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HST.161 Molecular Biology and Genetics in Modern Medicine  
Fall 2007

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## Lecture 24

## Review

35/65% split of old/new material on the final

First concept: how do you determine where the cause of a genetic disease is?

- What is the cause? Genetic factors? Environmental factors?
  - o Where's the intersection?
  - o How do we determine between the two?
    - Linkage (= study families)
    - Association studies/linkage disequilibrium
    - Parametric test: determine distance between marker and disease element ( $\theta$ ); mode of inheritance
    - Sib-pair analysis (both alleles shared? Or 1 allele the same? No shared alleles? Analyze the chances in each of these cases that the alleles are linked or unlinked)

Association studies:

- cases and controls
- look at alleles at a particular locus; can also look at millions of nucleotides and find associated SNPs (not that they're disease-causing, but they help us track alleles)

False positives: 1) population substructure; 2) auctioneer's curse (real value is lower than the "winning"/largest value), 3) statistics

TDT (transmission disequilibrium test): particular association study

- example: 4 families, one parent has allele A1, and all children (one per family) have the disease. Parents' disease states don't matter. What chance exists that each child will have the allele A1? 50% each time. If **all** children have A1, then it's said that A1's transmission is in disequilibrium).

Magnitude of effect – linkage analysis

Frequency in population – association study

If magnitude of effect and frequency are both large, you probably die. If both are low, ??

Epigenetics:

- 1) Rett Syndrome; MePC2 recognizes Me-DNA
- 2) Modification of DNA – Me-Cyt down-transcription
  - a. Chromatin (histones): Me-H3/H4 up/down, acetyl-H3/H4 up, etc.
- 3) Development: parental imprint
- 4) Allele specification
  - a. X-chromosome inactivation from "Xist" sequence that spread inactivation through non-coding RNA
- 5) Beckwith-Weidmann; Prader-Willi s. vs. Angelmann s.

Cytogenetics:

- 46 chromosomes

- Chromosomal diseases we encountered: Trisomy 21 (Down's Syndrome), Trisomy 18, Trisomy 13
- Translocations: can be balanced (genetic material preserved) or unbalanced (lost material). Balanced translocations can be reciprocal (trade material with another chromosome) or non-reciprocal (piece of one chromosome translocates to another, with nothing being traded).
  - o Balanced: Robertsonian: 13, 14, 15, 21 and 22 (acrocentric chromosomes)

Review of particular disorders:

**Myotonic dystrophy** (CTG expansion; polymerase slip)

**Thalassemia** (alpha: interchromosomal recombination; unequal cross-over) (beta: deletion)

**Hemophilia A:** factor 8 gene disrupted due to intrachromosomal recombination; inversion of the rest of the chromosome

**Colorblindness** (red-green): unequal cross-over, or cross-over in the middle of the red opsin gene

**Rett Syndrome:** MeCP2; no longer allows recognition of methylated DNA

**Beckwith-Wiedemann s.:** epigenetic imprinted disease on 11q

**PWS/Angelmann s.:** chr. 15q.11, imprinted, expression from only one parent, regardless of mechanism, can lead to PWS or AS

**Fragile X:** triple nucleotide expansion of CGG → no transcription.

**Huntington's:** expansion of CAG; creates many Glu's inside protein. Exhibits anticipation.

**Becker's muscular dystrophy/Duchenne's MD:** change in reading frame of dystrophin

**Friedrich's Ataxia:** triplet expansion, GAA, mechanism unknown

**PKU:** autosomal recessive; disorder of metabolism

**William's Syndrome:** microdeletion (due to interchromosomal recombination) of any number of genes related to WS; which genes are deleted corresponds to the particular phenotype you have

**Ankylosing Spondylitis:** HLAB27, autoimmune (wasn't really covered in class, but this is all you need to know about it anyway)

**Achondroplasia:** FGFR3; increasing paternal age is associated with increased risk

**Li-Fraumeni:** p53; familial cancer syndrome

**Cystic Fibrosis:** CFTR; most famous mutation is  $\Delta 508$

**HNPCC:** microsatellite instability

**FAP:** defect in APC gene

**Hypertrophic cardiomyopathy:** myosin-heavy chain, troponin I

**Patau:** trisomy 13; viable with birth

**Edward's:** trisomy 18

**Down's:** trisomy 21 (only trisomy you can really live with; others are usually selected against in utero, or else die in infancy)

**Wolf-Hirschhorn:** deletion of 4p

**Cri-du-chat:** deletion 5p

**Turner:** XO monosomy; can have mosaics (partially XO, partially XX)

**Klinefelter's:** X(n)Y (multiple X's; number of them has some correlation to severity of phenotype)

**Apert's:** CpG (hyper-mutable cysteine)

**FSHD:** 3.3 kb D4Z4 repeats

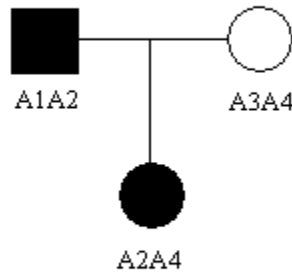
**Retinoblastoma:** Rb gene ; 90% penetrance

**Mitochondrial-inherited disorders:** variable phenotypes because you can inherit variable numbers of diseased versus WT mitochondria from your mother.

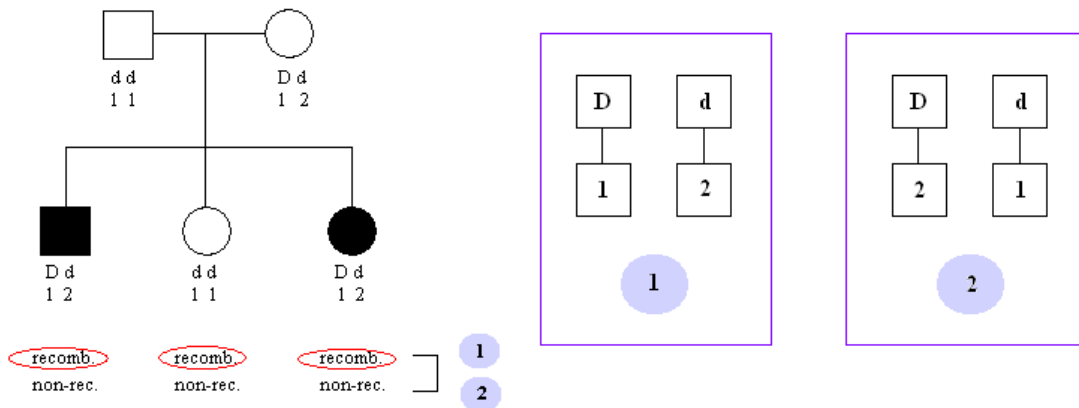
Linkage and LOD:

You have a disease allele D linked to some marker M. Occasionally you'll get a recombination, D with m or d with M.

D (disease gene) is linked to A1



Most informative case:  
D recombines with A2



$\theta^R(1-\theta)^{NR} / (1/2)^{R+NR}$  where R = # recombinants, NR = # non-recombinants

For this case :  $\frac{1}{2}(\theta^3(1-\theta)^0) / \frac{1}{2}^3 + \frac{1}{2}(\theta^0(1-\theta)^3) / \frac{1}{8}$

(You claim you have equal chances of all being recombinants and all being non-recombinants, so you multiply each by  $\frac{1}{2}$  and add them together.)

Then take the log:  $\log(\frac{1}{2}(\theta^3 / \frac{1}{8}) + (\frac{1-\theta^3}{1/8}))$

(If  $>3$ , then significant for linkage, for phase=unknown. For phase=known, you'd have to have a generation above the parents here.)

Meyerson lecture:

Detecting different kinds of defects, and some examples:

Mutation	exon resequencing	EC-FR, C-kit
Translocation	FISH	BCR-ABL, PML-RAR
Deletion	FISH, Southern blot	retinoblastoma
Amplification	SNP array	N-myc
Epigenetic stuff	methylation analysis (gene-specific; genome-wide)	APC, MLH-1

Retinoblastoma:

2 kinds: inherited, sporadic.

- both cases result from mutating both copies of Rb gene
- inherited: early onset, bilateral tumors
- sporadic: one cell needs to acquire 2 hits; single tumor, one eye, later onset

Colon cancer:

APC                      HNPCC -> MLH, MSH  
Normal → polyps → → malignant polyps  
FAP (lots of polyps)