Genetic studies are slowly leading to a better understanding of certain diseases as well as progress toward individualized drug therapy. Developments in DNA sequencing make it relatively simple to look for allelic (i.e., alternative) versions of a gene by examining samples of a specific gene taken from different members of a population (or from a heterozygous individual). Genetic variants that appear in at least 1% of a population are called polymorphisms. With the cutoff at 1%, one does not get sidetracked by spontaneous mutations that may have occurred in—and spread by the descendants of—a single family.

### 5-HTT Polymorphism

Genetic investigations have targeted all the major behavioral health diseases. So far, however, the research effort has been marked by a paucity of replicable direct gene-disorder associations.\(^1\) A significant complication appears to be that most behavior-gene effects are indirect and depend on gene-environment interaction. The best example is research on genetic polymorphisms of the serotonin transporter. A study by Caspi and colleagues\(^2\) first suggested that persons who possess either 1 or 2 copies of the short (S) variant of the 5-HTTLPR (serotonin transporter–linked polymorphic region) gene were more likely to develop major depression than those with the long (L) variant. The promoter region of the serotonin transporter contains a 44–base pair insertion (L allele) or deletion (S allele). Compared with the L allele, the S allele is associated with a lower level of serotonin uptake and transcriptional efficiency of the serotonin transporter. This may result in increased vulnerability to develop major depression. Although the results of the Caspi study have been replicated by other researchers,\(^3\) more than simple genetic variation is involved. A meta-analysis of the published investigations of S/L 5-HTT polymorphism and major depression, including 11 studies with 941 patients and 2110 controls, concluded that the association was not significant.\(^4\) However, another systematic review and meta-analysis that examined the association between 5-HTT polymorphism and “avoidance-related personality traits,” including neuroticism and related constructs (themselves strongly related to the risk of major depression), did find a modest relationship.\(^5\) According to Kendler and associates,\(^6\) the 5-HTT gene may be an example of a gene that influences vulnerability to major depression not by a direct effect but rather by indirectly increasing sensitivity to the environment’s pathogenic effects. Aaron T. Beck,\(^7\) the originator of cognitive psychotherapy, recently published an influential article in which he suggests that negative cognitive processing is the mechanism by which S 5-HTTLPR variant carriers are linked to major depression. He cites recent work showing that hyperreactivity of the amygdala in S 5-HTTLPR variant carriers is associated with increased sensitivity to negative stimuli and leads to negative bias in the processing or interpretation of emotional stimuli.\(^8\) Beck also highlights the work of Hayden and colleagues,\(^9\) who found that nondepressed children homozygous...
for the S allele showed greater negative processing on a self-referential encoding task following a negative mood induction than children with L genotypes. There are also other intriguing findings in persons with major depression who carry the S allele. For example, such persons show a poor response to SSRIs, increased risk of adverse effects with SSRIs, and increased risk of suicide attempts. So, is the S allele a marker for more severe illness or, alternatively, does it impair the serotonin system in a way that current SSRIs cannot remedy?

**BDNF Val66Met Polymorphism**

A completely different genetic variation, the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, also seems to play a role in the development of major depression in some persons. In the past few years, the BDNF Val66Met polymorphism, a single nucleotide polymorphism (SNP) in the human BDNF gene that produces an amino acid substitution (valine [Val] to methionine [Met]) at codon 66, has been shown to affect hypothalamic-pituitary-adrenal (HPA) axis activity in persons with depression. For example, homozygous carriers of the Met/Met genotype showed significantly higher HPA axis activity than patients carrying the Val/Val or Val/Met genotype. Since HPA axis dysregulation and reduced brain neuroplasticity are both thought to be heavily involved in causing and maintaining major depression, this study suggests a possible genetic linkage between a tiny SNP genetic variation and major depression in some persons.

**Polymorphisms in Cytochrome P-450 Enzymes**

An emerging understanding about polymorphisms in the cytochrome P-450 (CYP) enzyme system is already clinically relevant. Such genetic variation may explain why some persons have serious adverse effects with some drug combinations, whereas other patients do not. For example, in a recent study, Henry and colleagues discuss drug interactions in women with breast cancer in whom major depression develops. The researchers found that for women who take tamoxifen (which requires CYP2D6 activity in the liver to form its active metabolite), adding antidepressants such as paroxetine or fluoxetine (both of which inhibit CYP2D6 activity) is not recommended, especially for patients who may already have marginal CYP2D6 functioning on the basis of their CYP2D6 genotype. Other antidepressants, including venlafaxine, escitalopram, and fluvoxamine (which have little effect on CYP2D6 activity), are better choices.

**Conclusion**

Genetic polymorphism seems to play a role in major depression, but the relationship is complex and may involve interactions involving small genetic variations, thought patterns, environmental stress, and physiological systems.

**References:**

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