Pharmacogenomics

The value of control conditions for evaluating pharmacogenetic effects

The article by Leung et al. [1] provides a meta-analysis of *CHRNA5-CHRNA3-CHRNB4* rs16969968-rs1051730 and smoking cessation in the context of six treatment trials where all participants received nicotine replacement therapy. The authors found no evidence of significant association between the variant and successful smoking cessation, and in keeping with this, the authors conclude that "the alleles of rs1051730 and rs16969968 are not associated with smoking cessation." It is possible that this statement is essentially, universally true. However, we would like to emphasize that the authors' conclusion is based on analyses of trial data that comprised no placebo controls. It is possible that the genetic variants in question exert different effects in the presence of active pharmacotherapy versus placebo. For example, multiple genes can predict coronary artery disease outcomes, but examination of only individuals treated with statins will not reveal some of the genetic associations because these medications modify the genetic effect [2]. Similarly, the *CHRNA5* effect on smoking cessation may be moderated by nicotine replacement therapy [3], suggesting that meta-analyses of pharmacogenetic effects should include both placebo and active treatment arms. Indeed, many authors have urged that pharmacogenetic research such as the Leung et al. study analyze both placebo and active medication arms to fully understand genetic modifiers of treatment [4–6].

It is likely that some of the variability in genetic relations across studies and analyses reflects the complex moderation of genetic effects by environmental factors such as treatment, comorbidities and environmental events such as stressors and social contexts [3,7–8]. The genetic effect of *CHRNA5* on smoking cessation has been demonstrated in some research studies [3,7,9–15], but not in several other important studies [16–19]. We believe that such variability reflects the actions of important moderators related to treatment and sample characteristics. While the Leung et al. [1] study was not intended to detect such moderation, we believe that further research on such effects is needed for a methodologically principled approach to the application of Precision Medicine in order to best help out patients quit smoking.

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