Lecture 7: QTLs and Microarrays

I. Quantitative Trait Loci (QTLs)

Genetic basis of complex traits
Most traits have a complex genetic basis
No single gene shows perfect segregation with the trait
Generally, multiple loci contribute
Environmental effects are also important
Even with a single underlying gene, can have: incomplete penetrance, variable expressivity.

Phenocopies -- individuals showing the trait for strictly environmental reasons.

The Genetics of Human Disease
Can score individuals as affected / unaffected
Alternatively, if known, the appropriate underlying physiological variable can be used as a quantitative character, e.g., Blood pressure vs. hypertension (affected / normal). In most cases, we don't know underlying biochemical variables.

Mapping genes underlying complex traits

QTLs (Quantitative Trait loci) -- those underlying quantitative traits
DS (Disease susceptibility) genes -- those influencing an individual's susceptibility to a particular disease (e.g., heart disease, Alzheimer's). Note that DS genes are simply QTLs that influence a disease.

The basic strategy behind mapping quantitative trait loci (QTL) is illustrated below for the density of hairs (trichomes) that occur on a plant leaf. (a) Inbred parents that differ in the density of trichomes are crossed to form an F₁ population with intermediate trichome density. (b) An F₁ individual is selfed to form a population of F₂ individuals. (c) Each F₂ is selfed for six additional generations, ultimately forming several recombinant inbred lines (RILs). Each RIL is homozygous for a section of a parental chromosome. The RILs are scored for several genetic markers, as well as for the trichome density phenotype. In c, the arrow marks a section of chromosome that derives from the parent with low trichome density. The leaves of all individuals that have inherited that section of chromosome from the parent with low trichome density also have low trichome density, indicating that this chromosomal region probably contains a QTL for this trait.
Candidate locus approach
One looks for associations between the trait and the average values for particular alleles at the candidate locus

Example: D4 dopamine receptor (D₄DR)
*Variation in gene size due to length variation in exon III of D₄DR
*Individuals with long alleles higher in novelty seeking (more exploratory, thrill-seeking, excitable)
*Individuals with no long alleles lower in novelty seeking (more deliberate, rigid, and orderly)
D₄DR accounts for ~10% of all genetic variance in the trait

Marker–trait associations
High amounts of polymorphism at the DNA level
Two random humans differ by on average 20 million base pairs
These differences provide genetic (molecular) markers for mapping genes
Example: Manic–depressive illness
22 families with a total of 159 pairs of affected sibs were examined.
57% of doubly affected sib pairs shared the same allele from their parents at a microsatellite marker D18S56. This is significantly different from 50%, suggesting this marker is linked to a DS gene influencing depression.

Example: Genetics of sexual orientation.
Hamer (1993) examined 32 pairs of gay brothers. 22 of these shared the same marker allele from their mother (an X–lined marker in region Xq28).
freq = 22/32 = 67%, which (for this sample size) is significantly different from 50%, indicating a QTL influencing male sexual preference linked to this maker.
No such association was found in 36 pairs of lesbian sisters

II. Microarrays
Microarrays exploit the preferential binding of complementary single-stranded nucleic-acid sequences. The underlying principle is the same for all microarrays, no matter how they are made — the unknown sample is hybridized to an ordered array of immobilized DNA molecules whose sequence is known. Each array features thousands of different DNA probe sequences. Microarrays allow researchers to determine which genes are being expressed in a given cell type at a particular time and under particular conditions. They can be used to compare the gene expression in two different cell types or tissue samples, for example, healthy versus diseased tissue, and to examine changes in gene expression at different stages in the cell cycle or during different developmental stages.
General principle of microarrays

Control

Treatment A

RNA isolation

RNA labeling

Competitive hybridization to one binding site on array

Data analysis