Research Highlights

Highlights from the latest articles in pharmacogenomics

Progress in the pharmacogenomics of antidepressant response

Depression is a serious health problem that knows no geographic and cultural boundaries. Owing to its ubiquity, morbidity and associated mortality, depression has been projected by the WHO to rank second as a cause for global disease burden by 2020 [101]. Despite remarkable progress in pharmacotherapy and other treatment strategies for depression, more than half of patients fail to respond optimally, and many suffer from untoward effects [1].

In recent years, pharmacogenomic research has led to the identification of a number of promising 'candidate genes' for predicting antidepressant response. However, the interpretation of the literature is often complicated by ethnicity/race. In order to move forward it is increasingly

apparent that study designs including cross-ethnic comparisons and international collaborations are indispensable. The articles reviewed herein eloquently demonstrate the advantages of adopting such a perspective in pharmacogenomic research.

Reference

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Catechol-*O*-methyltransferase polymorphism and acute antidepressant response to sleep deprivation with light therapy

Evaluation of: Benedetti F, Barbini B, Bernasconi A *et al.*: Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-*O*-methyltransferase Val(108/158) Met polymorphism. *J. Affect. Disord.* (2009) (Epub ahead of print).

As a major player in the catabolism of dopamine and norepinephrine, catechol-*O*-methyltransferase (*COMT*) has long been implicated as a susceptibility gene for a number of major neuropsychiatric

disorders, including Parkinson's disease, schizophrenia and mood and anxiety disorders. Specifically, the *COMT* polymorphism at rs4680 G>A results in the substitution of valine with methionine, and decreased enzyme activity, which has long been known to influence the effect and dosing of levodopa and the related medications for Parkinson's disease [1]. Recent reports have suggested that *COMT* polymorphisms may also be associated with both antipsychotic and antidepressant responses [2]. However, findings from these studies were not consistent, probably reflecting in part the complexity of factors

determining medication response, including the time lag between treatment initiation and clinical improvement. In this study [3], the authors used total sleep deprivation (TSD) and light therapy (LT), the antidepressant effects of which are more immediate and easier to assess, to test the relevance of the *COMT* polymorphisms for antidepressant response. Similar in design to the group's previous studies focusing on serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) polymorphism [4], this study included 87 depressed bipolar inpatients who were subjected to one night of TSD plus LT, followed by LT after a second night with sleep. The results demonstrated a statistically significant advantage for Met/Met homozygotes after TSD plus LD. However, such differences disappeared after the recovery night and LT.

This pattern of response is similar to the effects of functional genetic polymorphisms of other genes influencing dopaminergic receptor signaling, but different from gene variants affecting serotonergic function, where the effect of genetic polymorphism persisted after the

recovery night [2]. Since such differential response patterns were also observed in studies involving antidepressant medications, the authors concluded that the effects of the two therapeutic approaches (LSD + LT vs medications) were mediated by similar mechanisms.

As the authors pointed out, limitations including a relatively small sample size, medium size effect, potential selection biases and other methodological issues necessarily caution against excessive enthusiasm over these findings and demand replication and clarification. In such a context, the following two issues may be of particular interest for future investigations. First, the fact that the study's results suggested similarities between bipolar and unipolar depression is intriguing, pointing to new avenues for further clarification. Second, as is true with the vast majority of functional genetic polymorphisms, the distribution of the allele types and genotypes of the *COMT* gene varies substantively across ethnic/racial groups (the Met variant occurs with a similar frequency to the Val variant in Caucasians, but is much more prevalent in practically all other ethnic groups, including those with East Asian and sub-Saharan African ancestral origins), and clinical outcomes associated

with these genotypes also often point to opposite directions across ethnicity. Such observations are fascinating and puzzling at the same time, indicating that the significance of an individual's ancestral backgrounds goes beyond 'population stratification', and deserves center spotlight in future pharmacogenomic research efforts.

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Monoamine transporter gene polymorphisms affect susceptibility to depression and predict antidepressant response

Evaluation of: Min W, Li T, Ma X *et al.*: Monoamine transporter gene polymorphisms affect susceptibility to depression and predict antidepressant response. *Psychopharmacology (Berl.)* 205(3), 409–417 (2009).

As the primary therapeutic target for selective serotonin reuptake inhibitors, the serotonin transporter gene *5-HTT* has been the focus of intense scrutiny [1]. This is particularly true with *5-HTTLPR*, a functional

polymorphism in the gene's promoter region that appears to be a risk factor for many neuropsychiatric disorders, including depression. The polymorphism also affects antidepressant response, with the *l* allele consistently showing advantages in Caucasians but conflicting results in East Asians, including some showing effects in a reverse direction. Ethnic variations are substantial with *5-HTTLPR*, as the *l* allele frequency ranges from 20% in East Asians to 50% in Caucasians and 70% in those of sub-Saharan African origins.

In a similar manner, polymorphisms of norepinephrine transporter (*NET*) have been expected to play a significant role in determining antidepressant response. However, much less literature is available in this regard, likely because far fewer antidepressants specifically targeting *NET* have been clinically available. In addition, most *NET* gene variants have been identified as either rare or possibly 'silent' (synonymous), with the recently discovered T182C polymorphism located in the promoter region as a possible exception [2].

Conducted by researchers from a major medical center located in Sichuan (West China), this study included 657 depressed patients and 473 healthy controls. Patients were assessed with standard protocols and treated with either one of the selective serotonin reuptake inhibitors (fluoxetine, paroxetine or citalopram) or a serotonin-norepinephrine reuptake inhibitors (velaxetine). Genotyping was done with the polymorphisms mentioned above, as well as for the *NET* G1287A, a synonymous variant in exon 9 in complete linkage disequilibrium with T102C. The major findings include the following: *NET*-T182C interacting with *5-HTTLPR*, was associated with the risk and severity of depression (*NET* c/c + *5-HTTLPR* s/s were less susceptible to depression and had less severe depression when symptomatic); *5-HTTLPR* l/l + *5-HTTST* in two 12 repeats were correlated with a better treatment response, while *NET* polymorphisms showed no such effect.

Despite some limitations listed by the authors toward the end of the paper, the study is unique in that it shows clear-cut

interactive (additive or synergistic) effects between two major *5-HTT* polymorphisms in relation to antidepressant response and similar interactive effects between *5-HTT* and *NET* genes in determining the risk and severity of depression. Such interactions are congruent with prevailing theories regarding the pathogenesis of depression (and practically all 'complex disorders'), but they were rarely demonstrated in previous studies, largely because of sample size limitations [3]. This study therefore represents a significant milestone in moving the field towards the goal of individualizing pharmacotherapy.

The relatively large sample size of this study also allows it to weigh in significantly on the long debate concerning the relationship between *5-HTTLPR* polymorphism and antidepressant response in East Asian populations. Some, but not all, previous studies demonstrated that in Asians, it was the *s* rather than *l* allele that conferred advantage in treatment response. The results of this study suggest that this might not be the case. Although

replication of, and extension from, the study will still be needed, this contribution does represent a major step towards the resolution of an important issue.

References

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BDNF and its association with major depression and antidepressant treatment response

Evaluation of: Licinio J, Dong C, Wong ML *et al.*: Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. *Arch. Gen. Psychiatry* 66(5), 488–497 (2009).

Although most of the earlier breakthroughs in medical genetics have resulted from the identification of specific alterations in single genes, such a strategy might not work with 'complex diseases', such as hypertension, diabetes and schizophrenia [1,2]. Accordingly, recent research efforts have focused on various common alleles (polymorphisms) in different genes believed to affect the pathogenesis of these disorders, each expected to have a modest contribution toward disease susceptibility. While

this will most likely remain as the guiding model, some researchers have started to voice an alternative view, emphasizing the contribution of multiple rarer variants, each with intermediate to large effects for complex disorders [3]. Such a model speaks for the importance of comprehensively screening and identifying all variants for key candidate genes, and examining their relevance to the susceptibility for and treatment response of related diseases. Following this logic, the authors selected *BDNF*, encoding a key peptide crucially involved in many aspects of the function of the brain, as the focus of this study [4]. *BDNF* sequencing was performed with genomic DNA collected from 272 Mexican-Americans with major depression and, approximately equal number of controls with same ethnic backgrounds. Patients were assessed according to standard protocols and treated with

either fluoxetine or desipramine. A total of 130 SNPs were detected, including 83 that had not been previously reported. When compared with published HapMap, ethnic variations in the frequency and pattern of these variants appeared large, which might be responsible for conflicting results regarding *BDNF*'s role in relation to depression in previous studies.

Of the six SNPs associated with depression, only one (rs12273539) remained significant after adjusting for multiple testing. In addition, two haplotypes also showed significant association with depression. A 5' untranslated region SNP, rs6188800, correlated with antidepressant response after multiple corrections.

In view of the potential importance of the rare variant/common disease model, the report demonstrates the significance of extensive sequencing of candidate genes. The results also show promise for

further clarification of the role of *BDNF* in the pathogenesis of depression and antidepressant response. It is laudable that the study focused on Mexican-Americans, an ethnic group that have not yet received adequate attention in genetic studies. It would seem important to extend the approach adopted in this

study to include other ethnic groups, as well as replication with a larger sample size or alternative methods to minimize population stratification.

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5-HT_{2A} gene variants and antidepressant response in Japanese and Italian mood disorder patients

Evaluation of: Kato M, Zanardi R, Rossini D *et al.*: 5-HT_{2A} gene variants influence specific and different aspects of antidepressant response in Japanese and Italian mood disorder patients. *Psychiatry Res.* 167(1–2), 97–105 (2009).

Serotonin receptor 2A (5HT_{2A}) is a key player in modulating the function of the serotonin system, and is a major target for antidepressant and antipsychotic medications. Previous studies identified the T102C and A-1438G polymorphisms, strongly linked with each other, as the most important functional polymorphisms of the gene [1]. A large number of previous reports, including those contributed by the authors, have revealed a strong association of these alleles with antidepressant response and propensity for side effects. However, the associations were in opposite directions between Caucasian and Asian (Japanese) populations. Such a phenomenon has been observed in a number of genes including *5-HT_{1A}* and *BDNF*, indicating that ethnicity is a crucial factor in understanding gene effects. Such discrepancies were usually speculated to be the consequence of other, as yet unidentified, alleles or genes.

In this paper, the authors propose an alternative or complementary explanation that may be even more compelling and testable. Namely, conflicting results across ethnic/cultural/geographical boundaries may be a reflection of differences in phenotypes that may be culturally and socially determined, such as the patterning of symptom presentation and the perception and reporting of treatment responses across a symptom cluster, rather than variations in the genome. In order to test such a hypothesis, the authors retrieved individual symptom item ratings from patients previously studied at the two participating institutions, in Japan and Italy. Patients were assessed according to identical protocols, and treated with either fluvoxamine or paroxetine. The results demonstrated that T102C affected responses in different dimensions across ethnic groups: in Japanese, the T allele was associated with less and slower reductions in delusion and activity scores, whereas in Italians it was the C allele that was less effective in the amelioration of somatic anxiety symptoms. The authors concluded that these findings were in congruence with the hypothesis that selective serotonin reuptake inhibitor response is not a unitary phenomenon, and discrepant findings across

ethnicity of any gene polymorphisms may be, in part, explained by their differential effects on different symptom dimensions.

In addition to the limitations listed by the authors including small sample size and the use of different medications (both, however, are selective serotonin reuptake inhibitors), questions may be raised regarding the underlying mechanisms that might be responsible for this observed genotype–phenotype interactions, which could lead to a whole new line of intriguing research. Other factors that might play a role in shaping such interactions include assessment biases between the two institutions, where raters might diverge in their sensitivity to the severity and changes of individual symptoms. Notwithstanding these issues, the authors have made a valuable contribution to the field by providing a useful model for examining the often observed cross-ethnic discrepancies in the effect of genetic polymorphisms in candidate genes.

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