Genetic mapping of cystic fibrosis and huntington's disease

Genetic Mapping

By the late 1970s, the list of genetic diseases in McKusick's catalog of genetic diseases had grown exponentially. But only a few of the actual genes were identified, leading to predictive diagnostic tests. It seems that finding a disease-linked gene in humans is like looking for a needle in a haystack.

Botstein/Davis Gene Mapping Technique

In 1978, David Botstein (1942-), a geneticist from MIT, attended a genetic mapping presentation in Utah. At the presentation, a graduate student was mapping a gene that happened to be sitting with a gene that existed in many easily identifiable variants. As Botstein listened, he was struck by an idea: gene mapping would become a trivial task if such variant signposts existed and were spread across the human genome.

Botstein knew that such a marker exists. Over centuries of evolution, thousands of minute variants in DNA sequence are created in the human genome. These variants are called polymorphisms, and are spread widely over the human genome.

Working with Ron Davis (1941-) and Mark Skolnick (1946-), Botstein published their new basis for the construction of human genetic maps in 1980.

Mapping Huntington's Disease (HD)

Nancy Wesler, a psychologist, heard about Botstein's gene-mapping proposal in October, 1979. Her mother and uncles all had suffered from Huntington's

disease, but she was still asymptomatic. Huntington’s disease causes the death of specific neurons in the brain, leading to jerky movements, physical rigidity, and dementia. Symptoms usually appear in midlife and worsen progressively.

At that time, Botstein’s method was still theoretical – thus far, no human gene had been successfully mapped with it. Botstein’s technique was crucially dependent on the association between a disease and markers: the more patients, the stronger the association, the more refined the genetic map. There were only a few thousand HD patients in scattered across the United States – seemed perfectly mismatched to this gene-mapping technique. However, Wexler had heard that there was a prevalence of HD on the shores of two villages in Venezuela.

In the winter of 1979, Wexler set off to Venezuela to hunt the Huntington gene. She hired a team of local workers to begin documenting the pedigrees of affect and unaffected men and women, collecting blood samples to be shipped to the laboratory of James Gusella, at the Massachusetts General Hospital in Boston, and to Michael Conneally, a medical geneticist at Indiana University.

In Boston, Gusella purified DNA from blood cells and cut it with a barrage of enzymes, looking for a variant that might be genetically linked to HD. Conneally’s group analyzed the data to quantify the statistical link between the DNA variant and the disease. In 1983, three years after the blood samples had arrived, the location of the HD gene, whose mutation causes Huntington’s disease, was mapped to chromosome 4 in 1983, making HD the

first disease gene to be mapped using DNA polymorphisms – variants in the DNA sequence. The mutation consists of increasing repetitions of “ CAG” in the DNA that codes for the protein huntingtin. The number of CAG repeats may increase when passed from parent to child, leading to earlier HD onset in each generation.

Mapping of Cystic Fibrosis (CF)

Davis and Botstein’s technique of mapping genes based on their physical positions on chromosomes – later called positional cloning – marked a transformative moment in human genetics. In 1989, the technique was used to identify a gene that causes cystic fibrosis, a devastating illness that affects the lungs, pancreas, bile ducst, and intestines.

Unlike Huntington’s disease, the mutated variant of the CF is common: one in twenty-five men and women of European descent carries the mutation. Human with a single copy of the mutant gene are largely asymptomatic. If two such asymptomatic carriers conceive a child, chances are one I four that the child will be born with both mutant genes. Until the 1980s, the average life span of a child carrying two such mutant alleles was twenty years.

In 1985, Lap-Chee Tsui, a human geneticist working in Toronto, found an “ anonymous marker” that was linked to the mutant CF gene. The marker was quickly pinpointed on chromosome seven, but the CF gene was lost somewhere in that chromosome. Tsui began to hunt for the CF gene by progressively narrowing the region that might contain it. In 1989, using a modified gene hunting technique called chromosome jumping, Tsui and his colleagues had narrowed down the gene hunt to a few candidates on

chromosome seven. The task was now to sequence the genes, confirm their identity and define the mutation that affect the function of the CF gene.

They discovered that only one gene was persistently mutated in both copies in affected children, while their unaffected parents carried a single copy of the mutation. The CF gene codes a molecule that channels salt across celluar membranes. The most common mutation is a deletion of three bases of DNA that results in the removal, or deletion, of just one amino acid from the protein. This deletion creates a dysfunctional protein that is unable to move chloride across membranes. The salt in sweat cannot be absorbed back into the body, resulting in the characteristically salty sweat. Not an the body secrete salt and water into the intestines, resulting in the abdominal symptoms.

Within a few months of the discovery, a diagnostic test for the mutant allele became available. Over the last decade, the combination of targeted parental screening and fetal diagnosis has reduced the prevalence of children born with CF by about 30 to 40 percent in populations where the frequency of the mutant is the highest.