**Epistasis: Gene Interaction and the Phenotypic Expression of Complex Diseases Like Alzheimer's**

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Did you know that genes can mask and alter the effects of other genes? Could this process, called epistasis, be a key to understanding complex conditions like Alzheimer’s disease and diabetes?

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When we think about factors that cause disease, we often think about specific mutations in individual genes or the environmental factors that contribute to a disease's phenotype. It is also important to consider [epistasis](http://www.nature.com/scitable/topicpage/Epistasis-Gene-Interaction-and-Phenotype-Effects-460), which involves the interaction between two or more genes (Figure 1; Carlborg & Haley, 2004). In fact, understanding epistatic interactions may be the key to understanding complex diseases, such as Alzheimer's disease, diabetes, cardiovascular disease, and cancer.

**How Common Is Epistasis in Disease Susceptibility**

Epistatic gene-gene interactions are perhaps more common than we think. Indeed, some scientists believe that epistasis is ubiquitous in biology and has been ignored for too long in studies of complex traits (Moore, 2003; Carlborg & Haley, 2004). Research has shown that genes don't function alone; rather, they constantly interact with one another. These biological interactions are critical for gene regulation, signal transduction, biochemical networks, and numerous other physiological and developmental pathways (Moore, 2003; Greenspan, 2001). As depicted in the schematic in Figure 2, some genes (depicted as grey hexagons) have positive interactions with one another (blue lines), while other gene pairs have negative interactions (red lines). Together these gene-gene interactions result in an output phenotype. Certain genes are known to modify the phenotype of other genes, which results in differences in disease [penetrance and expressivity](http://www.nature.com/scitable/topicpage/Phenotype-Variability-Penetrance-and-Expressivity-573).

Epistatic interactions can complicate a scientist's search for the gene responsible for a complex disease. For instance, the results of most studies focusing on an initially promising candidate gene have not been able to fully explain complex disease phenotypes in patients with the same disease once more individuals were studied (Moore, 2003). This implies that multiple genes may be involved, and that multiple genes may interact to increase or decrease disease susceptibility. If the effect of the disease-bearing gene is masked or altered by the effects of a second gene, then identifying the first gene can be complicated. In addition, if more than one epistatic interaction occurs to cause a disease, then identifying the genes involved and defining their relationships becomes even more difficult. There are, however, a number of ways to study epistasis in populations by adapting methods used to detect quantitative trait loci (Carlborg & Haley, 2004).

**Epistasis in Alzheimer’s Disease**

To better understand how epistasis affects disease development, it helps to consider an example of a complex disease. Alzheimer's disease, for instance, is a progressive neurodegenerative disorder that causes memory loss and dementia. In the early 1990s, a number of scientists found that a gene called apolipoprotein E4 was associated with a higher risk of developing Alzheimer's disease (Corder *et al.*, 1993; Saunders *et al.*, 1993; Strittmatter *et al.*, 1993). However, the researchers also noted that while having one or two copies of apolipoprotein E4 increase one's risk of Alzheimer's, not all carriers of apolipoprotein E4 develop the disease. This suggested that other genes and/or gene-gene interactions were involved in the development of Alzheimer's.

Onofre Combarros and his colleagues thus set out to study the role of epistasis in the onset of Alzheimer's disease (Combarros *et al.*, 2008). Because the research team realized that studying candidate genes individually had met with little success, the team instead opted to measure interactions between genes. In fact, Combarros *et al.* evaluated the likelihood of over 100 published suggestions of epistatic association in sporadic Alzheimer's disease. Some of these alleged epistatic effects had been hypothesized to occur between pairs of genes, but they had never been statistically tested. Thus, in order to evaluate whether epistasis occurred, the researchers measured both the size and the statistical significance of interactions between pairs of implicated genes.

Eventually, Combarros *et al.* confirmed 27 different significant epistatic interactions using this method, which were grouped into five categories: cholesterol metabolism, beta-amyloid production, inflammation, oxidative stress, and other networks. Some interactions were synergistic, while others were antagonistic. The synergistic interactions indicate that the pair of involved genes together increase the risk of Alzheimer's disease. Meanwhile, the antagonistic relationships indicate a protective relationship between two genes. The strongest interactions involved the pairing of apolipoprotein E4 with three different genes: alpha(1)-antichymotrypsin, β-secretase, and butyrylcholinesterase K (Combarros *et al.*, 2008). Thus, it is clear that epistatic interactions are involved in complex diseases like Alzheimer's disease, and that these genes are not acting alone, but in pathways that affect one another.

Many of the other predictions of epistasis between genes could also prove to be significant if a larger population of Alzheimer's patients was studied. Indeed, now that there is a foundation for understanding epistatic interactions between pairs of genes in sporadic Alzheimer's disease, future studies can focus on epistatic interactions between combinations of three or more genes and between additional pairs of genes.

**Evidence for Epistasis in Other Diseases**

Diabetes is another complex disease that is influenced by both epistatic and environmental factors. Only in rare cases does the disease appear to be monogenic, and generally, multiple genes seem to be involved (Florez *et al.*, 2003). While it is known that diabetics have insufficient levels of insulin and high blood sugar levels, the specific factors underlying disease susceptibility are still being researched. For instance, interactions have been detected between loci on chromosomes 2 and 15, as well as between loci on chromosomes 1 and 10, in patients with type II diabetes. While we do not know the identities of these genes now, it is hoped that they can eventually be mapped and identified.

Evidence also exists that epistasis is involved with other complex diseases, including cardiovascular disease, hypertension, autism, cleft lip and/or palate, and schizophrenia and other neurological disorders, as well as sporadic breast cancer, bladder cancer, and other types of cancer (Combarros *et al*., 2008; Vieira, 2008). Understanding the causes and genetic basis behind these diseases proved elusive when using single-gene studies. However, now that there is a greater focus on epistatic interactions, there may be more progress toward understanding the manifestation of these complex human diseases.

**Making Sense of the Complex**

It is now becoming possible to identify gene relationships, networks, and epistatic interactions on a systems level. Today, high-throughput experimental tools are available to measure molecular and biochemical data. For example, DNA microarrays allow scientists to gather hundreds of thousands of data points from cells, with transcription level used as the measured phenotype. Then, computational and bioinformatics methods can be used to sift and sort though the massive amounts of biological data to search for epistatic interactions. Once we identify and understand epistatic relationships using techniques such as these, we can apply this knowledge to better diagnose and treat complex diseases