Lecture 34 -- Genetic Determinants of Neurological Disorders -- Gilliam

I. Neurological Traits/Disorders that Result from Mutations in a Single Gene

In simple organisms, and sometimes in humans, a single gene may control a trait or disorder by encoding a protein that affects the function of individual nerve cells in a specific neural circuit. In more complex organisms, the circuitry is more complex and behavioral traits are generally shaped by the actions of many genes.

1. Phenylketoneuria is a Model Example.

Mutations in phenylalanine hydroxylase lead to a severe impairment of cognitive function and affect 1 in 15,000 children. The enzyme normally converts the amino acid phenylalanine to tyrosine. Individuals who carry one abnormal copy of the gene have no symptoms; thus this is an autosomal recessive disorder. Children who lack both copies of the gene build up high blood levels of phenylalanine, which in turn leads to the production of a toxic metabolite which interferes with normal maturation of the brain.

Phenylketonuria is a clear example of how a person's phenotype depends on the interaction of genes and environment. A change in diet (limitation of protein intake) can rescue the genetic defect and mental functioning.

2. Trinucleotide Repeat Mutations in the *Huntingtin* Gene Result in Huntington's Disease.

Huntington's disease (HD) is a rare degenerative disorder of the nervous system characterized by motor and cognitive impairments and death 15-20 years after the onset of symptoms. It is inherited as an autosomal dominant disorder with full penetrance, i.e. a person who inherits the disease mutation always develops the disease.

HD involves the death of neurons in the caudate nucleus, a part of the basal ganglia involved in regulating movements. The function of the *Huntingtin* gene is not known at this time.

The CAG codon that encodes glutamine is repeated 19-22 times in the normal gene but 48 or more times in the mutated gene. This expansion is "genetically unstable" because DNA polymerase cannot faithfully replicate this region. Subsequent generations often inherit longer stretches of the trinucleotide repeat, a process referred to as "anticipation".

Hypotheses for the action of the polyglutamines include a gain-of-function that is destructive to the cell, an alteration in ability, or an increased propensity to bind other proteins required for normal cellular function.

3. Other Neurological Disorders Involve Similar Expansions in Trinucleotide Repeats.

Whereas CAG encodes polyglutamine stretches in the coding region of the disease gene, some disorders result from the upstream or downstream effect of trinucleotide repeats sequences. Fragile X mental retardation results from long stretches of repeats upstream of the translational start site of the FMR-1 protein. The resulting altered methylation patterns silence gene transcription, leading to reduced levels of FMR-1 protein.

4. Single Gene Mutations Can Encode Normal Behavioral Variations in Worms and Flies.

Recent studies indicate that single gene alterations (allelic variants) can contribute to individual differences in naturally occurring behavior, including social behavior. Some *C. elegans* worms are solitary foragers, while others are social foragers, aggregating together on the food while they feed. The difference in these two behaviors results from a single amino acid variation in a gene that resembles the neuropeptide Y receptor, a G protein–coupled receptor that is ubiquitous and important in mammals for feeding. It is thought that an as yet unknown ligand is released upon digestion of food that activates the receptor to activate the secretion of a sensory repellant. Thus, feeding worms naturally secrete a sensory attractant that induces the social, clumping behavior. Worms with the receptor variant fail to secrete the counterbalancing repellant while solitary worms do counterbalance the attractant.

A similar behavior is present in the fruit fly (*Drosophila*) leading to the "rover" and "sitter" allelic variants. The gene responsible for this phenotype shares significant sequence homology with the nematode gene, suggesting functional conservation as well.

5. Single Genes may be Critical Factors in Certain Human Behavioral Traits

a. Serotonin has been implicated in the regulation of mood states, including depression, anxiety, food intake, and impulsive violence. Several studies link aggressive behavior in animals with decreased activity of serotonergic neurons. Genetically altered mice lacking the serotonin 1B receptor are much more aggressive than their wild type littermates.

b. Novelty-seeking behavior is characterized by exhilaration or excitement in response to stimuli that are novel. Twin studies suggest that novelty-seeking behavior has a heritability of about 40% (40% of the natural population variation in this behavior is determined by heritable factors and 60% by non-genetic factors such as environment or stochastic events). Studies indicate that perhaps 10% of the genetic component arises from a polymorphism in the D4 dopamine receptor.

6. Complex Behaviors Can Result from Mutations in a Single Gene.

Mutations of single genes in *Drosophila* can produce abnormalities in innate behaviors, such as circadian rhythms. Mutations in either the *Per* (period) or *Tim* (timeless) genes affect circadian rhythms. Per and Tim bind as a diamer to enter the nucleus, where they block transcription of themselves as well as other, hitherto unidentified, genes. During

light hours, Per protein builds up but Tim protein is degraded, thus preventing diamerization, entry into the nucleus, and transcriptional inhibition. After dusk, sufficient Tim protein is produced to form diamers and gene transcription is inhibited. By morning, both Per and Tim proteins have fallen to low enough levels to no longer repress transcription.

Despite the interaction between the two gene products, circadian rhythms are classified as single gene traits rather than multigenic since disruption of a single gene (Per or Tim) disrupts the phenotype. In multigenic traits, disruption of a single gene may predispose to the phenotype but, in the absence of additional gene variants, it does not itself alter the phenotype.

II. Most Complex Heritable Phenotypes in Humans are Multigenic.

Multigenic includes both *oligogenic* and *polygenic* traits. An oligogenic trait or disorder is determined by a small number of genes, each contributing to the phenotype in a significant way. A polygenic trait is the result of many genes, each with a small effect on the phenotype. Complex trait alleles (gene variants that predispose individuals to multigenic disorders) predispose to illness rather than cause illness. A multigenic trait/disorder probably develops from the combination of several predisposing gene variants together with environmental factors. In some unknown proportion of multigenic traits/disorders, epistatic protein-protein interactions will be essential. Thus, alterations in protein X or protein Y may have no effect upon a phenotype, whereas alterations in both predispose to the trait. In such circumstances, it is possible that complex trait alleles might reach considerable frequencies in the general population.

Twin and adoption studies are often used to estimate the degree to which a human phenotype is determined by genetic factors. Identical (MZ) twins share all genes. Fraternal (DZ) twins, like normal siblings, share (on average) half their genetic information. Scientists often determine concordance for a given trait/disorder among MZ twins and then compare this figure with concordance among DZ twins. For a fully penetrant, single gene disorder such as HD, the MZ ratio is 100% and the DZ ratio is 50%. For complex traits like schizophrenia, MZ twins are about 50% concordant compared to 18% for DZ twins. From these figures, we can estimate that about 50% of the normal population variance among patients with schizophrenia is determined by genetic factors.

The search for gene variants that predispose to multigenic disorders such as schizophrenia and manic depressive illness has been complicated by a number of factors. Among complex disorders, Alzheimer's disease (AD) stands out in terms of relative success from gene mapping efforts.

Genetic Study of Alzheimer's Disease.

AD is a degenerative disorder of the CNS that leads to progressive declines in cognitive functions. First degree relatives of patients with AD are at somewhat increased risk for developing illness, indicating a heritable component. Environment plays a key role as well.

AD is characterized by the presence of amyloid plaques at greater than normal age-related density and by the presence of neurofibrillary tangles. A major component of the plaques is a 42 or 43 amino acid peptide (Aβ) which is enzymatically cleaved from amyloid precursor protein (APP), a membrane protein. Individuals with Downs's syndrome inherit an extra complete copy, or segment, of chromosome 21. Such individuals develop AD symptoms in their third or fourth decade with much greater frequency than other individuals. The genetic mapping of APP to the DS segment of chromosome 21, followed by identification of disease-specific mutations in APP in a few families, identified APP as a rare target for AD. Presenilins 1 and 2 are additional targets for single-gene forms of familial AD. Together, APP and the presenilins account for about 5% of all cases of AD.

Genetic linkage studies show that apolipoprotein E (apoE) is linked to risk for common forms of AD. Of the three variant forms of apoE, the apoE4 allele is a significant risk factor for AD. Individuals who inherit one or two copies of the E4 allele have a dose-dependent risk for both earlier age of onset of symptoms and for increased deposits of the Aβ peptide. It is estimated that apoE may account for as much as 50% of the overall genetic risk for developing AD. Typical of multigenic etiology, approximately half of all AD cases have no E4 allele and some individuals with two E4 alleles do not develop AD.