Genetic Predisposition for Autoimmune Encephalitis

You might have your dad's brown eyes or your mother's curly hair. Traits like eye color are heritable, which means they are passed from parents to offspring. While we can inherit a lot of good traits from our parents, risk for certain diseases can also be inherited. Some diseases, like Huntington's, are strongly linked to genetic risk factors. If someone's parent has Huntington's Disease, there is a 50% chance that they will develop it as well[1]. This is because Huntington's disease is caused by a specific, heritable mutation in the DNA.

Not many disorders have such a clear genetic cause. However, the set of genes inherited from the parents can increase someone's risk, or predisposition, for developing certain diseases, even if it doesn't directly cause the disease. For example, people can have genetic predispositions for some types of cancer, psychiatric illnesses, and health risks like high cholesterol[2,3,4]. Recent research suggests that certain types of autoimmune encephalitis (AE) may also be linked to genetic factors that put some people at higher risk of developing this disease than others[5].

Genes and Heritability

Let's step back to understand how genetic risk is transferred from parents to offspring by taking a look at DNA. DNA is the biological material that makes us who we are. Humans and animals inherit half of their DNA from their mother and half from their father. The DNA itself is made up of four nucleotide base pairs called adenine (A), thymine (T), cytosine (C), and guanine (G). You can see in Figure 1 that the nucleotides form pairs with each other (A with T and C with G) on the two strands of the DNA double helix. The human genome has 3 billion of these nucleotide pairs[6]. The order of the nucleotides makes up a genetic "code" that dictates what proteins are made and eventually what traits we have. At every single position, a person can have one of these four nucleotides. Variation in the nucleotide sequence at particular locations on the DNA is what makes each individual unique. Changes of nucleotides at some positions, however, can increase risk for certain diseases.
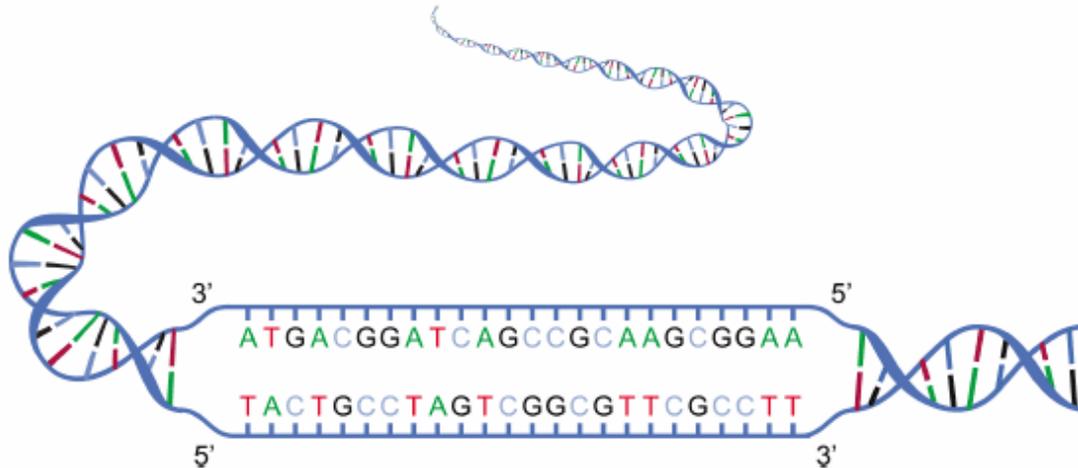
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Figure 1. Cartoon schematic of a DNA double helix with nucleotide base pairs (A,T,C, and G). At each position on the DNA, a person can inherit one of the four nucleotides and variation in the sequence produces the genetic code.

Genetic Risk for AE

Researchers can learn about genetic risk factors for specific diseases or conditions by collecting data about individuals' genotypes. A genome-wide association study (GWAS) is used to assess the whole genomes of many people to identify genetic mutations that are associated with that disease. Researchers have conducted GWAS studies in patients with autoimmune encephalitis (AE) to search for clues about genetic predisposition[5]. In contrast to a GWAS study that looks at the entire genome, other genetic research focuses only on select genes that are hypothesized to relate to a disease. AE is a disorder that involves the immune system incorrectly targeting the brain's own cells. In the case of AE, researchers often look at genes that encode proteins involved in the immune system, which are likely locations for genetic mutations that might increase risk for this disease.

It turns out that some types of AE, like limbic encephalitis, are more closely tied to genetic risk factors than others[7]. The main genetic factor that has been associated with limbic encephalitis is called human leukocyte antigen (HLA). HLA genes are found on chromosome 6 and are categorized into three classes, class I, II, and III, which have genes that encode different proteins that help to regulate the immune system[7]. Mutations in these genes have been associated with a variety of disorders that involve autoantibodies, including limbic encephalitis[7].

The most common form of limbic encephalitis that is not caused by cancer involves anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibodies[7]. Anti-LGI1 limbic encephalitis is associated with a mutation in part of the class II HLA gene complex. Anti-LGI1 antibodies

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are in the IgG4 isotype, which has been associated with HLA genes in a variety of autoimmune conditions[7,8]. A genetic mutation called DRB1*07:01 was found to be carried in up to 90% of people with anti-LGI1 encephalitis[9]. This suggests that this specific HLA mutation is associated with the development of limbic encephalitis, although the exact biological mechanisms are still unknown[7].

In contrast to anti-LGI1 limbic encephalitis, anti-NMDAR encephalitis has not been found to have a strong relationship to HLA mutations[7]. A GWAS study found evidence for some weak links with HLA mutations, but there were no genetic mutations common to both anti-LGI1 limbic encephalitis and anti-NMDAR encephalitis[5]. Anti-NMDAR encephalitis is caused by antibodies of the IgG1 isotype, which may explain why there is a weaker association with genetic variations in HLA, which are more strongly associated with the IgG4 isotype[7]. One study did find differences in genes that encode inflammatory cytokines related to anti-NMDAR encephalitis in a small Southern Han Chinese population[10], but more research is needed to determine if this association holds true in other populations.

The heterogeneous nature of AE makes it hard to pinpoint exact genetic risk factors. It is clear, however, that the *interactio*n between a person's genes and their environment is a stronger predictor of whether they will experience a particular outcome than genetics alone. For example, environmental factors like contracting a virus can lead to AE. Someone with a genetic predisposition may be more likely to get AE after a virus than someone without those genetic mutations. Although researchers have learned that individuals with particular mutations in HLA genes are likely at greater risk for developing limbic encephalitis, more work will be needed to understand the biological mechanisms and links with environmental risks that lead to AE. Ultimately, the goal would be to use what we can learn about a person's genetic risks to predict and prevent AE.

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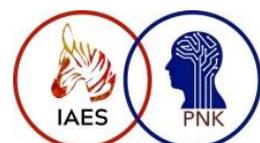
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