HUMAN GENETICS

High Anxiety

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Why do humans behave so differently from one another? There is perhaps no question more fascinating, important, or controversial. Heritability studies tell us that if we look hard enough, variants of genes that influence behavior will be identified. And in fact, much of the variation in personality traits and in diseases such as schizophrenia, bipolar affective illness, and alcoholism is genetic in origin, at least when examined in one population at a single time point. On page 1527 of this issue, Lesch *et al.* provide a very clear example of this principle: The amount of neuroticism, a personality trait that can be quantified by testing (*1*), is influenced by two alleles of a gene encoding a transporter for the neurotransmitter serotonin. One allele results in more protein—and more neuroticism—and the other, less protein and less neuroticism.

One of the alleles of the transporter (called *l* for long allele) contains a 44–amino acid insertion in a regulatory region of the gene. As a result, this *l* allele is transcribed more efficiently than the short (*s*) allele and more protein is made, leading to twice as much serotonin uptake. There was a significant association of the presence of the *s* allele with higher scores for neuroticism. This is the second recent analysis of quantitatively analyzed personality traits that is taking behavioral genetics back to its Galtonian roots. Two reports related the presence of an allele of the dopamine DRD4 receptor that contains a 16–amino acid repeat to novelty seeking (*2*).

Why examine neuroticism, which is seemingly much harder to get a handle on than the psychiatric diseases whose genetic bases have been a greater focus of attention? Arguably replicated linkages—but not yet genes—have been identified for both bipolar affective illness (*3*) and schizophrenia (*4*). For alcoholism, both aldehyde dehydrogenase and alcohol dehydrogenase alleles are protective. In fact, neuroticism too is a reliably measured trait, although like the behavioral diseases, it has a complex architecture and highly heterogeneous origins. In addition, neuroticism predicts other behavioral phenotypes such as anxiety and depression and can also tell us about psychiatric illnesses, which may be extremes of behavioral continua.

The identification of the functional serotonin promoter variant is illustrative of an old, but recently neglected, strategy that is nevertheless decisively successful and deserves a new look by psychiatric geneticists. This strategy—testing candidate alleles—is a forward genetics approach, which looks for a relation between the phenotype and a variant that alters gene structure and the function or expression of the gene product. Thus, what is being searched for is not identity of the genetic marker by descent but identity by state. It is the actual presence of the allele that is important, not, as is true for reverse genetics, linkage to a nearby structural difference in the DNA. Reverse genetic linkage, with markers chosen for informativeness and genomic location, has advantages and disadvantages in power and genome coverage. A whole genome can be analyzed by linkage with panels of highly informative markers; today, the candidate gene approach can only examine a few thousand DNA bases at a time. However, for common phenotypes that are determined by multiple genes, as are most behaviors, the power of linkage to detect loci responsible for a small portion of the variance (for example, <10%) is very low (*5*). Thus, under realistic models of frequency and transmission, no region of the genome can be excluded. Even less likely may be the detection of most or all of the loci that contribute a larger portion of the variance (for example, 50%). Furthermore, the low prior probability to detect valid linkages by whole-genome scanning predicts that many detected linkages will prove to be artifacts, exactly as has occurred. Finally, to detect association in populations, disequilibrium of the marker with a functional variant is required. Until the marker density is much higher, perhaps on the order of hundreds of thousands of markers (*5*), this will dilute, perhaps fatally, the power to detect the effect of the nearby allele.

Relating a functional variant of a gene to a phenotype—the candidate allele approach—has its own pitfalls. One difficulty is evaluating the significance of an association. It is true that the prior probability for legitimate association is higher with an allele that alters function. Also, if the mode of action of the allele is known, the grouping of genotypes by the "presence of allele–absence of allele" for statistical analysis can be justified. The reader will have to judge whether new results from the Lesch *et al.* data from 10 individuals of three genotypes establish a dominant mode of action of the *s* allele or whether their grouping of homozygous *s/s* and heterozygous *l/s* genotypes is ad hoc. This "presence of allele–absence of allele" grouping method has frequently been misapplied in marker association studies where there were no functional data or where the marker alleles were nonfunctional [as with the marker for the DRD2 dopamine receptor (*6*)]. These arbitrary groupings of data remove degrees of freedom and inflate the significance levels, leading to nonreplications later. Indeed, the DRD4/novelty seeking association (*2*), which was based on arbitrary genotype groupings, did not replicate in a large sample of Finns (*7*).

The serotonin transporter polymorphism is one of an important but still very small list of candidate alleles for behavior that alter synthesis or function of the gene product in humans. Others include the serotonin receptors 5HT2A $His^{452}Tyr$ (which alters transduction) (*8*) and 5HT2C $Ser^{23}Cys$ (ligand affinity) (*9*), and the dopamine DRD2 $Ser^{311}Cys$ variant (transduction) (*10*) and the DRD4 16–amino acid repeat (*11*). Identification of candidate alleles is one important approach for elucidating the origin of the measured heritabilities of behavioral traits and psychiatric diseases.

Fortunately, the brevity of the list of candidate alleles is a situation that cannot last. The number of potential candidate genes—genes that can in any way alter brain function—is formidable: the cloned neurotransmitter biosynthetic metabolic, receptor, and transductional genes alone number more than 200. Many of these will possess functional variants that contribute differently to behavior—after all, alleles are why behaviors are heritable. As Barton Childs wrote, "...such is the nature of mutation that whenever a student meets the gene product—an enzyme, a receptor, a cell-adhesion molecule—he should think of potential variation and potential disease" (*12*).

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