UCLA Genetic Study

By Susan Smalley, Ph.D.

The focus of the UCLA AD/HD Genetic Study is to identify the complex interplay between genetic influences of AD/HD and the environment. Our knowledge of the genes involved in AD/HD will lead to earlier and better diagnostic tools for this condition and the development of more effective interventions targeting genetic differences.

Finding susceptibility genes and their interplay with environment in the development of AD/HD is a formidable task. Why is it so difficult? Human behavior is a very complex trait, which means there are many different genes and environmental influences that contribute to one's liability to behave or think a certain way. No one gene or environmental agent is sufficient to "cause" AD/HD or is necessary in its development. Rather, AD/HD can be thought of as an extreme along a dimension of impulsivity, activity and/or attention. Just as height, weight and IQ are dimensional in nature, one's liability (or risk) to develop AD/HD is as well.

Since AD/HD is an 'extreme' along a dimension of liability, we need to think of AD/HD not as a deficit but rather as a difference. Second, individual differences along dimensions such as height, weight, attention, impulsivity, etc., are part of nature -- normal variation -- and -- something that makes us human. We want to cherish our differences but also design appropriate interventions when being at an extreme leads to functioning difficulties.

The Genetic Component of AD/HD

What has science told us about AD/HD in the last decade? First, it is clear that our differences along the liability to AD/HD are strongly influenced by genes. If one looks at families of a child with AD/HD, 10-30 percent of moms and dads are affected with AD/HD and 20-30 percent of brothers and sisters are affected -- data clearly supporting familial clustering of AD/HD. Twin studies demonstrate a strong role of genetic influences. For identical twins, which share 100 percent of their genes, 60-80 percent of the time when one twin has AD/HD, the other twin has it as well. Fraternal twins on the other hand, who share only 50 percent of their genes in common, are similar for AD/HD about 20-30 percent of the time (note: about half the similarity of identical twins, consistent with genetic degrees of relationship).

These family and twin studies supporting genetic influences have led to numerous molecular genetic investigations in AD/HD. The UCLA AD/HD Genetic Study is an NIMH-funded five-year research project designed to uncover susceptibility genes in AD/HD. The focus of this research is to carry out a genome scan to find genes

underlying AD/HD.

Conducting a Genome Scan

In our case, the genome scan is a lengthy process that begins with families with two or more affected children (with AD/HD regardless of subtype, e.g. inattentive, hyperactive or both), coming to UCLA. We conduct psychiatric evaluations and psychoeducational testing to determine the diagnoses of AD/HD and other possible neurobehavioral difficulties, such as anxiety disorders, mood disorders, oppositional behavior and learning disabilities. Parents undergo psychiatric evaluations as well so that we can determine to what degree AD/HD runs in families and further explore how susceptibility genes are expressed in adulthood.

Next, blood is drawn to isolate DNA (deoxyribonucleic acid), the basic blueprint of life. We then test each individual's DNA for hundreds of known molecular markers -- pieces of DNA that we know something about. The molecular markers mark particular positions among the 100,000 genes that make up our genetic makeup or genome. We pick about 450 markers so that they are equally spaced throughout our genome and thus we have a good chance of finding susceptibility genes to AD/HD near one of the markers. By using markers, we then study AD/HD siblings and ask, are they alike for any particular marker more than we would expect by chance alone? For genes, chance is like flipping a coin. Each person carries two copies of every marker. We all have 23 pairs of chromosomes (the molecules that carry our DNA). Each pair carries thousands of genes which are inherited from our moms and dads (one member of each pair comes from the mom, one member of each pair comes from the dad). Since every parent carries two copies of a marker (call them "heads" or "tails"), there is a 50:50 chance of "heads" being transmitted to a child. For brothers or sisters, we expect about 50 percent of the markers to be the same because they share 50 percent of their genes. When we select siblings because of AD/HD, any gene that contributes a risk to AD/HD (i.e., a susceptibility gene) and lies close to a marker along a chromosome will be shared more than 50 percent. We then look for a frequency of sharing greater than 50 percent in siblings and use this information to zero in on a susceptibility gene for AD/HD.

"Genetic" Does Not Mean "Fixed"

We have already collected data on 200 families and still plan to collect an additional 100 in the next few years. We are completing our genome scan (search through all the markers) in the next year. With that information, we can refine our search for susceptibility genes in AD/HD to really identify where they are and what they do in brain development.

How will the discovery of susceptibility genes for AD/HD change our diagnosis and treatment of this condition? First, once genes are identified we can begin to diagnose AD/HD better (e.g., from a simple blood test and/or saliva sample). We can learn how different combinations of genes result in different clinical features (e.g., the presence of learning disabilities with AD/HD, depression or conduct disorder). Second, we can figure out what the genes do in the developing brain and see if there are better ways to modify outcome. By this, I mean the following: "genetic" does not mean "fixed." That is, just because a gene can be identified to contribute to a trait or disease, the trait or disease state is not fixed; i.e., one may be able to prevent or change the expression of the trait or disease state. A well-known example of this phenomenon is the genetic disease phenylketonuria (PKU). In this rare genetic condition, individuals with PKU do not produce an enzyme called phenylanine hydroxylase. Without this enzyme, the amino acid phenylalanine builds up in the body and its byproducts lead to severe mental retardation. We now have newborn screening programs in place in which all newborns are tested for PKU. With early detection of a PKU child, the infant is placed on a restricted diet eliminating phenylalanine, which is found in many foods. By eliminating phenylalanine through diet, one can change the outcome of kids with PKU and they will not develop mental retardation.

While we do not yet know what the new interventions will be in AD/HD, it is clear that finding susceptibility genes and learning about what they do in the brain will be a first step toward better interventions. It is also clear that identification of genetic influences will remove the false belief that AD/HD is not a real condition and erase the stigma of the "lazy" child. Finally, recognition that all children learn and think differently -- and that many of these differences are biologically determined -- may help spearhead more rapid changes in our current educational programs by designing programs that reflect and capitalize on such differences.

We are actively recruiting families to participate in our research. Research participants receive free psychological and diagnostic assessments for their children, in addition to intelligence, academic achievement and neuropsychological testing. Written feedback is provided to families. If you are interested to participating in our study, making referrals and/or would like additional information, please contact the University of California-Los Angeles, AD/HD Genetic Study, at (310) 825-8660.

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