Trends in Genetics

CellPress

Review

Epistasis in Neuropsychiatric Disorders

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The contribution of epistasis to human disease remains unclear. However, several studies have now identified epistatic interactions between common variants that increase the risk of a neuropsychiatric disorder, while there is growing evidence that genetic interactions contribute to the pathogenicity of rare, multigenic copy-number variants (CNVs) that have been observed in patients. This review discusses the current evidence for epistatic events and genetic interactions in neuropsychiatric disorders, how paradigm shifts in the phenotypic classification of patients would empower the search for epistatic effects, and how network and cellular models might be employed to further elucidate relevant epistatic interactions.

Trends

Identifying epistatic interactions through hypothesis-free genome-wide approaches remains challenging and the contribution of epistasis to neuropsychiatric risk remains unclear.

Many hypothesis-led studies have shown risk-increasing interactions between common variants.

There is also evidence that genetic interactions contribute to the pathogenicity of rare multigenic copy-number variants.

Current efforts to reduce the phenotypic heterogeneity within cohorts may help to identify the underlying perturbed molecular networks and thereby aid the identification of interactions between their constituent genes.

Defining Epistasis

Epistasis was historically defined by Bateson to describe the masking, or modifying, effect that one allele may exert over another allele at a different locus and later by Fisher more quantitatively as deviation from additivity of two genetic variants on a phenotypic trait [1,2]. Although epistatic effects arise due to interdependencies at higher levels of organisational complexity (e.g. interorgan dependencies), much of the focus of our understanding has been directed at dependencies within molecular pathways. Proteins act together in pathways to enact biological functions. Inevitably, dependencies within pathways, such as rate-limiting steps or events requiring the presence of multiple proteins, mean that the consequence of genetic variation affecting the functioning of one constitutive member may be not be independent of variants affecting other members. Where the outcome of a molecular pathway results in a measured trait, these dependencies may condition the trait effect of a particular variant, giving rise to non-independent, or epistatic, effects. Synergistic epistasis occurs when the combination of alleles together exacerbates the effect of each allele independently, while antagonistic epistasis occurs when their joint effect is diminished. However, the concepts of synergy and antagony are really only sensible when considering interactions between two alleles and are difficult to apply at higher-order interactions between three or more alleles. This review is focused on our current understanding of the role of epistasis in neuropsychiatric disorders. There have been several excellent reviews introducing epistasis from both a systems and a population genetics perspective and that summarise our current understanding of the contribution of epistasis to human disease more broadly [3–7].

The Problem of Phenotype

The determination of whether an effect arising from the combination of multiple alleles is deemed to be additive or epistatic is dependent on the assumption that the scale underlying a trait/phenotype is linear and well behaved. From our knowledge of molecular systems – for example, rate-limiting steps – this is very unlikely to be true [7]. If we treat disease status in the simplest manner as a dichotomous trait, either present or absent, it is a convenient assumption to think that the measured risk of each disease-predisposing variant independently moves a healthy individual along an imaginary linear scale toward a hard cliff edge beyond which their

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categorical status is changed to disease. Genetic variants that contribute to highly complex traits – for example, height or IQ – might appear additive simply due to the summation over a high number of synergistic and antagonistic interactions with many other alleles, or their combined effects might be genuinely additive as they affect different and distinct processes, with each process independently contributing to an aspect of the same trait. In many statistical genetics approaches, the contribution of epistasis is considered only after first explaining as much as possible through additive or dominance effects, which will act to downplay the epistatic contribution while inflating additive and dominance contributions [6]. To truly understand the contribution of epistatic effects, we must first understand each of the molecular mechanisms that quantitatively determine the trait/phenotype of interest and the impact of each allele on that mechanism. Thus, the more closely a trait is determined by a well-elucidated molecular process, the more easily the true picture will be revealed.

Unfortunately, an outstanding problem for disorders such as autism or schizophrenia is that the wide spectrum of phenotypes associated with each disorder according to current Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria is likely to belie a large number of distinct underlying molecular aetiologies [8–13]. Recent efforts to address the phenotypic heterogeneity in neurological disorders include the Research Domain Criteria (RDoC) framework, which seeks to move away from the study of patients grouped together through a common overarching clinically consistent classification (e.g., schizophrenia) and to deconstruct these disorders into the contributing behavioural traits or endophenotypes and their underlying neurological circuits and systems [14–17]. As epistasis between alleles at different loci suggests their participation in the same disease-relevant molecular pathway [18,19] and given that genes that disrupt the same molecular pathway are more likely to influence similar phenotypes [20], refining the search for epistatic effects to more specific neurophysiological or anatomical traits may prove fruitful. As illustrated below, the use of neuroimaging to identify specific anatomical intermediate phenotypes influenced by epistatic interactions in healthy populations has been a successful strategy that will only grow in power as the size of imaging cohorts increases [21–24].

Another important reason to decompose these disorders and study their contributing traits is the significant degree to which different neurological disorders are influenced by the same genetic variants, suggesting common molecular pathways between disorders. For example, although schizophrenia and bipolar disorder (BPD) are clearly distinct disorders as evidenced by their patients' differential therapeutic responsiveness, the genetic correlation among the disease-predisposing common variation between these disorders is very high (0.68 ± 0.04 SEM), revealing significant shared genetic liability [25]. For rare genetic variants, which due to their greater effect sizes ought to be more deterministic in their phenotypic consequences, specificity of risk is similarly unclear. For example, rare **CNVs** (see Glossary) associated with schizophrenia are also risk factors for intellectual disability (ID) and autism spectrum disorder (ASD). Similarly, a meta-analyses of rare coding variants observed in patients across four disorders – namely, ASD, epileptic encephalopathy, ID, and schizophrenia – identified 53 candidate genes that were causally associated with more than one of the four disorders examined [26]. The effect of the genetic background and/or the environment in modulating the effect of highly penetrant gene variants is most clearly illustrated by large-scale analyses revealing that many healthy people appear to possess homozygous deletions of recessive disease-associated genes and even of genes thought previously to be essential [27,28].

While it might reasonably be hoped that a greater degree of aetiological homogeneity may be found by examining the underlying traits that contribute to a disorder, it is unclear at which point in the levels of the organisation of connectivities in the brain that the modifying effects of the genetic background or environment to generate the diversity in resulting phenotypes. If

Glossary

Copy-number variant (CNV): a deletion or duplication of over 1 kb of DNA.

Single-nucleotide polymorphism (SNP): a nucleotide base pair variant in the population with a minor allele frequency greater than 1%.