Brain expression—is it all in our SNPs?

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Biology traditionally began as a study of phenotypes, their differences and similarities. The discovery of DNA, the molecule encoding an organism’s phenotype in its four-letter sequence, shifted the focus of biological research towards deciphering this information. Now, with the complete genome sequences of human and many other organisms available, it is the connection between genotype and phenotype that frustrates biologists the most. In the new study published in Nature Genetics (Myers et al., 2007), the authors attempt to bridge this gap by examining both genetic and gene expression variation in 193 human brain samples, all from neuropathologically normal individuals.

In each of the 193 samples, the authors used microarray technology to survey the gene expression levels of approximately 25,000 human genes and determined the sequence composition of half a million of the single nucleotides distributed throughout the human genome and known to be polymorphic among humans (single nucleotide polymorphisms or SNPs). In the brain, they reliably detected signals for more than half of all the transcripts (14,078) and more than two-thirds of all the SNPs (366,140) present on the arrays. Following the approach implemented in several previous studies conducted on human cell lines or the mouse brain, the authors used gene expression levels as quantitative traits that can be associated with the SNP profiles of the individuals (Morley et al., 2004; Stranger et al., 2005; Hovatta et al., 2007). The sheer amount of data gives the authors considerable power to detect such associations. Indeed, they succeed in linking gene expression differences to SNPs for as many as 2,975 transcripts. Surprisingly, in almost 97% of the cases (2,876 transcripts), the corresponding SNPs were located far away from the expressed gene (further one million nucleotides from each side). This is unusual, given that the majority of the expression differences observed between various mouse strains—a sort of artificial equivalent of different human populations—are caused by nucleotide polymorphisms in cis-regulatory elements as well (Hovatta et al., 2007). It is thus intriguing to speculate that, unlike in mice, in humans much of the expression variation observed among individuals may be caused by mutations in trans-acting expression regulators, such as transcription factors or microRNAs, rather than by polymorphism in the regulatory elements adjacent to the gene, such as promoters.

More generally, the study provides important insight into the effect that nucleotide variation among humans has on gene expression in one of the most complex tissues—the brain. It will greatly facilitate future studies of gene expression and SNP variation in cognitive disorders by providing an essential reference for identifying pathological changes associated with disease.

Still, with regard to the connection between genotypic and phenotypic variation, the step from gene expression variation to an organism’s phenotype remains obscure. The authors make all their observations using brains of neuropathologically normal individuals; thus, all genetic and expression variation should be compatible with normal human brain activity. Does it mean that all this variation is completely neutral with respect to the phenotype? One could argue that some variation may reflect individual differences in cognitive, social or emotional traits. Yet the extent or even the existence of such a functional connection between gene expression in the brain and one’s personality is far from certain. It could also be argued that gene expression variation observed in brain does not necessarily need to be restricted to brain. Given that the vast majority of expression variation is not caused by SNPs located in close proximity of the gene, that is, in the promoter region, we may expect that their effect will be shared among many tissues. If true, this complicates the connection between gene expression and phenotype even further: the same expression difference may be functional in one tissue, such as heart or liver, but irrelevant in the brain.

These problems, however, are not drawbacks of the study. Instead, they underscore the vastness of the gap that remains in our understanding of the connection between genetic variation and phenotype. The authors take a significant step toward bridging this gap by uncovering a large chunk of the mechanistic connection between nucleotide polymorphism and gene expression variation. If we continue at such a pace, we can hope that one day we will perhaps be able to reconstruct an organism’s phenotype by looking at its DNA, just like a tooth from a long extinct creature can reveal wonders about its appearance and habits.
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