1. Introduction to Medical Genetics

# Introduction to Medical Genetics

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2. Base Pairs

| | |
|---|---|
| Human Genome | 3,000,000,000 bp |
| Chromosome | 150,000,000 bp |
| Gene (avg.) | 50,000 bp |
| Coding Sequence | 3,000 bp |
| Unit of Genetic Code | 3 bp |
| Mutation | 1 bp |

3. Non-Mendelian Genetics Part 1

# NON-MENDELIAN GENETICS
# Part 1

- Mitochondrial Genetics
- Multifactorial Traits

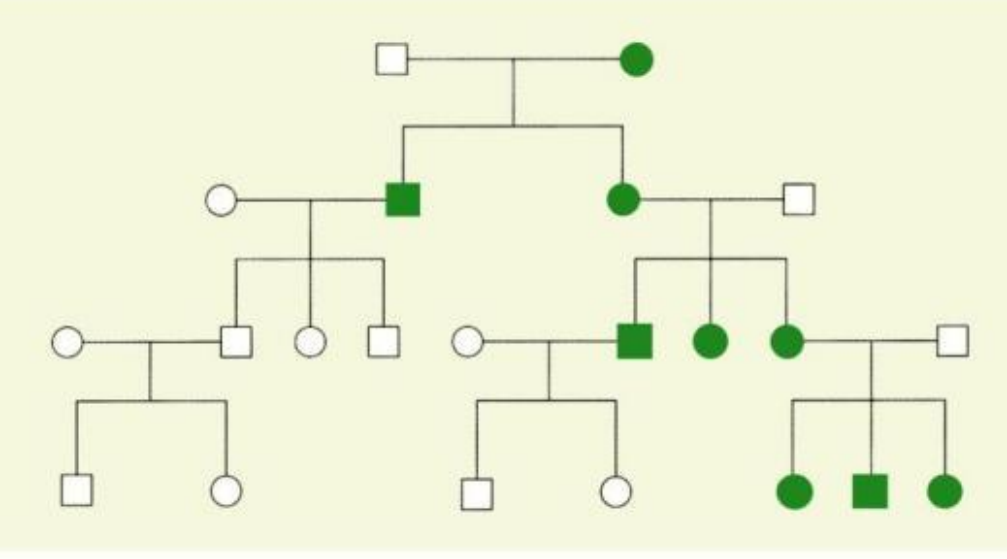


4. Mitochondrial Inheritance

## Mitochondrial Inheritance

- MITOCHONDRIA HAVE THEIR OWN DNA!!!!
- 16.5kb circular dsDNA containing 37 genes
- 2 rRNAs, 22 tRNAs, 13 ox. phos. subunits
- only mitochondria from **oocyte** contribute to zygote
- MATERNAL INHERITANCE

5. Diagram



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6. Mitochondrial Inheritance

## Mitochondrial Inheritance

- Each cell contains hundreds of copies of mtDNA
- ***HETEROPLASMY***: mixture of normal and abnormal mtDNA
- ***HOMOPLASMY***: all mtDNA is the same (either normal or abnormal)
- with cell division, the many copies of mtDNA segregate randomly into the 2 daughter cells

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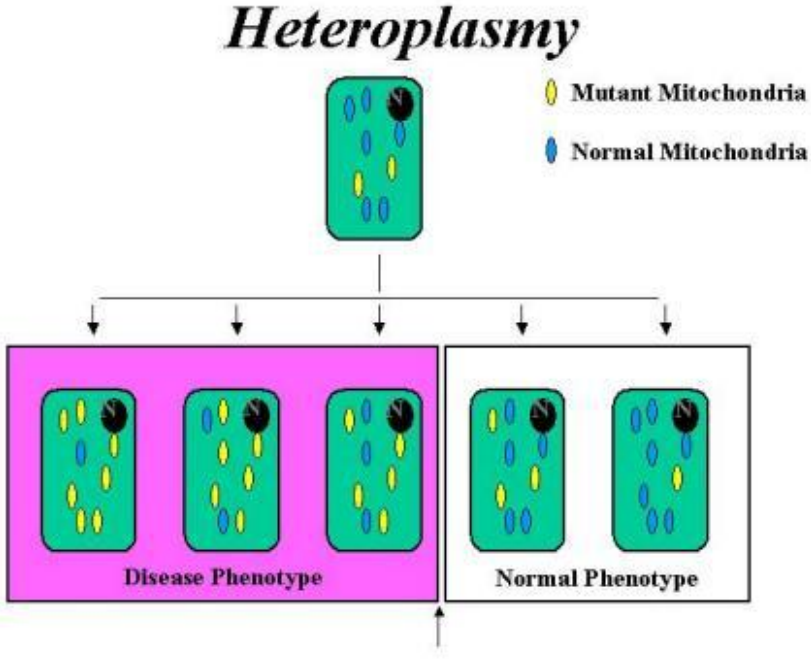
7. Heteroplasmy

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8. Mitochondrial Inheritance

## Mitochondrial Inheritance

- Different eggs can vary from mostly normal mtDNA to mostly abnormal
- Clinical phenotype will vary according to %-age of abnormal DNA
- %-age of abnormal DNA can change over time due to **random drift** as cells divide, or to a possible **replicative advantage** of one type of mtDNA over another

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9. Mitochondrial Inheritance

## Mitochondrial Inheritance

- Tissues with **high energy requirements** are most likely to be affected (brain, muscle)
- Symptoms typically progress with age
- Often need **muscle biopsy** to confirm diagnosis
- Prenatal diagnosis is possible but prognosis difficult to predict due to heteroplasmy

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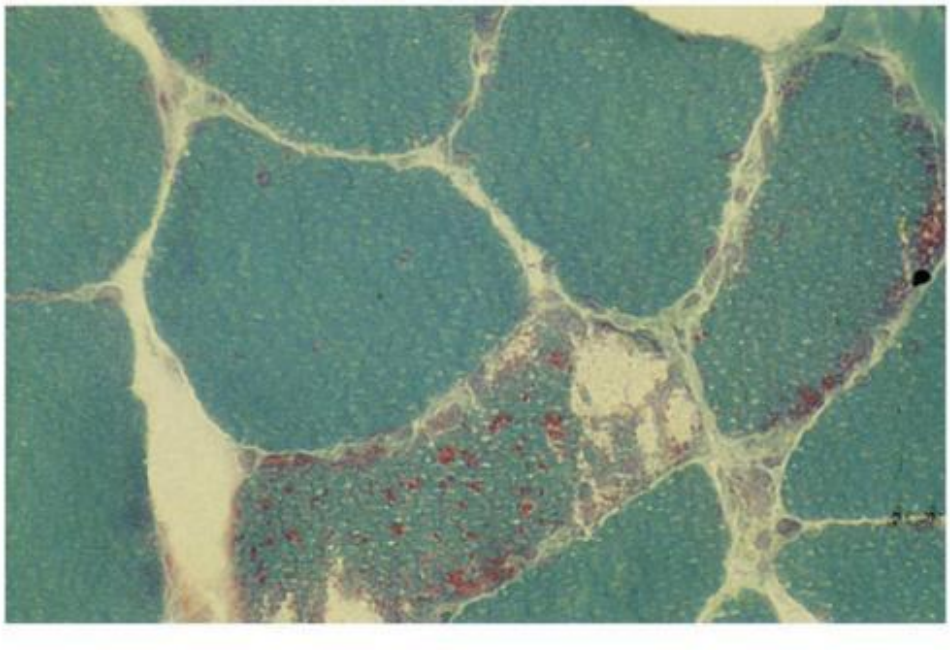
10. Slide



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11. Multifactorial Inheritance

## Multifactorial Inheritance

- Polygenic trait results from the combined influence of multiple genes.
- Multifactorial trait results from the combined influence of multiple genes and environmental factors

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12. Multifactorial Inheritance

## Multifactorial Inheritance

- **Quantitative Trait**:
  - results from the additive effect of multiple genetic and environmental factors
  - can be measured on a numerical scale (height, weight, blood pressure, intelligence)
  - follows a normal, or 'bell-shaped' distribution in populations

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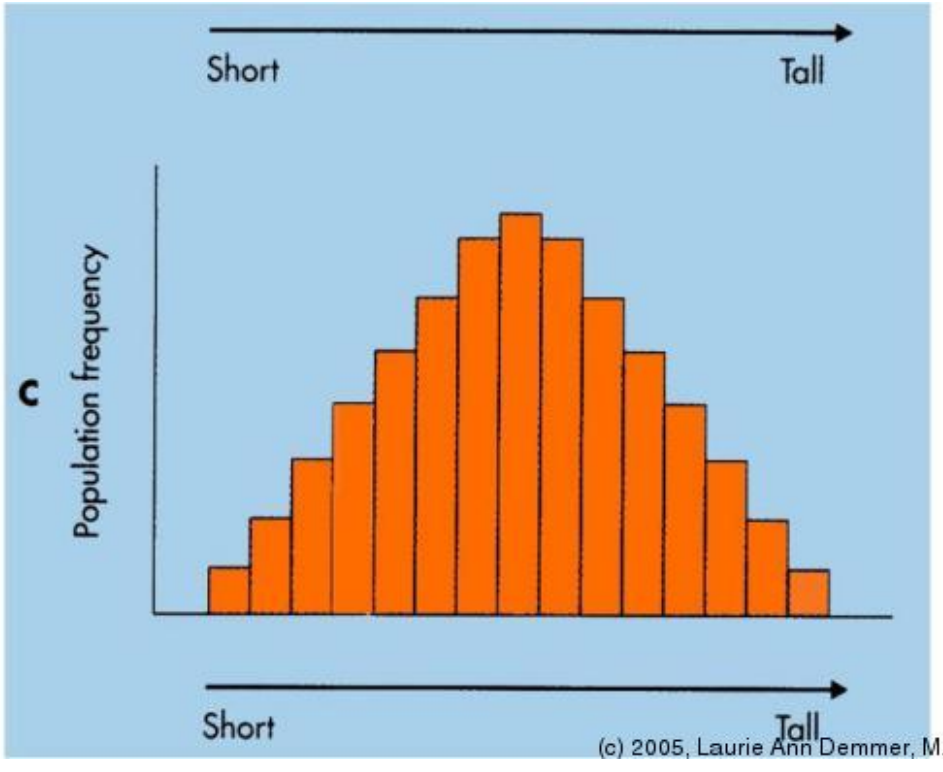
13. Short and Tall




14. Threshold Traits

## Threshold Traits

- Trait is either present or absent (club foot, diabetes, cleft lip)
- bell-shaped distribution in the population with respect to **liability** to a trait
- only those individuals exceeding the **threshold** on the liability scale will express the trait

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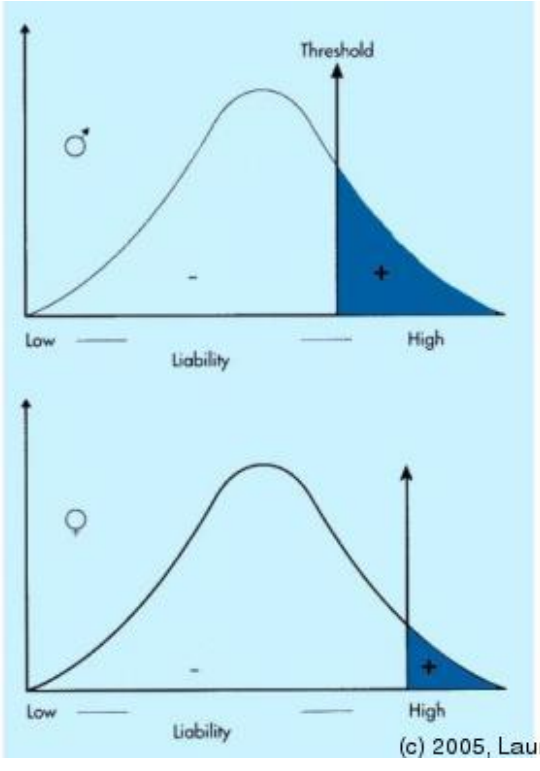
15. Threshold and Liability

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16. Multifactorial Inheritance

# Multifactorial Inheritance

- Can see a familial concentration without a set pattern of inheritance
- absence of clear biochemical defects resulting from a single abnormal gene
- considerable variation in severity and expression of the phenotype
- often sex differences in the frequency of occurrence

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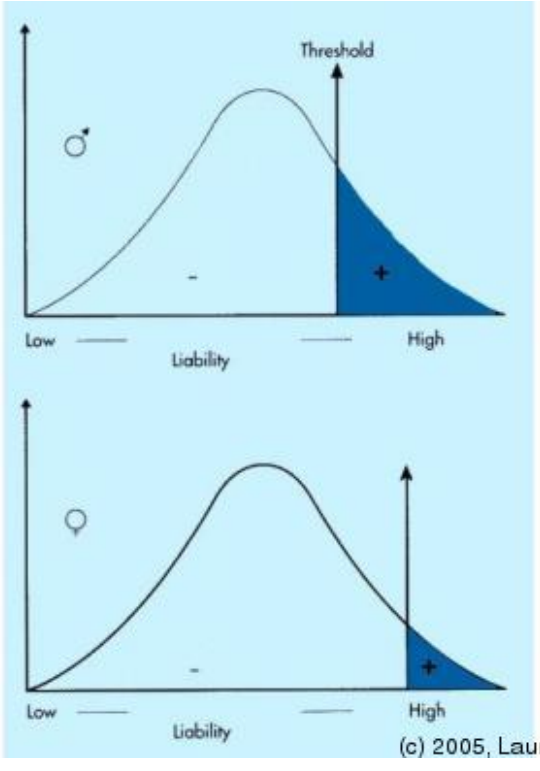
17. Threshold and Liability

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18. Recurrence Risk for Siblings of Pyloric Stenosis Patients

## Recurrence Risk for Siblings of Pyloric Stenosis Patients

| | Males | Females |
|---|---|---|
| Brothers | 3.8% | 9.2% |
| Sisters | 2.7% | 3.8% |

Harper, 1991

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19. Rules of Multifactorial Inheritance

## Rules of Multifactorial Inheritance

- Recurrence risk is higher if more than one family member is affected
- The greater the severity, the higher the recurrence risk
- Recurrence risk is greater if the proband is of the less commonly affected sex

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20. Rules of Multifactorial Inheritance, cont.

## Rules of Multifactorial Inheritance, cont.

- Recurrence risk decreases rapidly in more remotely related individuals.
- Recurrence risk for first degree relatives is approximately the square root of the population incidence of the trait.

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21. Congenital Heart Disease: Incidence and Recurrence Risk in S...

## Congenital Heart Disease: Incidence and Recurrence Risk in Sibs

| Defect | Pop. Incidence | Calculated | Actual Recurrence |
|---|---|---|---|
| VSD | 1/575 | 4.2% | 4.3% |
| PDA | 1/1200 | 2.9% | 3.2% |
| ASD | 1/1500 | 2.6% | 3.2% |
| Aortic Stenosis | 1/2200 | 2.1% | 2.6% |

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22. Multifactorial Inheritance

## Multifactorial Inheritance

- Recurrence for most isolated birth defects can be estimated at about 3-5%.
- If, however, the birth defect is part of an underlying genetic syndrome, the recurrence risk would be much higher (autosomal dominant) or lower (Down Syndrome).

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