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Therapygenetics: moving towards personalized psychotherapy treatment

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Abstract

New research suggests that genetic variation predicts response to cognitive behavior therapy (CBT) for the treatment of pediatric anxiety. We discuss this intriguing finding, review its implications for understanding the etiology of psychopathology, and suggest that psychosocial treatment research would strongly benefit from routinely assessing genetic variation in clinical trials.

A recently published article by Eley and colleagues [1] provides tantalizing preliminary evidence that variation in the promoter region of the serotonin transporter gene (i.e., *5-HTTLPR*) predicts response to cognitive behavior therapy (CBT) among children diagnosed with an anxiety disorder. Specifically, children with two copies of the low expressing S-allele had better symptomatic response to treatment at follow-up (i.e., 6 months after completion of CBT) than children with one or two copies of the L-allele.

These findings are fascinating and provocative for a number of reasons. They provide additional evidence that interactions between genetic variation and environmental experiences (G×E) can influence the development (or in this case remission) of psychiatric outcomes. Although most prior G × E work has examined the interaction between genetic variation and naturally occurring experiences, Eley *et al.* [1] directly manipulate environmental influence by providing a putatively efficacious psychotherapy for anxiety. Although it would have been ideal for this study to include a no-treatment control to account for passage of time, and we eagerly await replication studies, these data nevertheless support a G × E framework.

Within the larger framework of G × E research, there has been vigorous debate about whether the *5-HTTLPR* polymorphism in particular contributes to the etiology of mood and anxiety symptoms by influencing sensitivity to the environment [2]. Much of the early debate focused on whether *5-HTTLPR* facilitates negative consequences in adverse environments. However, more recent data, including Eley *et al.* [1], suggest that *5-HTTLPR* is also linked with positive outcomes in supportive environments. Rather than only

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increasing vulnerability to negative outcomes, the *5-HTTLPR* genotype may flexibly influence behavior depending on environmental context [3]. This plasticity model may explain why the S-allele is maintained in the human population over evolutionary time given that selection pressures should favor polymorphisms associated with adaptive outcomes.

Given that CBT is a multimodal intervention that influences a variety of cognitive and behavioral processes, it is possible that *5-HTTLPR* variation might have even greater predictive power for a more focused treatment. There is consistent evidence that *5-HTTLPR* is associated with biased attention for emotion cues [4]. Importantly, one emerging form of treatment for anxiety is attention bias modification [5] – a procedure that trains anxious individuals to shift attention away from threat stimuli. It follows that anxious S-allele carriers may be particularly responsive to attention bias modification [6]. Clinical trials examining whether *5-HTTLPR* variation moderates the impact of attention training on anxiety symptoms among clinical samples are forthcoming.

We also look forward to future research that examines whether other putatively functional variants in the serotonin transporter (*SLC6A4*) and other genes influence response to psychotherapy. To do so, newly developed analytic strategies, such as a cumulative genetic score (CGS), which attempt to aggregate genetic effects across polymorphisms and/or genes [7], would be particularly useful. The CGS approach is substantially different from examining a single polymorphism in isolation. CGS analyses combine contributions from multiple polymorphisms into a single parameter in an effort to increase variance explained, whilst simultaneously accounting for ‘genetic background’ that might otherwise obscure single variant effects. Thus, this innovative analytic approach could have far more explanatory power than analyses examining a single polymorphism, the dominant approach for candidate gene association studies.

Furthermore, a model that integrates genetic, neurobiological, psychological, and behavioral levels of analysis (among others) could provide a roadmap for how to treat mood disturbance more effectively. Currently, most treatments target a single level of analysis; an integrated model could suggest a more synergistic approach to treatment. For instance, improving prefrontal cortical function may facilitate the efficacy of CBT for depression [8]. Similarly, D-Cycloserine, a partial agonist of the N-methyl-D-aspartate receptor that enhances extinction learning, has been used to augment CBT for panic disorder [9]. Genetic information could be used to determine who is most likely to respond to these forms of treatments. We believe that integrating knowledge across levels of analysis has the potential to substantially improve treatment efficacy.

Although genotyping for personalized medicine will potentially increase the costs of existing treatment strategies, genotyping costs are dropping rapidly due to advances in technology. More importantly, increased treatment costs can still be cost-effective to the extent that the incremental costs improve patient functioning and increase treatment success rates. For example, use of antidepressant medication increases the cost of treatment in a value-added fashion that justifies the incremental cost, even though antidepressant medication can take weeks to show an effect [10]. Just as pharmacogenetic strategies aspire to match patients to medications to improve efficacy and reduce noncompliance due to side effects, genetically targeted behavioral treatments may also reduce time to remission. Use of a genetic test as a biomarker of a neurocognitive vulnerability (e.g., attention bias) may allow more focused and effective treatments to be provided to those who are most likely to benefit. With an estimated cost of \$700 per day for in-patient treatment for depression, the reduction of hospitalization even by a single day by using a successful genetic matching strategy more than covers the cost of genotyping. The possibility that genetic testing can increase value of treatment efforts more than the cost of the testing itself is an intriguing

possibility that has not yet been examined for psychiatric outcomes. This is an important avenue for future research.

In conclusion, we believe that the Eley *et al.* [1] study is an excellent example of why genetic variation can (and should) be incorporated into psychosocial treatment research. This will require close collaboration among experts from diverse fields (e.g., psychologists, geneticists, neuroscientists, statisticians). However, doing so promises to deliver a fuller, more nuanced understanding of psychopathology which, in turn, could enhance the ability to tailor treatments to individuals based on genetic profile, increase the effectiveness of psychosocial treatments, and ultimately alleviate substantial suffering associated with psychiatric illness.

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