TACKLING COMPLEX DISEASES WITH EPISTASIS

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Epistasis is a biological concept that was coined approximately a hundred years ago by the biologist William Bateson. Epistatic interactions, also known as gene-gene interactions, have been studied in relation to complex human diseases, such as Alzheimer's disease and multiple sclerosis, which are caused by a combination of genetic, environmental, and lifestyle factors. Some research proposes that epistasis further complicates the search for the genetic basis of such diseases; however, examining epistasis could be key to understanding complex diseases in depth.[3] Recent research also presents new insight into the role of epistasis and its ability to help further scientists' understanding of several complex diseases.

Understanding the underlying cause of complex diseases has its basis in the two Mendelian concepts of inheritance: the principle of segregation (two members of a pair of alleles separate during gamete formation) and the principle of independent assortment (alleles assort independently from each other). Not all complex diseases exhibit simple patterns of Mendelian inheritance—that is, they do not demonstrate single-gene dominant or single-gene recessive Mendelian pattern of inheritance.[9] Diseases such as cystic fibrosis and sickle-cell disease are caused by mutations in one gene, whereas more pervasive diseases, such as Type 2 diabetes and heart disease, are due to effects of multiple genes.

Bateson first used the term "epistatic" in 1909 to describe how a particular allele at one locus prevents the other allele from expressing its effect.[2] For example, two loci, B & G, both influence hair color in mice.[2] Locus B has two possible alleles, B and b, and locus G has two possibilities, G and g. There are three possible phenotypes: black, white, and grey. Regardless of the genotype at locus B, any individual with copies of the G allele (genotype G/G or G/g) has grey hair. If the genotype at locus G is g/g, an individual with any copies of B allele has black hair since at locus B, B is dominant to b. Given that the genotype at locus G is not g/g, the effect at locus B is not observable since individuals with any copies of G allele have grey hair regardless of genotype at locus B. Thus, locus G is said to be epistatic to locus B.

Multiple definitions of epistasis have been given. Nonetheless, the presence of epistasis signifies that there is something of interest in the mechanisms and pathways involved in a particular disease (more specifically, the biological interaction between specific proteins) based on a qualitative assessment where the mechanism of one factor is affected by the presence or absence of another.[2] Epistatic interactions are also highly context-dependent; a disease-causing mutation in one individual does not necessarily have the same effect in all individuals.[5] While detecting epistatic gene action may provide little value in revealing the underlying process behind a disease, the understanding of different modes of interaction between potential disease loci can help with the detection of genetic effects.[2]

Evidence for epistatic interactions comes from studies in model organisms such as

C. elegans (nematodes) and *Drosophila* (fruit flies), where systematic screens have revealed the presence of epistasis.[1] Since epistasis is so prevalent in these "simple" model organisms, the assumption is that they should occur in humans as well.[1] Experimentally, mapping epistatic interactions requires large sample sizes.[8] Multiple hypotheses must be tested, by which a severe statistical penalty is easily incurred, and a large number of tests must be evaluated computationally.[8] Because the effects of one locus (the target locus) vary depending on the allele frequency of an interacting locus, epistasis can have varying effects across populations.[8] For instance, since an interacting locus's allele frequency can vary among populations, the target locus's effect could be significant in one population but not in the other.[8] Many human diseases and disease-related phenotypes are quantitative traits whose variance is due to interactions between many different genetic loci.[1] Thus, the difference between biological epistasis (gene action) and statistical epistasis (variant alleles) should be noted.

Because more genes are expressed in the brain than in any other tissue, neuropsychiatric diseases are an ideal class of disease to study the role of epistasis in disease development.[7] Multiple genes may be involved in a disease phenotype, and multiple gene-gene interactions may or may not increase disease susceptibility. However, a single gene, apolipoprotein E (APOE), represents multiple epistatic interactions for Alzheimer's disease (AD), which is a complex neurodegenerative disorder that leads to memory loss and dementia.[7] Researchers in the 1990s found that while carriers of one or more apolipoprotein E4 (APOE4) genes have higher risk of developing AD, not every individual who carried the genes developed the disease.[4] This indicated the likely presence of other gene-gene interactions involved in the development of AD. Combarros et al. presented 27 significant epistatic interactions categorized into five groups: cholesterol metabolism, β-amyloid production, inflammation, oxidative stress, and other networks.[4] These included synergistic interactions that yielded increased risk for developing Alzheimer's, as well as antagonistic interactions that indicated a protective gene-gene interaction.[4] APOE4 yielded the strongest interactions with three different genes: α(1)-antichymotrypsin, β-secretase, and butyrylcholinesterase K.

APOE variants have consistently been linked with clear evidence to late-onset AD (LOAD); many LOAD studies also demonstrate important epistatic interactions involving APOE.[7] APOE's effects are expressed through physiological processes such as cholesterol metabolism, which is diagnostically assessed by inflammation.[7] However, it should be noted that APOE4 interactions are not necessary for predicting AD onset as the strength of APOE's effects depends on a number of genes and pathways APOE interacts with to affect risk of developing LOAD.[7]

The immune system is also a rich source of epistatic interactions. Since epistasis operates at direct interfaces between proteins, understanding these interactions provides functional and genetic insight into the risk and susceptibility of acquiring autoimmune diseases. Immune cell function is controlled by receptor-mediated activation of intracellular signalling pathways, which initiate transcriptional and non-transcriptional processes affecting the cell state.[6]

"Bateson first used the term 'epistatic' in 1909 to describe how a particular allele at one locus prevents the other allele from expressing its effect."

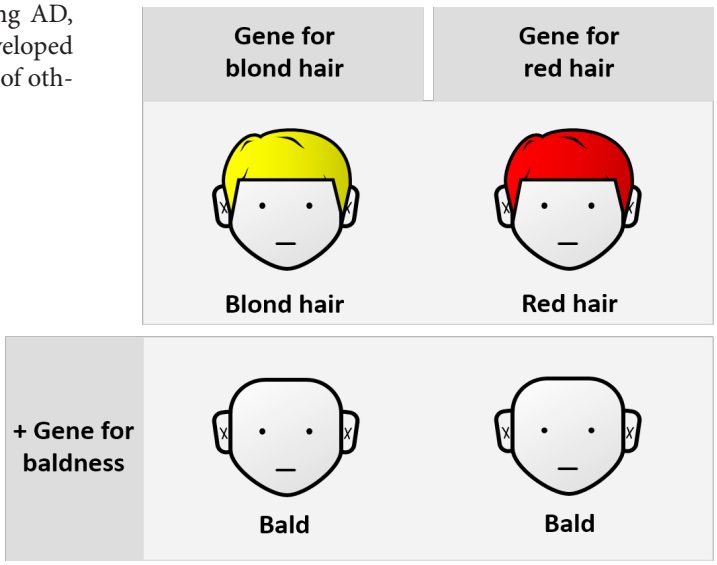

Figure 1. The gene for baldness is shown in this example to be epistatic to the gene for both blond hair and red hair.[11]

“A single gene, apolipoprotein E (APOE), represents multiple epistatic interactions for Alzheimer’s disease (AD).”

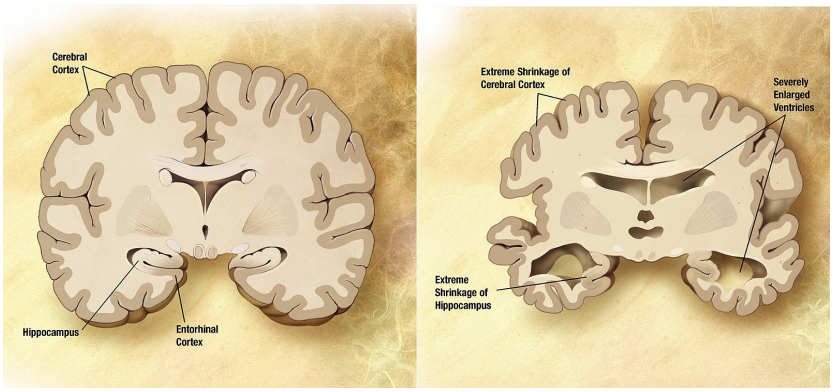

Figure 2. The APOE gene represents multiple epistatic interactions that are potentially responsible for developing Alzheimer’s disease.[7]

Epistasis occurs in multiple sclerosis, an inflammatory disease of the central nervous system in which activation of CD4+ T cells induces an influx of inflammatory cells that eventually causes demyelination, neuronal pathology and neurological dysfunction.[6]

Since treatments for various diseases are constantly being developed, understanding the genetics of diseases through epistasis could provide useful insight. Considering epistatic effects of a disease can potentially help provide better personalized disease treatments.[7]

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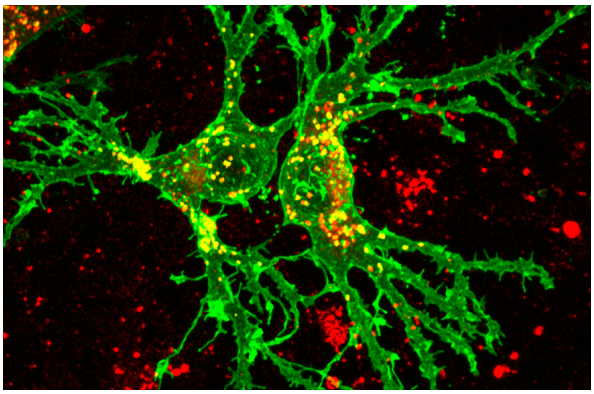

Figure 3. Epistatic interactions in multiple sclerosis induce demyelination, neuronal pathology, and neurological dysfunction.[6]

IMAGE REFERENCES

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