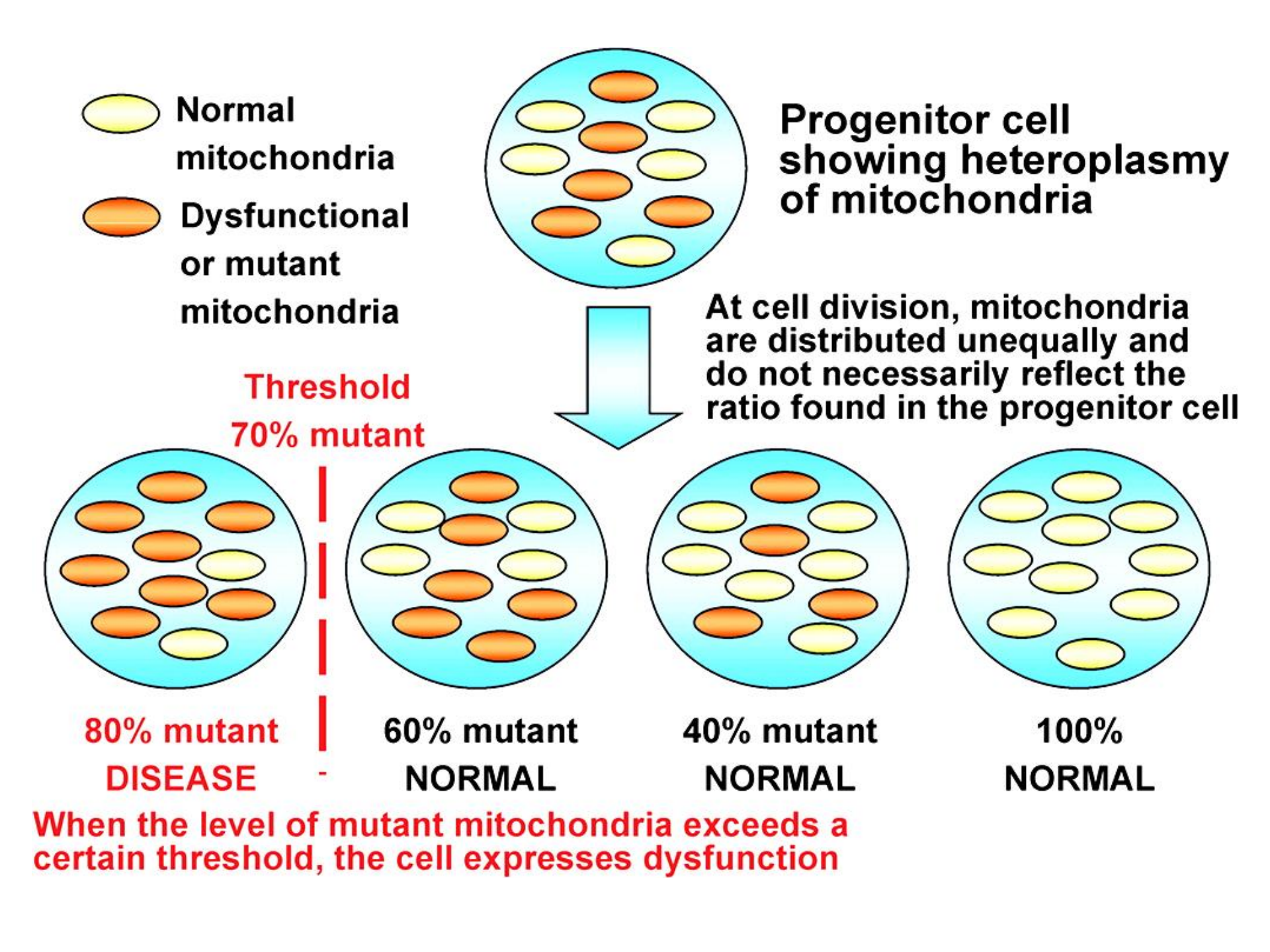
- In humans, at fertilization, the ovum contributes significantly more cytoplasm to the zygote than does the sperm.
- The sperm mitochondria degenerate upon penetration of the ovum.
- Mitochondria in offspring are exclusively maternal in origin.
- Phenotype results from maternal transmission

Mitochondrial Inheritance

- Mutations in mitochondrial genes are also the cause of several single gene disorders.
- Mutation rate in mt is 10 times more than in nuclear DNA due to the lack of DNA repair mechanism and free oxygen radicals?
- No Introns

Mitotic segregation

- % of mutant mtDNAs in daughter cells can shift at cell division
- Produces rapid changes of genotype that may lead to crossing of threshold

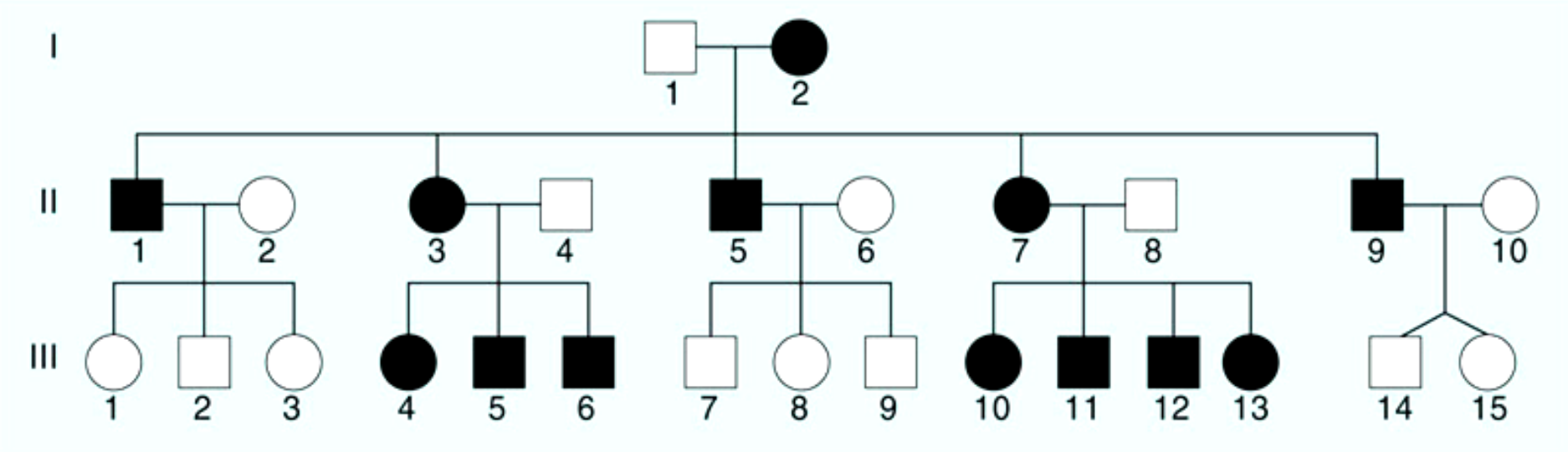

Normal mitochondria
Dysfunctional or mutant mitochondria
Progenitor cell showing heteroplasmy of mitochondria
At cell division, mitochondria are distributed unequally and do not necessarily reflect the ratio found in the progenitor cell
Threshold
70% mutant
80% mutant
DISEASE
60% mutant
NORMAL
40% mutant
NORMAL
100%
NORMAL
When the level of mutant mitochondria exceeds a certain threshold, the cell expresses dysfunction

Threshold effect

- % of mutant mtDNAs must be above a threshold to produce clinical manifestations
- % of mutant mtDNAs needed to cause cell dysfunction varies according to tissue oxidative requirements
- Disease signs especially manifest in
  - Tissues with a high energy expenditure: Dependent on oxidative metabolism
  - Specific tissues: Brain, Heart & Muscle

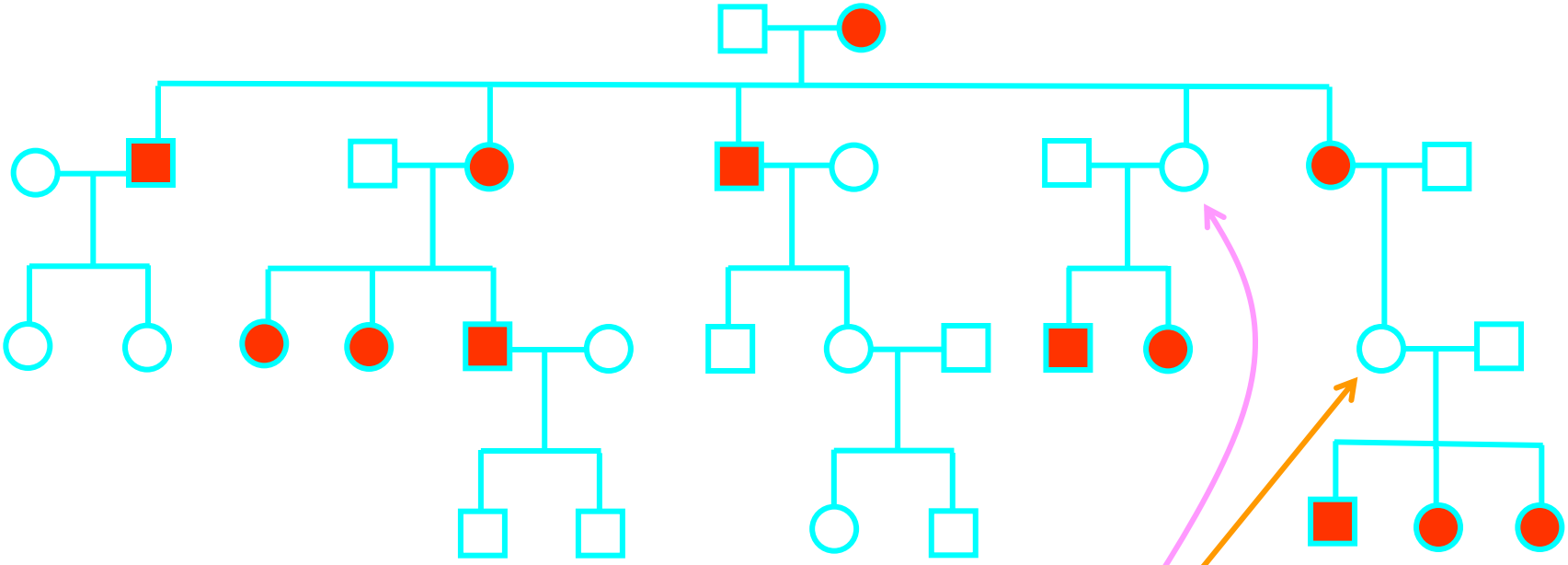
Pattern of Inheritance!

- What features characterize this pattern of inheritance?



- Mother's children all inherit the trait.
- Father's children never inherit the trait!

Mitochondrial inheritance



Complications

- Incomplete penetrance
- Variable expression

Mitochondrial Disease

- More than 40 known types
- Mitochondrial disease is a difficult disorder to identify because it can take many forms, and range from mild to severe.
- The problems it causes may begin at birth or not occur until later in adult life.

Mitochondrial Disease

- Mitochondrial disease is a chronic, genetic disorder that occurs when the mitochondria of the cell fails to produce enough energy for cell or organ function.
- The incidence about 1:3000-4000 individuals .

Examples of Diseases Due to Mutations and Deletions in Mitochondrial DNA

Abbreviation	MIM No.	Designation
LHON	535000	Leber's hereditary optical neuropathy (Missence M)
MELAS	540000	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
	540050	Lactic acidosis with stroke-like signs (Single base M)
MERRF	545030	Myoclonic epilepsy and ragged red fibers (Single base M)
MMC*	590050	Maternally inherited myopathy and cardiomyopathy
NARP*	551500	Neurogenic muscular weakness with ataxia and retinitis pigmentosa
CEOP*	258470	Progressive external ophthalmoplegia
KSS*	530000	Kearns-Sayre syndrome (ophthalmoplegia, pigmental degeneration of the retina, and cardiomyopathy)
PEAR*	557000	Pearson syndrome (bone marrow and pancreatic failure)
ADMIMY*	157640	Autosomal dominant inherited mitochondrial myopathy with mitochondrial deletion in the D loop (type Zeviani)

Mitochondrial DNA Diseases

This table lists only some of the disorders that can be caused by mutations in mitochondrial DNA. Certain of these conditions can also be caused by nuclear mutations or other processes that hinder mitochondrial function.

DISORDER	FEATURES
Alzheimer's disease	Progressive loss of cognitive capacity
CPEO (chronic progressive external ophthalmoplegia)	Paralysis of eye muscles and mitochondrial myopathy [see below]
Diabetes mellitus	High blood glucose levels, leading to various complications
Dystonia	Abnormal movements involving muscular rigidity; frequently accompanied by degeneration of the basal ganglia of the brain
KSS (Kearns-Sayre syndrome)	CPEO combined with such disorders as retinal deterioration, heart disease, hearing loss, diabetes and kidney failure
Leigh's syndrome	Progressive loss of motor and verbal skills and degeneration of the basal ganglia; a potentially lethal childhood disease
LHON (Leber's hereditary optic neuropathy)	Permanent or temporary blindness stemming from damage to the optic nerve
MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes)	Dysfunction of brain tissue (often causing seizures, transient regional paralysis and dementia) combined with mitochondrial myopathy [see below] and a toxic buildup of acid in the blood
MERRF (myoclonic epilepsy and ragged red fibers)	Seizures combined with mitochondrial myopathy [see below]; may involve hearing loss and dementia
Mitochondrial myopathy	Deterioration of muscle, manifested by weakness and intolerance for exercise; muscle often displays ragged red fibers, which are filled with abnormal mitochondria that turn red when exposed to a particular stain
NARP (neurogenic muscle weakness, ataxia and retinitis pigmentosa)	Loss of muscle strength and coordination, accompanied by regional brain degeneration and deterioration of the retina
Pearson's syndrome	Childhood bone marrow dysfunction (leading to loss of blood cells) and pancreatic failure; those who survive often progress to KSS

Extra Slide

The types of mitochondrial diseases are categorized according to the organ systems affected and symptoms present. Mitochondrial diseases might affect the cells of the brain, nerves (including the nerves to the stomach and intestines), muscles, kidneys, heart, liver, eyes, ears, or pancreas. In some patients, only one organ is affected, while in other patients all the organs are involved. Depending on how severe the mitochondrial disorder is, the illness can range in severity from mild to fatal.

Depending on which cells of the body are affected, symptoms might include:

Symptoms of abnormal mitochondrial

- Poor growth
- Loss of muscle coordination, muscle weakness
- Visual or hearing problems
- Developmental delays, learning disabilities
- Mental retardation
- Heart, liver, or kidney disease
- Gastrointestinal disorders severe constipation

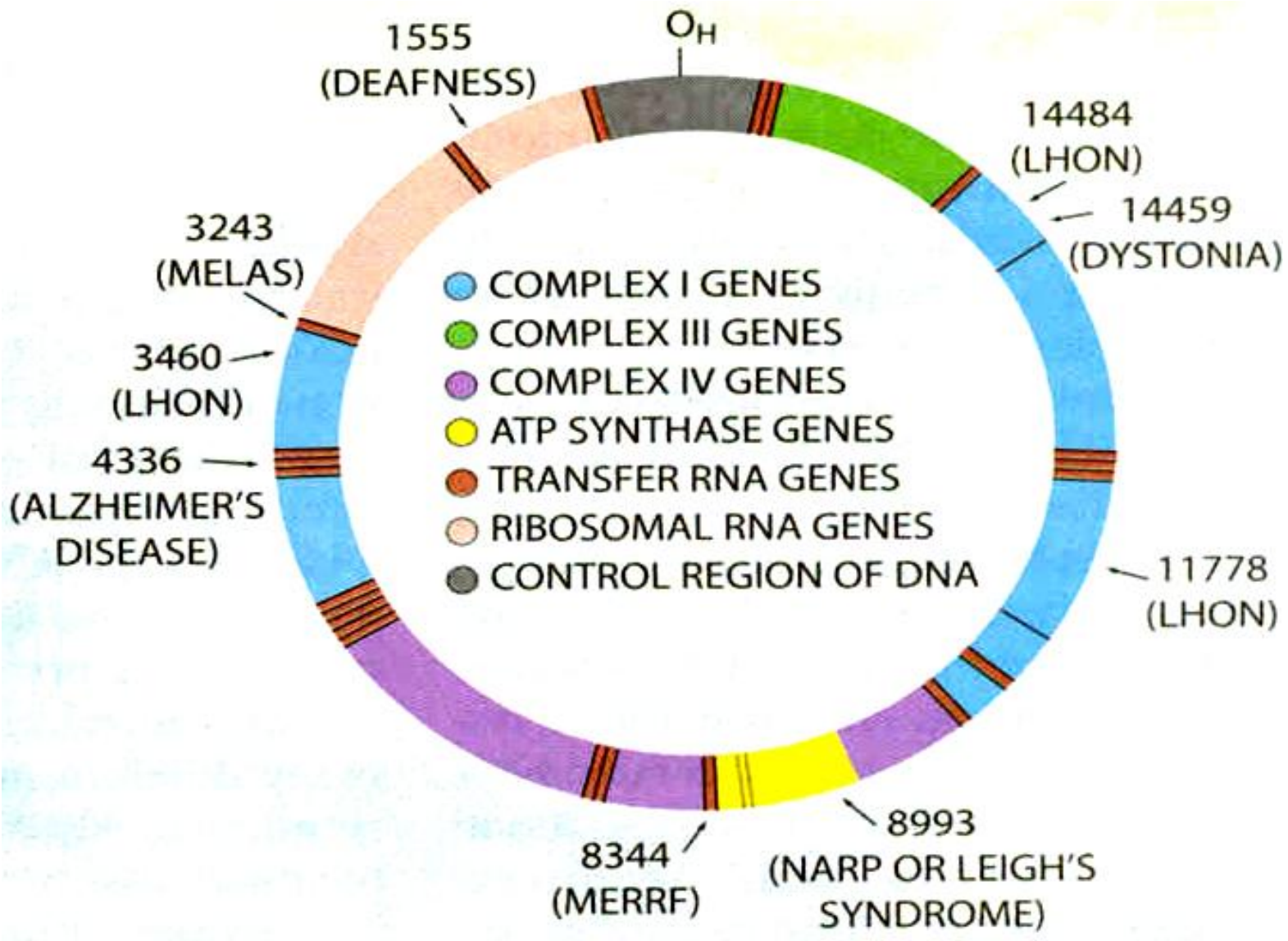
Symptoms of abnormal mitochondrial

- Respiratory disorders
- Diabetes
- Increased risk of infection
- Neurological problems, seizures
- Thyroid dysfunction
- Dementia

Laboratory Investigations

- DNA Analysis mutation Type
- Lactic acidosis: Variable, Blood & CSF
- Serum CK: Normal to 2x high (32%)
- Biochemistry
  - Respiratory chain dysfunction
  - Reduced activity of Complexes I & IV
- Muscle pathology
  - No ragged red fibers
  - EM mitochondria: Diffuse increase in number and size; Disorganized cristae
  - Preservation of myofibrils

Mitochondrial DNA mutations in human genetic



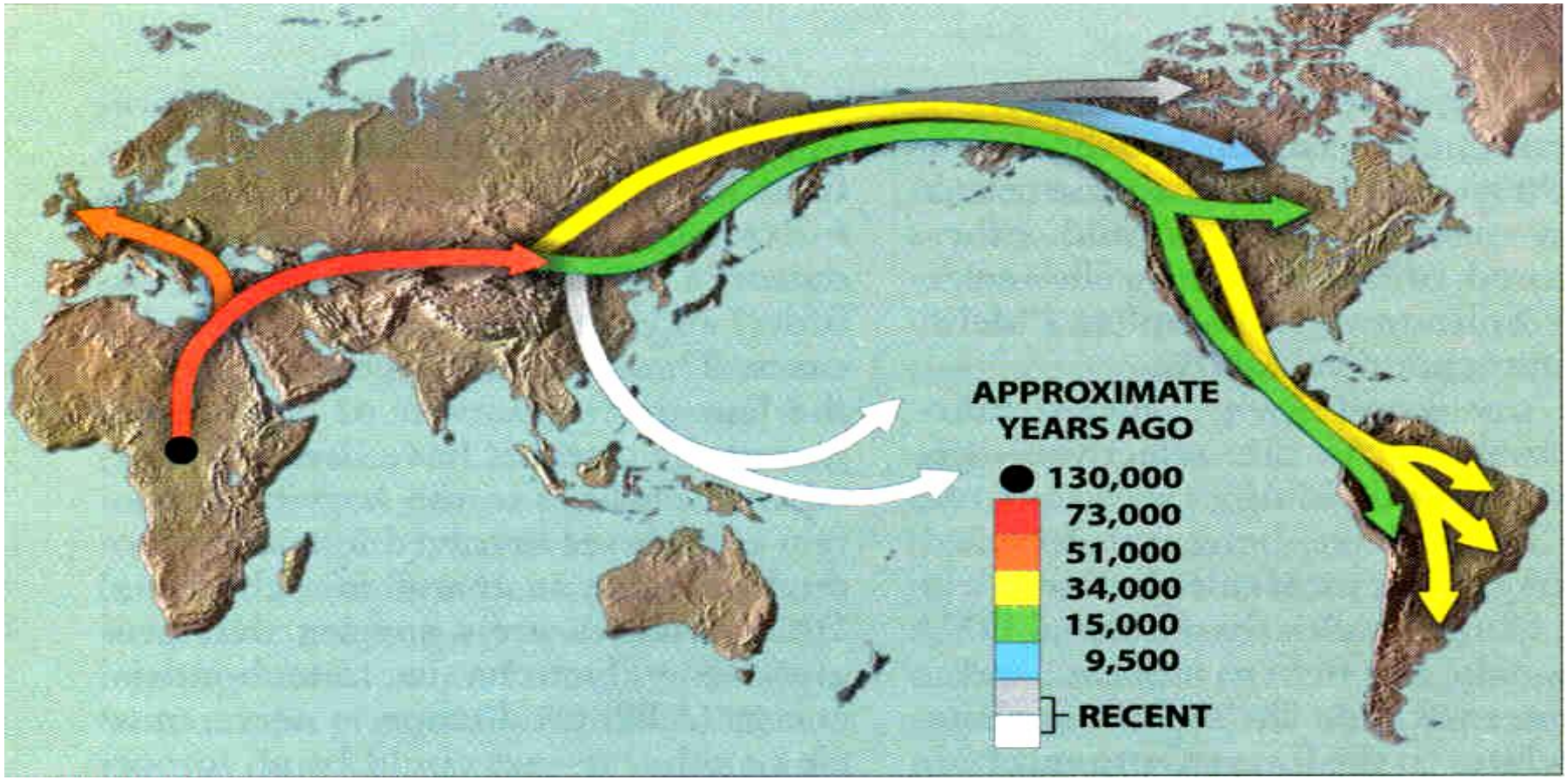
Treatment

- **There is no cure for mitochondrial disease**
- Some helpful treatments include vitamins such as thiamine (B1), riboflavin (B12), vitamin C, and vitamin E. Lipoic acid and coenzyme Q-10 are also useful supplements.
- Some researchers are examining using drugs to block lactic acid buildup in the body that is common in mitochondrial disease. Others are trying very low carbohydrate diets to reduce the workload for mitochondria.

Mitochondrion

- A cellular organelle probably of endosymbiotic origin that resides in the cytosol of most nucleated (eurkaryotic) cells.
- This organelle produces energy by oxidising organic acids and fats with oxygen by the process of **oxidative phosphorylation** and generates oxygen radicals (reactive oxygen species ROS)as a toxic by-product
- Contains small circular DNA.
- No crossing over or DNA repair.
- Many copies of the mitochondrial genome per cell.
- 37 genes, no histones, no introns.
- Maternal inheritance

Mitochondrial DNA polymorphisms track human migrations

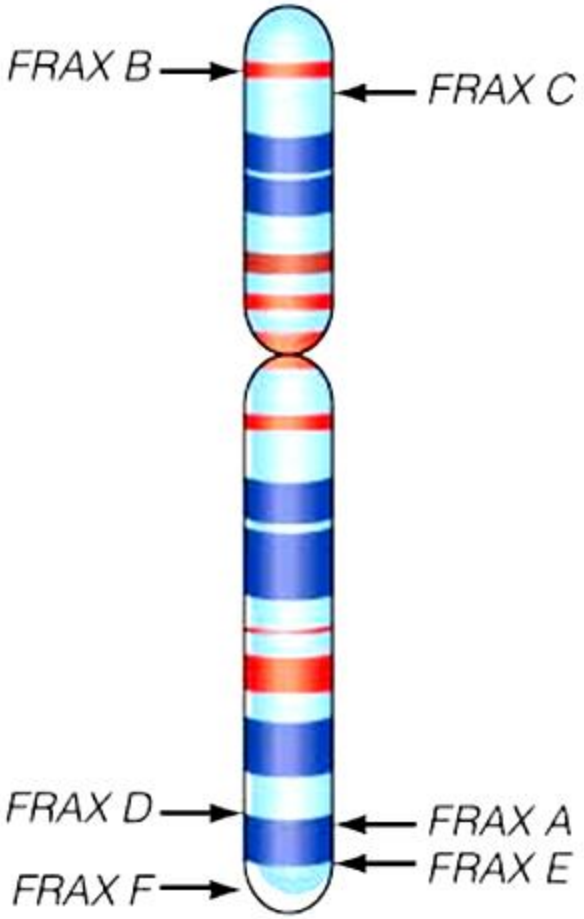


All humans descend from a small group of Africans
This group originated in central Africa ~200,000 years ago
The founding group was small (10^2-10^4 people)
Descendants of this group replaced all other hominids everywhere in the world

FRAGILE X SYNDROME

What is Fragile X Syndrome (FXS)?

- Inherited disease cause of MR
- X-linked disease
- Incidence of 1:4500 males, 1:9000 females
- Premutation carrier 1:1000 males, 1:400 females



Fragile X Syndrome:
One gene, Three Major Disorders

Fragile X syndrome: in males and females with full mutation (200-2,000 repeats) or mosaicism (full mutation+premutation). Life-long disorder.

Fragile X tremor ataxia syndrome (FXTAS): predominantly older (>50 years) males with premutation (61-199 repeats). Manifestations: gait ataxia, intention tremor, cognitive impairment (frontal lobe dementia).

Premutation-related disorders: (FXPOI), POI, females with emotional problems and perseverative thinking, children (mainly boys) with intellectual disability and/or autism.

Intermediate or gray zone (41-60 repeats) : ??

Premutation

- People with a fragile X premutation do not have fragile X syndrome but might have another fragile X-associated disorder.
- Some people with fragile X premutations have noticeable symptoms, and others do not.
- Mild intellectual disability
- Shy personality and selective lack of speech

Premature Ovarian Failure/Primary Ovarian Insufficiency POF/POI

POF/POI is a condition in which women develop loss of regular menstrual cycles. Infertility, and ovarian hormone deficiency not normally observed until the age of menopause. In approximately 96% of cases , no mechanism can be identified to explain the OI.

- ~15% of women with *FMR1* premutation
- 0.8-7.5% *FMR1* premutation in sporadic POI
- 13% *FMR1* premutation in familial POI

Wittenberger et al. Fertil Steril 87:456-465, 2007

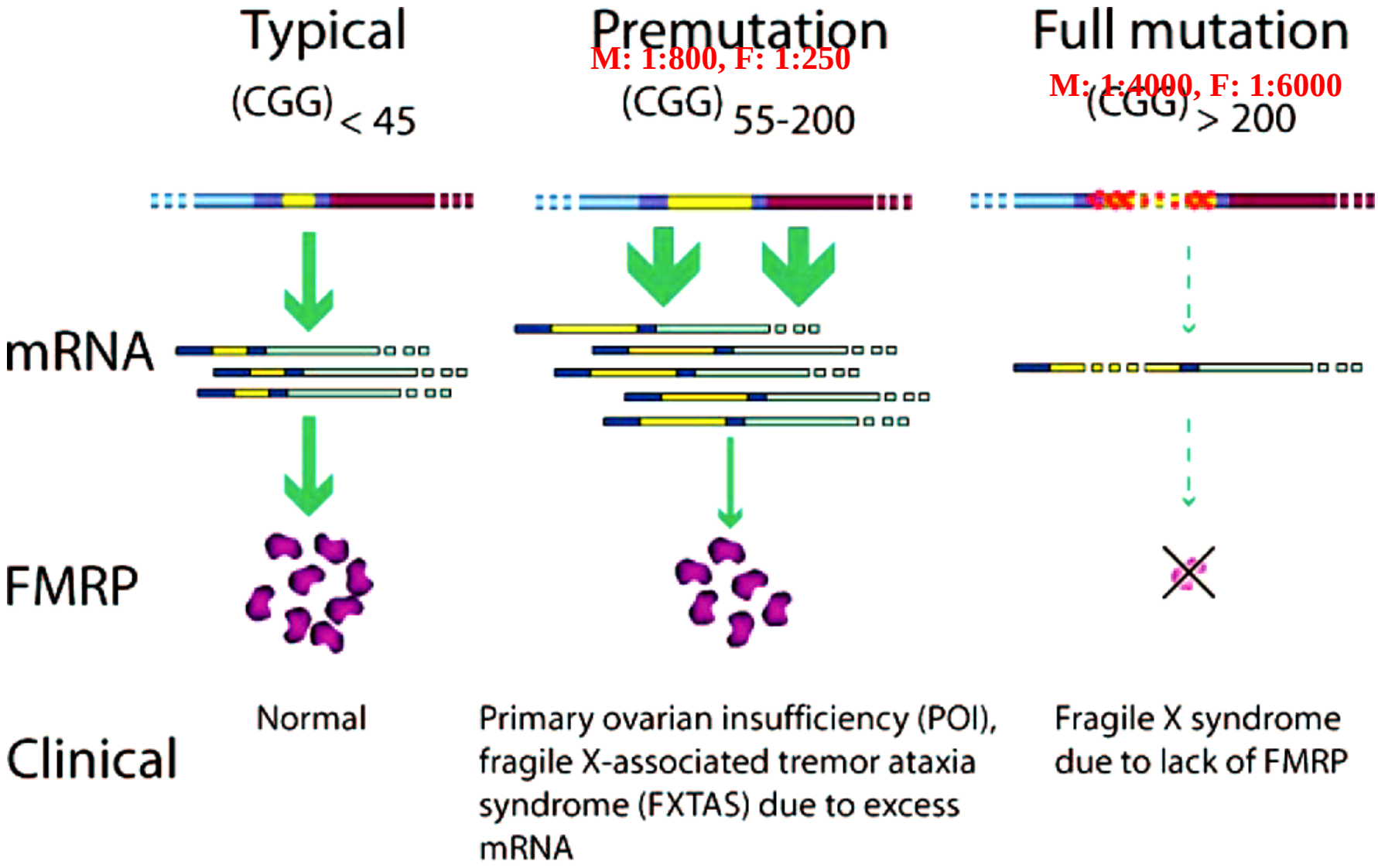
FMR1 Expression

- Mutation is located at Xq27.3
- Mutation of Fragile X Mental Retardation (FMR1 Gene)
  - Polymorphic $(CCG)_n$ repeat in the 5' untranslated reagion of exon 1
  - Hypermethylation of a CpG island upstream of the mutation
- Expressed in highest levels in the Brain and Testes
- Slightly lower level in the Placenta, Lungs, Liver, and Kidneys
- FMR1 expression turned on early in embroyonic development
- This gene could not produce protein which is necessary for brain development

Autism and FXS

- Autism - characterized by impaired Social Interaction and Communication , and by restricted and repetitive behavior.
- Autism → behavioral diagnosis
- FXS → genetic diagnosis
- 15 - 33% of FXS children have autism
- 2 - 6% of children with autism is diagnosed with FSX

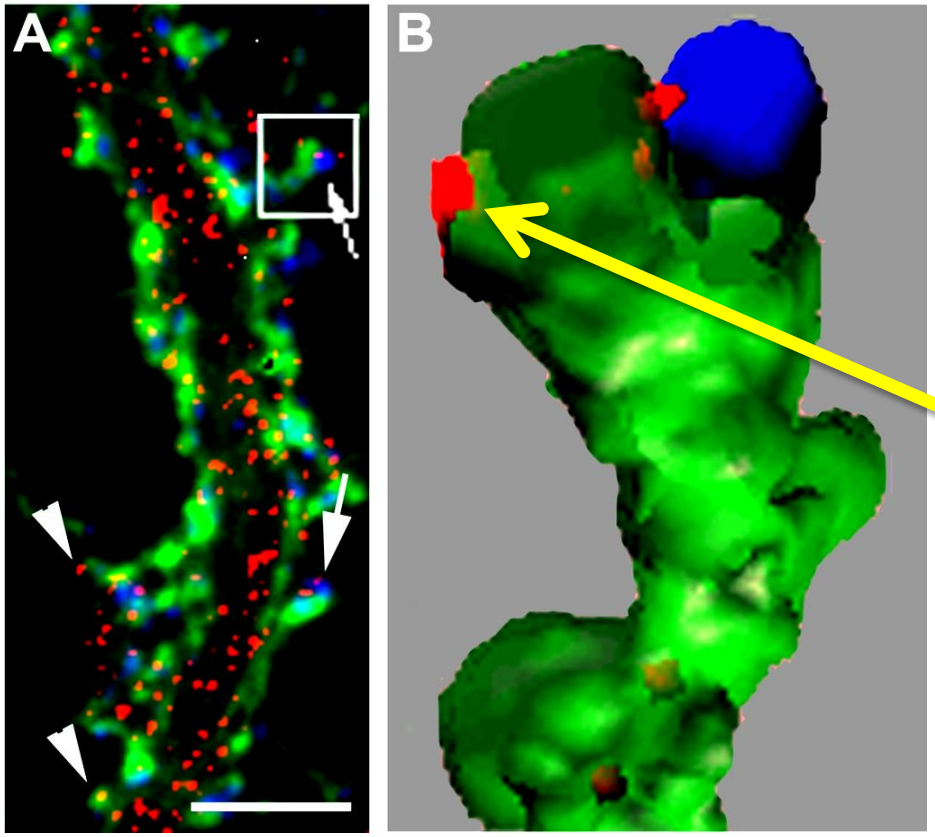
One Gene (*FMR1*):
Three (or More) Disorders



The FMR protein (FMRP)

- The FMRP protein probably forms has a key role in regulation of translation.
- Binds a subset of brain mRNAs including its own.
- In brain, it shuttles a subset of mRNA to the dendritic spines.
- Absence of the protein (deletion) cause immature dendritic spine morphology.

FMRP in Dendrites (Brain Connections)



FMRP in RED in tip of neural dendrites and where processes are forming

Antar et al, J. Neurosci 2004

FMRP regulates proteins made at brain connections (in dendrites) - proteins have to be made in right amount for connection to mature and work right.

Fragile X syndrome

Clinical manifestations

- Cognitive difficulties
- Attention and behavioral problems
- Macro-orchidism
- Mild facial dysmorphologies, Large prominent ears and a long face
- Intellectual disability
- Speech and language delay
- Emotional problems
- Connective tissue abnormalities
- Anticipation

Co-Occurring Conditions and Characteristics

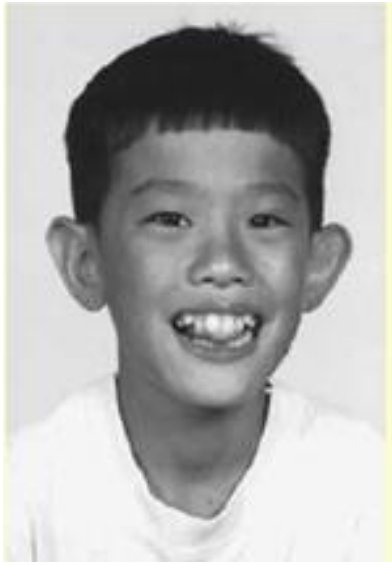
Males

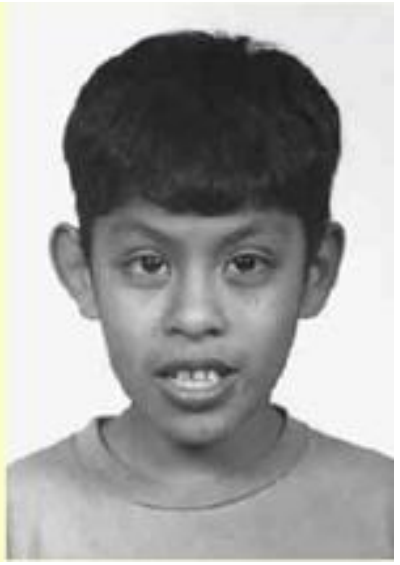
- Developmental Delay (DD) or Intellectual Disability (ID)
- Attention Problems
- Anxiety
- Hyperactivity
- Autism
- Self-Injury
- Aggressiveness
- Seizures
- Depression

Females

- Attention Problems
- Developmental Delay or Intellectual Disability
- Anxiety
- Hyperactivity
- Depression
- Autism
- Aggressiveness
- Self-Injury
- Seizures

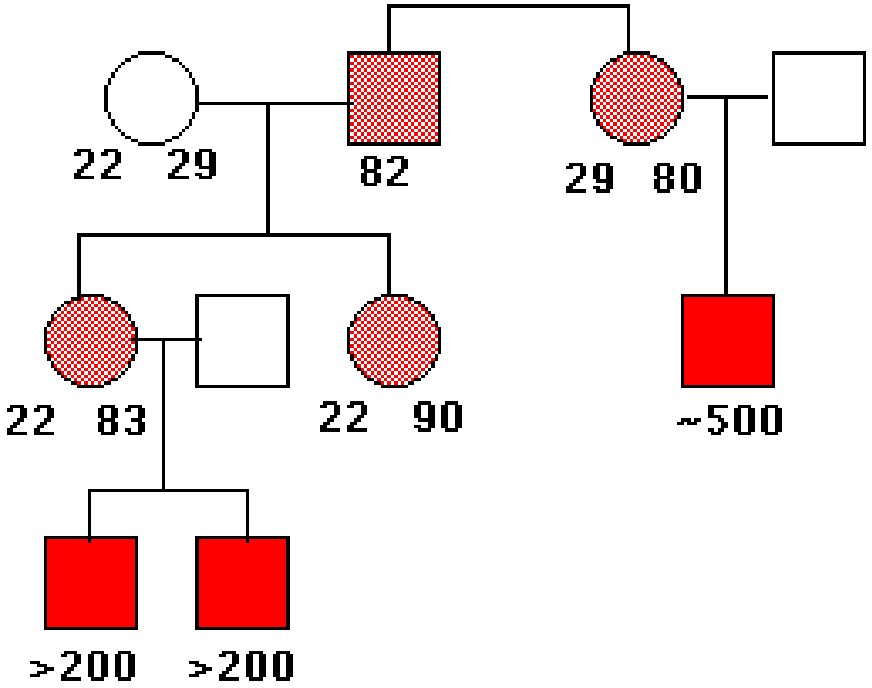
FRAGILE X SYNDROME



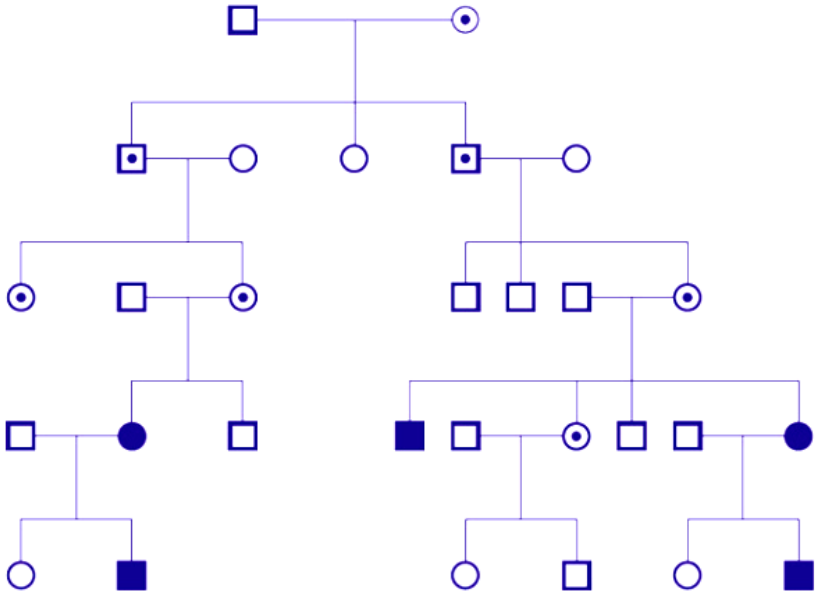


Genetic Anticipation Explained

A Fragile X family



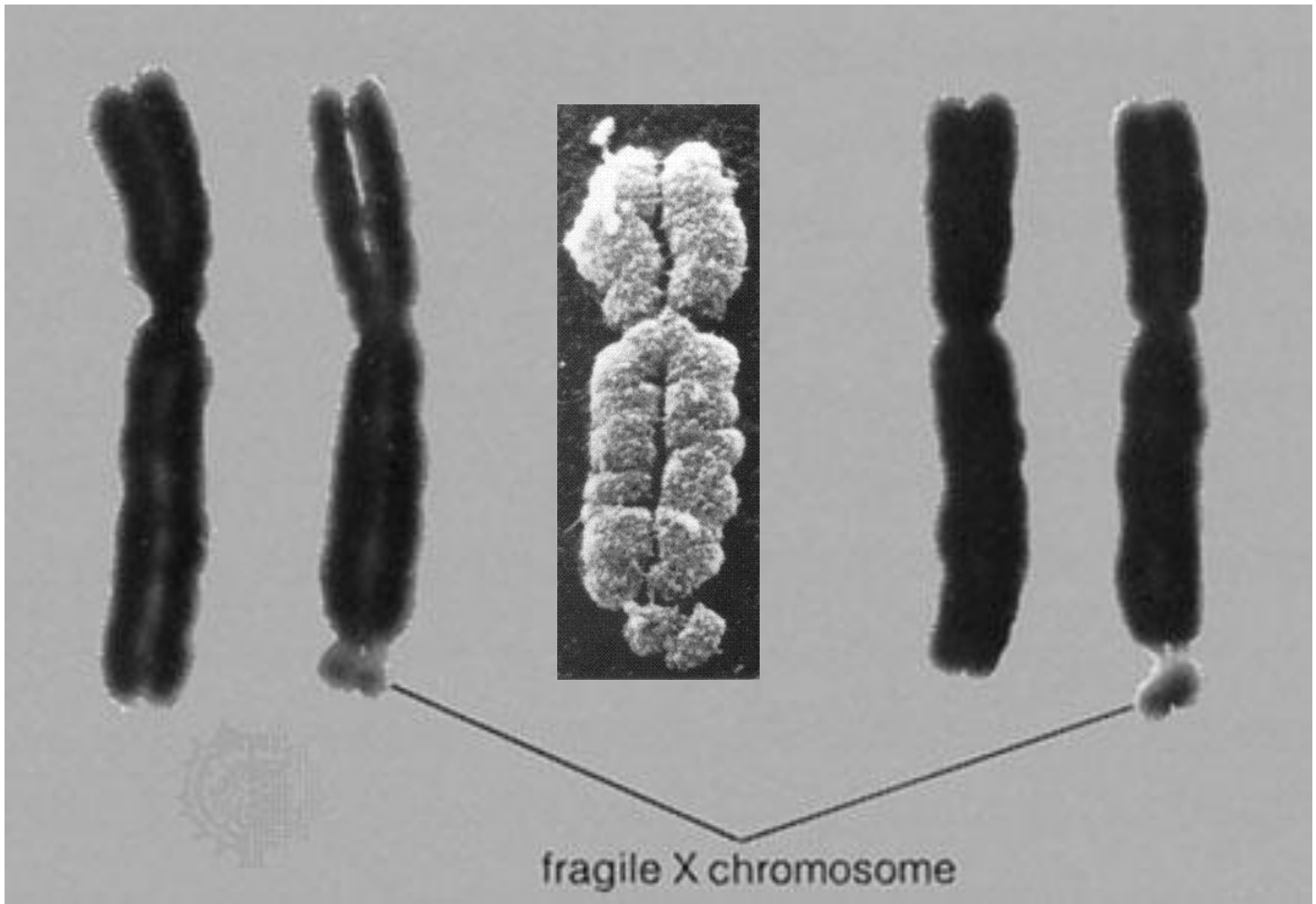
Fragile X syndrome has a complicated inheritance



- Progressive increase in size of CGG repeat
- Requires a female transmission to go to full mutation

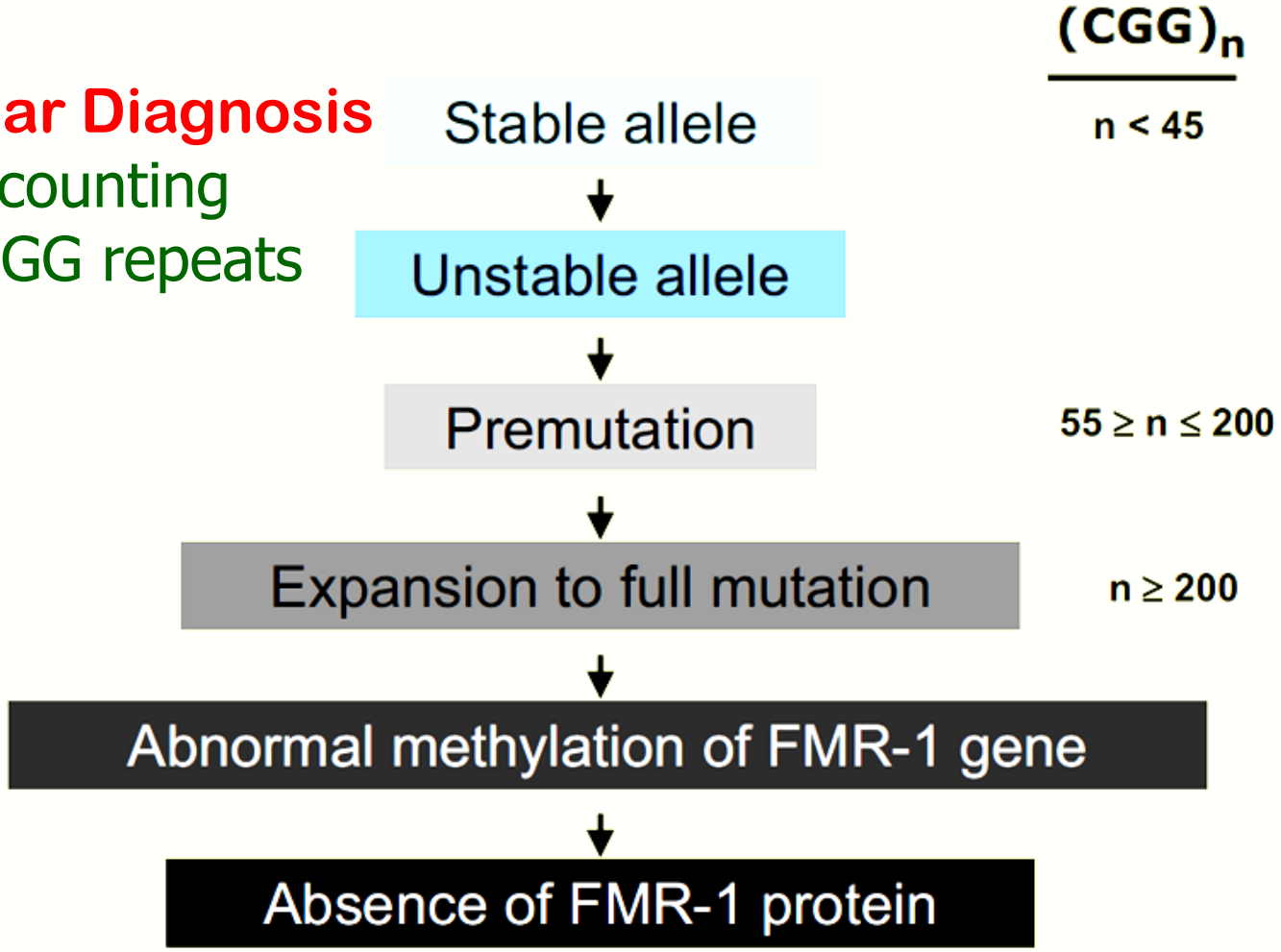
FRAXA- rare folate-sensitive fragile sites: mutation stages

- The fragile site is seen cytogenetically



FMR-1 gene: a triplet repeat disease

Molecular Diagnosis
By counting
the CGG repeats



Rules of Inheritance

Autosomal Recessive

- Appears in both sexes with equal frequency
- Trait tend to skip generations
- Affected offspring are usually born to unaffected parents
- When both parents are hetzyg. ~1/4 of the progeny will be affected
- Appears more frequently among the children of consanguine marriages

Autosomal Dominant

- Appears in both sexes with equal frequency
- Both sexes transmit the trait to their offspring
- Does not skip generations
- Affected offspring must have an affected parent unless they posses a new mutation
- When one parent is affected (het.) and the other parent is unaffected, ~ 1/2 of the offspring will be affected
- Unaffected parents do not transmit the trait

Mitochondrial

- Trait is inherited from mother only
- All children of a mother are at risk to be affected or carriers
- An individual will be affected with a mitochondrial disorder if the percentage of mitochondria possessing mutated mtDNA reaches a threshold value beyond which the normal mtDNA does not compensate for the mutated mtDNA.

X-Linked Dominant

- Both males and females are affected; often more females than males are affected
- Does not skip generations. Affectd sons must have an affected mother; affected daughters must have either an affected mother or an affected father
- Affected fathers will pass the trait on to all their daughters
- Affected mothers if heterozygous will pass the trait on to 1/2 of their sons and 1/2 of their daughters

X-Linked Recessive

- More males than females are affected
- Affected sons are usually born to unaffected mothers, thus the trait skips generations
- Approximately 1/2 of carrier mothers' sons are affected
- It is never passed from father to son
- All daughters of affected fathers are carriers

Y-Linked Dominant

- Only males are affected
- It is passed from father to all sons
- It does not skip generations