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Sequence and function in pharmacogenomics

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A key issue in phenotype to genotype pharmacogenomic studies is the choice of genomic targets to sequence. Even though changes that do not affect protein function may be truly associated with a phenotype, it is understandable that interest is greater when an association exists between the phenotype of drug response and sequence variation that impacts on function. In this issue this topic is elegantly addressed by Lin and Uhl (pp 159–168). They studied the human dopamine transporter (DAT), a 12 transmembrane domain protein that decreases the synaptic availability of dopamine. Cocaine and amphetamine, among other psychostimulants, block this key membrane transporter, thereby contributing to the rewarding properties of those drugs. In previous human studies, the authors identified the presence of alanine/valine substitution variants V55A, located in DAT's intracellular N-terminus and V382A, located in DAT's fourth extracellular loop. They now characterize these two variants.

The data show that these two naturally occurring human DAT variants have effects on DAT expression patterns, pharmacology, and physiology that differ from the wild-type molecule. Their results suggest that the individuals with these variants could have altered dopaminergic neurotransmission and might respond differently to drugs that affect dopamine pathways. Owing to these interesting results, these two variants become logical candidates for genetic studies of diseases in which dopamine function is thought to be of etiological relevance, as well as in pharmacogenomic studies of drugs that act through dopaminergic pathways. As the number of targets for genotyping has increased considerably, the characterization of the functional relevance of variants in key genes becomes increasingly important. Variants with higher physiological impact would become logical candidates for association studies.

As data sets containing phenotypes of drug response are accumulated, it is necessary to delineate criteria for choice of SNPs and haplotypes. As we discussed previously,[1] should one look in great detail at a few genes thought to be particularly relevant to the effects of a specific drug, or should one look at functionally relevant variations across a wide number of genes? It is possible to look at myriad candidates, but each sample has only a certain amount of power. These important points will certainly be considered during the course of work in this area.

In this context, the work of Lin and Uhl is particularly relevant because it identifies the functional impact of variants of an important molecule that is relevant to drug response. Future work should examine the frequencies of the V55A alleles V382A in populations that received drugs affecting dopaminergic neurotransmission.

Additional points to consider include the final effect on dopamine function of a combination of these variants with others that are known to affect function, such as the A559V in transmembrane domain 12 and E602G in the C-terminus. Moreover, the interactions of variants in the dopamine transporter with those in other related molecules, such as dopamine receptors, should be examined in future pharmacogenomic studies. This type of work on the functional relevance of variants identified in genetic studies highlights the need for crossdisciplinary interaction at the interface of genetics and neuroscience.

REFERENCES

1 Wong M-L, Licinio J. *Nat Rev Neurosci* 2001; **2**: 343–351.

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