Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression: A Meta-analysis

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Context: Substantial resources are being devoted to identify candidate genes for complex mental and behavioral disorders through inclusion of environmental exposures following the report of an interaction between the serotonin transporter linked polymorphic region (5-HTTLPR) and stressful life events on an increased risk of major depression.

Objective: To conduct a meta-analysis of the interaction between the serotonin transporter gene and stressful life events on depression using both published data and individual-level original data.

Data Sources: Search of PubMed, EMBASE, and PsycINFO databases through March 2009 yielded 26 studies of which 14 met criteria for the meta-analysis.

Study Selection: Criteria for studies for the meta-analyses included published data on the association between 5-HTTLPR genotype (SS, SL, or LL), number of stressful life events (0, 1, 2, 3) or equivalent, and a categorical measure of depression defined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) or the International Statistical Classification of Diseases, 10th Revision (ICD-10) or use of a cut point to define depression from standardized rating scales. To maximize our ability to use a common framework for variable definition, we also requested original data from all studies published prior to 2008 that met inclusion criteria. Of the 14 studies included in the meta-analysis, 10 were also included in a second sex-specific meta-analysis of original individual-level data.

Data Extraction: Logistic regression was used to estimate the effects of the number of short alleles at 5-HTTLPR, the number of stressful life events, and their interaction on depression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated separately for each study and then weighted averages of the individual estimates were obtained using random-effects meta-analysis. Both sex-combined and sex-specific meta-analyses were conducted. Of a total of 14,250 participants, 1,769 were classified as having depression; 12,481 as not having depression.

Results: In the meta-analysis of published data, the number of stressful life events was significantly associated with depression (OR, 1.41; 95% CI,1.25-1.57). No association was found between 5-HTTLPR genotype and depression in any of the individual studies nor in the weighted average (OR, 1.05; 95% CI, 0.98-1.13) and no interaction effect between genotype and stressful life events on depression was observed (OR, 1.01; 95% CI, 0.94-1.10). Comparable results were found in the sex-specific meta-analysis of individual-level data.

Conclusion: This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.

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Gene-Environment Interactions

Biologically Valid Pathway or Artifact?

THERE HAS BEEN INTEREST IN THE POSSIBILITY OF GENE-ENVIRONMENT INTERACTIONS (G×E) FOR MANY YEARS. However, in the field of psychopathology, prior to the development of molecular genetics, the study of G×E required inferences in which the G concerned the totality of anonymous genes. Not surprisingly, therefore, there were few replicated examples of G×E, and most behavioral geneticists concluded that G×E was sufficiently rare and unimportant that it could be safely ignored.2 The situation was transformed by the ability to identify individual genes and by the development of methods to provide rigorous tests of environmental mediation.3 A series of 4 articles based on the Dunedin longitudinal study, each showing no main genetic effect but a significant G×E,4-7 led to a new public and professional interest in G×E and a flurry of replications. It came to be assumed that there were sufficient robust findings to conclude that G×E was a real phenomenon, important for both science and, potentially, for policy. The recent article by Risch et al in JAMA8 claims to put this assumption in serious doubt by basing the claim on meta-analysis of a minority subset of studies concerned with life events, the serotonin transporter promoter gene, and depression, using recoded data in an attempt to ensure consistency across investigations. What the published literature had shown is a mixture of both positive replications and failures to replicate (with the former outnumbering the latter).9 In this circumstance, it was entirely reasonable to review the studies’ combined findings, to determine whether there has been adequate support for the original study.
Before turning to the details of the Risch et al study, attention must be paid to the biological plausibility of what is being studied. It may be noted that $G \times E$ is to be expected because (1) to suppose that it does not exist would imply that susceptibility to the environment is almost the only biological feature outside the influence of genetics, (2) it would cast doubt on fundamentals of evolutionary theory in which genetically influenced variations in responses to the environment constitute the key mechanism, and (3) it would have to assume that genetics played no role in the well-documented huge heterogeneity of responses to all manner of environments. Also, as in all science, it is crucial to use multiple research strategies and never to rely on just one (as with Risch and colleagues’ exclusive focus on epidemiological studies).

It is also necessary to note that there is a sharp divergence in approach according to the form of the normal model chosen, divergence from which is used as evidence for interaction. Different perspectives tend to favor different null models, as is illustrated by the famous dispute between Fisher and Hogben. Tabery concluded, and we agree, that (as a biologist) Hogben was right in arguing that biological interactions must be the focus if health benefits are to be derived from an understanding of the biological pathways involved. Both Hogben and Fisher, as statisticians, were agreed, nevertheless, that there were crucial statistical issues and problems that had to be dealt with to elucidate the biology. Risch and colleagues’ meta-analysis is solely concerned with the statistical concept and, hence, fails to review the biological evidence, a point to which we return. Moreover, it argued that the focus must be on a multiplicative synergistic interaction using a logarithmic scale. Most biological researchers favor a focus on additive synergistic interactions because they better match biological concepts. The choice cannot be decided on purely statistical grounds, and it must be appreciated that the two can give rise to different conclusions.

The first decision in any meta-analysis concerns the criteria for inclusion or exclusion of particular studies. This is always problematic because of variations in the methods used in different studies. Risch et al specified their criteria, but some excluded studies appear to meet those criteria and 1 included study did not, in that the reference cited for it did not deal with $G \times E$. The latter involved larger samples, but at the cost of weaker measurements. Little is said about the relative qualities of measurement within the studies considered. Some, like the Caspi et al study, involved repeated prospective assessment, whereas others relied on single waves, with variations in the (sometimes very extended) periods of retrospective recall. It is also troubling that the recoding of the data transformed positive replications into nonreplications, with this being neither highlighted nor explained. Moreover, whereas the meta-analysis reasonably sought to make all studies conform to the genetic model used by Caspi et al, there is no agreement regarding which model operates.

The authors emphasized that they wanted to closely follow the Caspi et al study in all respects but they focused only on life events, whereas the Dunedin study also showed $G \times E$ with respect to maltreatment. Similarly, their recoding aimed to replicate the Dunedin approach in all respects. With variability in both outcome and risk factor measures, this may not be the ideal approach because considerable loss of power can arise through the unreliable transformation of one measure to another. In any case, more confidence should be placed on replications that are robust across variations in measures and contexts, provided there is consistency in the construct being assessed. The Caspi et al study was scrupulous in testing that consistency, checking for scaling artifacts and testing for possible $G \times G$ to account for the claimed $G \times E$. None of this is readily accomplished in a meta-analysis.

Risch et al claim that all studies of $G \times E$ must start with a statistically significant main effect for the genetic polymorphism. The statistical claim is unwarranted on 3 separate grounds. First, if there is a crossover, as has been found in the case of asthma, there will be no consistent main effect for $G$. In samples in which the variation in risk exposure spans the crossover point, there may be no main effect, only an interaction. In samples in which exposure is largely to the left or right of the crossover point, a main effect may be identified but with a different risk allele in each case. Second, if the $G \times E$ applies to individuals without psychopathology (which has been found in human experimental studies), there will be no $G$ main effect for the psychiatric disorder outcome. It might be reasonable to require a main effect for $G$ if there were identified genes known to affect environmental susceptibility, but these data are not yet available. Third, statisticians are divided on the merits and demerits of testing for main effects before interactions or vice versa. Each approach has advantages and disadvantages, and it is misleading to claim that only 1 has validity. The order should be determined by the plausibility of the science.

Finally, and most crucially, the Risch et al article is seriously flawed in casting doubt on all $G \times E$ findings on the serotonin transporter promoter gene without reviewing its role in drug response, considering animal models or discussing the human experimental studies of $G \times E$ or the relevant basic science findings. Even within the narrow compass of the studies used in their meta-analysis, they fail to ask why they find no significant $G \times E$, whereas several of the original articles did find significant $G \times E$. It is always necessary to ask why some findings are positive and some negative. In addition, Risch et al use their meta-analysis to cast doubt on other $G \times E$ research without reviewing examples from the rest of internal medicine.

In summary, we conclude that the totality of the evidence on $G \times E$ is supportive of its reality but more work is needed to understand properly how $5HTT$ allelic variations affect response to stressors and to maltreatment. The Risch et al article is useful in reminding us of the importance of replication, but the goal must be to gain a biological understanding. Regardless of how well the meta-analysis is done, it summarizes only some of the available scientific data for just 1 risk factor and 1 outcome. It would be extremely damaging to use it alone to call a halt on further $G \times E$ studies. Rather, we need more such studies but they must be of high quality, seek
to examine the causes of divergent findings, and make thoughtful use of multiple research strategies.

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REFERENCES