Neurological Diseases
Genetic factors
External factors (agents, drugs, virus)
Internal factors (hormones)

Genetic diseases in the nervous system

*Human Genome Project*

The U.S. Human Genome Project is a 15-year effort coordinated by the U.S. Department of Energy and the National Institutes of Health (Started in 1990).

* Identify all the genes in human DNA.
  (~30,000 genes and many expressed in the nervous system)

* Determine the sequences of the 3 billion chemical bases that make up human DNA.

* Store this information in databases.

* Develop tools for data analysis.
Meiosis and recombination

1. Replication of chromosomes
2. Tetrad formation and recombination
3. Separation of homologues into 2 haploid daughter cells
   Meiosis I
4. Sister chromatids separation into 4 haploid cells
Recombination frequency
frequency of an event that separates two genes by recombination
-proportional to the amount of DNA between the two genes

1% recombination frequency (RF) ⇒ 1 centiMorgan (cM) = 1000kb
physical meaning: Separation occurs every 100 meiotic events.

Linkage analysis
Measurement of RF among genes ⇒ establishment of their linear order and the distance between genes ⇒ a genetic map of the chromosome
What is the RF of FIX and mcf-2?
Assume 100 kb between the two.

FIGURE 2. Genetic and physical map of a region of the X chromosome. The relationship between loci is measured in genetic maps as the frequency of recombinations between them, and in physical maps as the distance in nucleotides. These maps have the same linear sequence, but there is no direct correlation of distances. The human X chromosome is shown on the left in metaphase with its characteristic Giesma banding pattern. To the right of it are two genetic maps giving the distance between loci in cM's, with progressively finer detail in the telomeric region of Xq. Two loci, FIX (factor 9) and mcf-2, are tightly linked. The physical map of large genomic fragments was resolved by digestion of these regions with restriction enzymes, which recognize rare sites (e.g., BstHI and EcoRI), and hybridization to probes for these loci. These procedures generate a long-range restriction map and place these loci near each other in the same 1300-kb fragment. (After C. Nguyen et al., 1987, EMBO J. e: 3285–3289.)
Detection of mutant allele
Genetic markers
- any gene or locus that is used as a reference point
Polymorphism can be used as a marker
**RFLP analysis:** restriction fragment length polymorphism
Linkage analysis using polymorphic DNA marker (Fig. 3, p. 501)
Cue to location of the disease gene in the chromosome

1. Disease itself
   example: a. affects male $\Rightarrow$ X chromosome
   b. chromosomal alteration (translocation, deletion)

2. Linkage analysis
   If two genes (a disease gene and a genetic marker) cosegregate more often than would be expected by chance, it constitute the evidence of linkage.
   *This probability can be estimated by Lod Score Analysis (Box A in p.505).*
   *(computer programs: LIPED, MLINK)*

   If two are tightly linked, probability of co-segregation in 10 meiotic events $= 1^{10} = 1$
   If the two loci are not linked, $p = (1/2)^{10}$.

   (Relative probability is thus $1 : (1/2)^{10} = 1024 : 1$, if complete co-segregation is observed)

   **In general, if lod score is greater than 3, the loci of the two genes are considered to be linked.**

Factors have to be known before the analysis
   1. autosomal or X-linked
   2. dominant or recessive
   3. Should be a single gene disorder
Strategies to identify the disease gene
Assume that by linkage analysis, the disease gene is placed in a chromosomal region that contains a known gene.

This gene can be considered as a candidate gene for the disease.
How do we check?
Cosegregation of the disease gene and the candidate gene.
If segregated away by recombination during multiple meioses, it is not.
If they co-segregate, it supports the identity of the disease gene
Further proof: mRNA expression in patient's tissue.
Protein level: expression function
Transfection of the cell by cDNA

FIGURE 6. Allele association of a marker allele with a disease gene.