

1. Intro

# Non-Mendelian Genetics Part 2

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2. Non-Mendelian Genetics

## NON-MENDELIAN GENETICS

- Mosaicism
- Uniparental Disomy
- Genomic Imprinting
- Triplet Repeat Disorders

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3.

## Mosaicism

### Mosaicism

- Mosaicism: presence of more than one cell line in an individual
- Somatic Mosaicism: usually caused by a post-zygotic mutation which affects a certain percentage of cells in an individual
  - Mosaic Down Syndrome
  - Segmental Neurofibromatosis
  - McCune-Albright Syndrome

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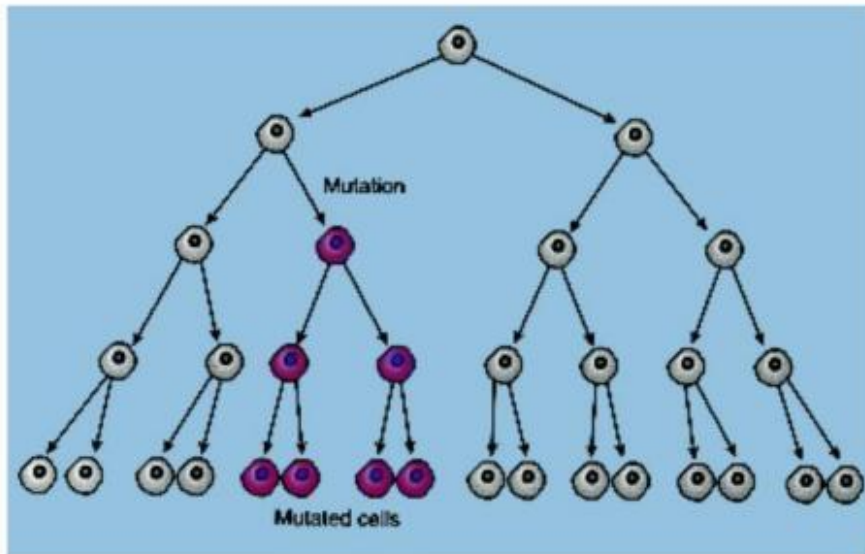
## Gonadal Mosaicism

### Gonadal Mosaicism

- Gonadal Mosaicism: presence of more than one cell line in the gonads but not in the rest of the body (somatic cells).
- Mutation occurred in a precursor sperm or egg cell and is passed on to all derivatives of that cell. The remainder of germ and somatic cells in the body do not carry the mutation.

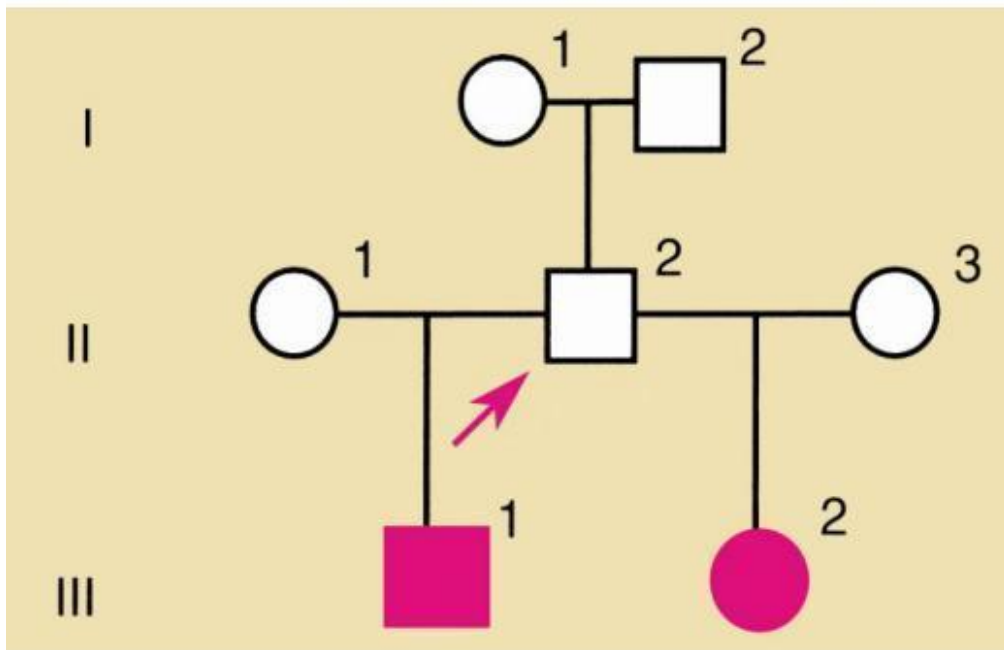
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5. Mutation Diagram



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6. Diagram



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## Gonadal Mosaicism

### Gonadal Mosaicism

- Detected when 2 or more offspring present with an autosomal dominant disorder in the face of a negative family history
- neither parent has the disorder, although one has gonadal mosaicism for the mutation
- cannot test individual sperm/eggs, so must use empiric recurrence risks and offer prenatal diagnosis in all subsequent pregnancies

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## Uniparental Disomy

### Uniparental Disomy

- Presence of two homologous chromosomes inherited from only one parent
- ISODISOMY: parent passes on two copies of the same chromosome (non-disjunction in meiosis II)
- HETERODISOMY: parent passes on one copy of each homolog (non-disjunction in meiosis I)

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9. Uniparental Disomy: postulated mechanisms

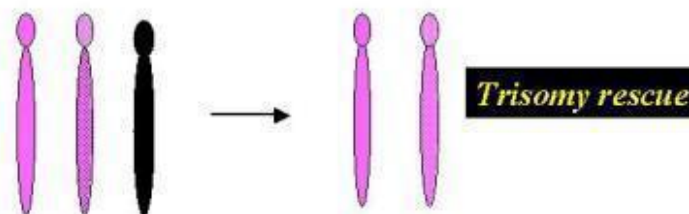
## Uniparental Disomy: postulated mechanisms

- Trisomic conception with postzygotic loss of a chromosome
- fertilization of a nullisomic gamete by a disomic gamete
- compensatory duplication in a monosomic cell

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10. Heterodisomy and Isodisomy

### Heterodisomy



### Isodisomy



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## Uniparental Disomy

### *Uniparental Disomy*

- ☞ **Clinically significant when it involves chromosomes with imprinted genes.**
- ☞ **Likely to play role in the etiology of pregnancy loss and unexplained IUGR**
- ☞ **Known clinical phenotypes exist with Paternal UPD 6, 11, 14, 15 and Maternal UPD 7, 14, 15, 16**

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## Genomic Imprinting

### Genomic Imprinting

- Differential modification of the maternal and paternal genetic contributions to the zygote
- some genes are expressed preferentially in either the maternal or paternal genotype
- this can lead to differences in phenotype if a patient has uniparental disomy or a heterozygous deletion for an imprinted region of a chromosome

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13. Mechanism of Imprinting

## *Mechanism of Imprinting*

### *☞ DNA Methylation*

- ☞ 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)

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14. Prader Willi and Angelman Syndromes: Imprinting

## Prader Willi and Angelman Syndromes: Imprinting

- Both syndromes are caused by an identical deletion on chromosome 15
- Prader Willi: (hypotonia, mental retardation and obesity) - deletion from paternal allele
- Angelman: (severe mental retardation, movement disorder and seizures) - deletion from maternal allele

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15. Prader Willi and Angelman Syndromes: Imprinting

## Prader Willi and Angelman Syndromes: Imprinting

- Genes from the 'critical' region for Prader Willi Syndrome are only actively transcribed on the chromosome marked as having been passed on from the dad
- if the 'critical' region is deleted in the paternal chromosome, (and normally turned off on the maternal chromosome), then these critical genes go unexpressed, and the syndrome will result.

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16. Prader Willi and Angelman Syndromes: Imprinting

## Prader Willi and Angelman Syndromes: Imprinting

- Angelman Syndrome: 'critical' gene is expressed only on the chromosome passed on from mom
- deletions on maternal chromosome 15 result in no expression of 'critical' gene. (Normally that gene is turned off on the chromosome marked as having come from dad)

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17. Genetic Amplification: Triplet Repeat Disorders

## Genetic Amplification: Triplet Repeat Disorders

- Genetic Amplification (anticipation): increase in severity of a phenotype in successive generations
- now known to be due to specific areas of instability in the genome
- normally triplet repeat sequences are stable during meiosis and mitosis
- sequence copy number is transmitted as a polymorphism from parent to child

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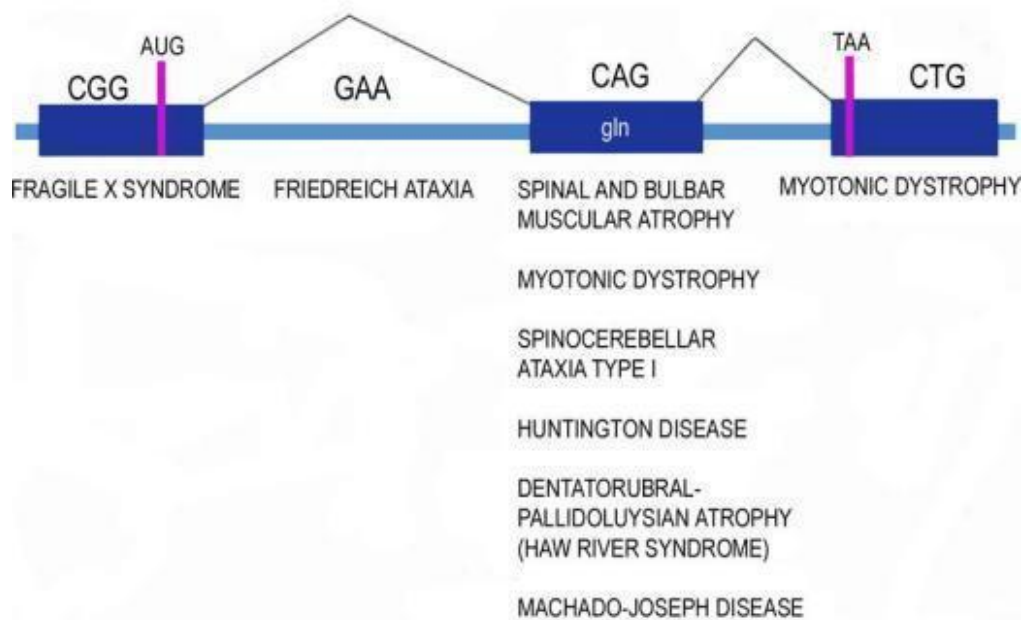
18. Genetic Amplification

## Genetic Amplification

- In affected families, the area is unstable and can lead to progressive amplification of the gene sequence with each succeeding generation
- often see a direct relationship between severity of phenotype and repeat copy number
- can see 'premutation' in clinically asymptomatic individual

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19. Diagram



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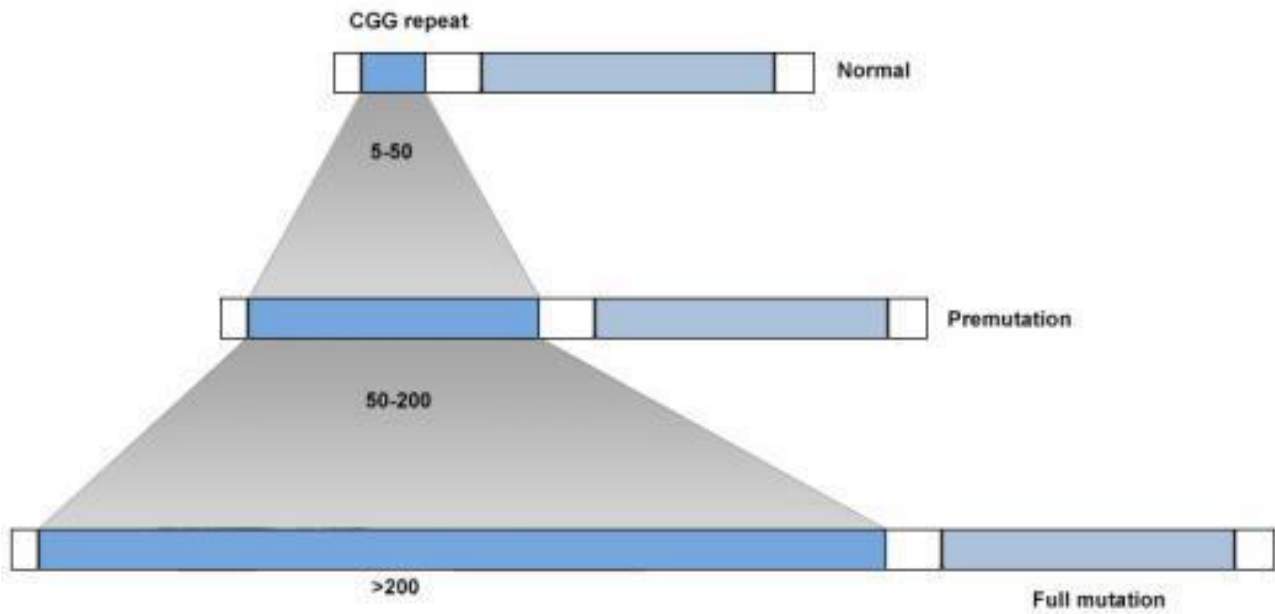
20. Fragile X Syndrome

### *Fragile X Syndrome*

- ☞ **Most common inherited form of mental retardation (1/1000 males)**
- ☞ **Due to unstable CGG repeat at Xq27**
- ☞ **All full mutations derive from a premutation (56-200 repeats)**
- ☞ **Expansion from pre- to full mutation only occurs through female meiosis**
- ☞ **Severity of disease correlates with # of CGG repeats**

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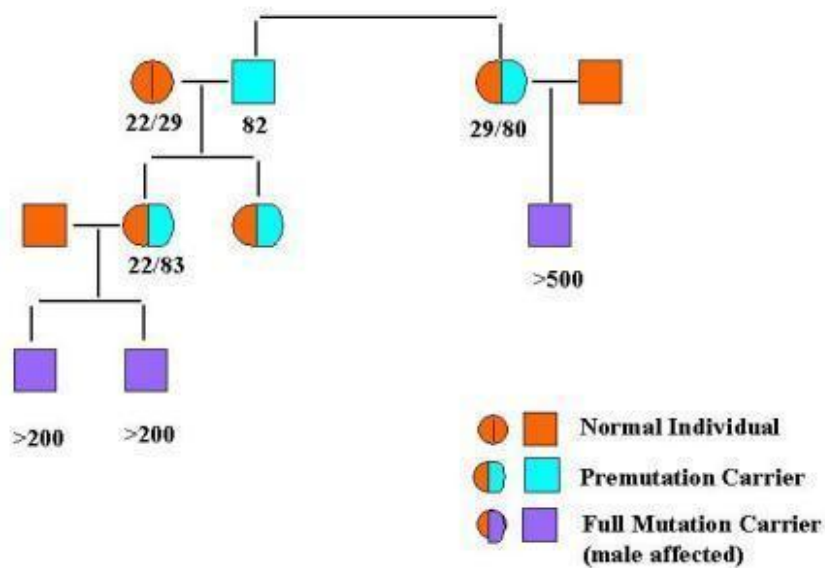
21. Normal, Premutation, Full Mutation



Adapted from *Human Genetics*, 2nd ed. Kod  
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22. Fragile X Syndrome Pedigree

*Fragile X Syndrome Pedigree*



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23.

## Myotonic Dystrophy

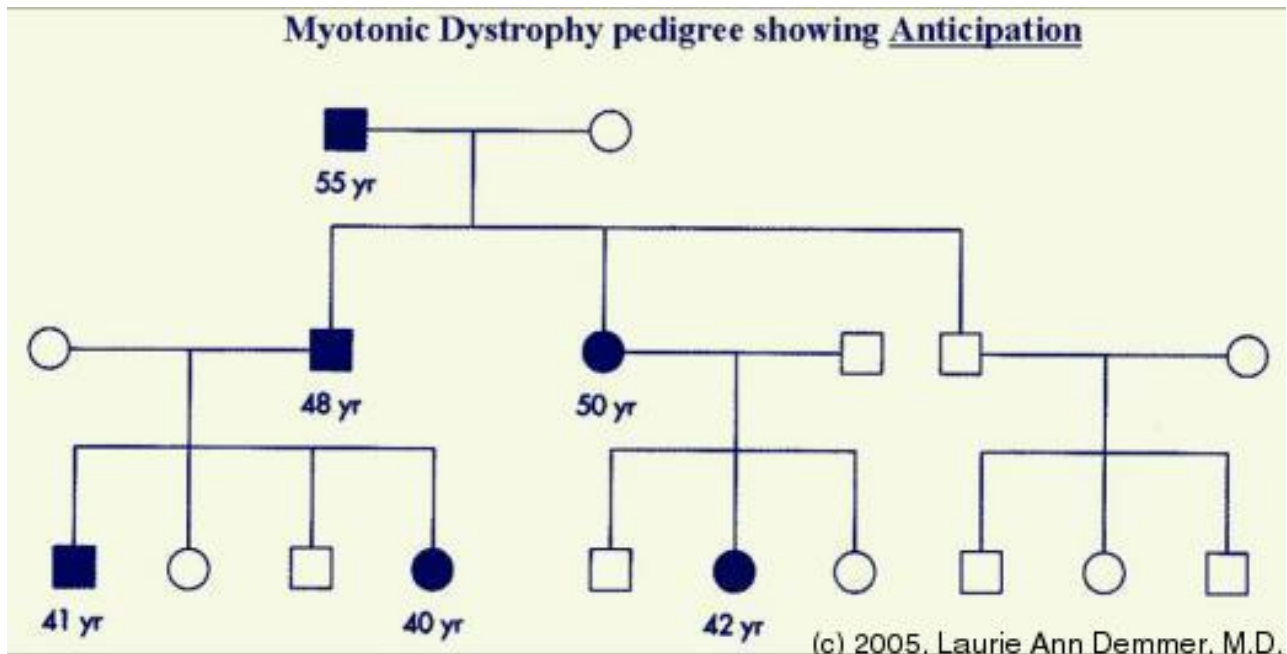
### Myotonic Dystrophy

- Autosomal Dominant Disease showing anticipation
- Clinical findings include myotonia, cataracts, cardiac arrhythmias, temporal balding, endocrinopathies
- Unstable GCT repeat in the MT-PK gene
- Congenital form with maternal transmission only

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## Myotonic Dystrophy



25.

## Huntington Disease

### Huntington Disease

- Autosomal Dominant Disorder; typically without anticipation
- occasional juvenile-onset: always paternal transmission
- Clinical findings include progressive involuntary movements and cognitive loss, leading to complete debilitation. Psychiatric problems (depression) also common

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## Huntington Disease

### Huntington Disease

- Onset typically in the 30's and progresses for 10-20 years until death
- Caused by expansion of a triplet encoding glutamine in the 5' end of the gene.
- Normal allele: 11-34 repeats
- Disease allele: 42-66 repeats
- Pre-symptomatic testing is available, but since disease is incurable, careful education and counseling need to be provided to at-risk individuals

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