

## Editorial Policy on Candidate Gene Association and Candidate Gene-by-Environment Interaction Studies of Complex Traits

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The literature on candidate gene associations is full of reports that have not stood up to rigorous replication. This is the case both for straightforward main effects and for candidate gene-by-environment interactions (Duncan and Keller 2011). As a result, the psychiatric and behavior genetics literature has become confusing and it now seems likely that many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge. The reasons for this are complex, but include the likelihood that effect sizes of individual polymorphisms are small, that studies have therefore been underpowered, and that multiple hypotheses and methods of analysis have been explored; these conditions will result in an unacceptably high proportion of false findings (Ioannidis 2005).

Because of this, the Editor and Editorial Board have increasingly erred on the side of caution in considering candidate gene association studies of complex traits. To avoid publishing findings that will not replicate, we recommend that authors conduct a direct replication analysis (Sullivan 2007), prior to publication, such that the same predictor(s), outcome variable, and statistical model are tested in an independent sample. Such replication does not guarantee that the result is correct as there are still many ways to obtain and replicate an artifactual result, but it does reduce the probability that the original finding was due to chance (a Type-I error) or to biases of other kinds that are more difficult to quantify. Direct replication should be a minimum requirement for candidate gene association

studies of complex traits, especially when reporting complex interaction effects based on novel phenotypes and groupings. Of course, we understand that this has not been done routinely—sometimes it is not practical—and so authors have preferred to publish the initial paper without such replication. We also recognize that there are historical examples where early failures to replicate were themselves misleading because of heterogeneity or poor methodology.

However, for a candidate gene or candidate gene-by-environment interaction study of a complex trait to be considered for publication in *Behavior Genetics* it should *usually* have one or more of the following characteristics:

- It is a rigorously conducted, adequately powered, direct replication study of a previously reported result; for well conducted replication studies, there is no editorial preference in *Behavior Genetics* for or against null, positive, or contradictory findings.
- It was an exploratory study or test of a novel hypothesis, but with an adequately powered, direct replication study reported in the same paper.
- It was an exploratory analysis or test of a novel hypothesis in the context of an adequately powered study, and the finding meets the statistical criteria for genome wide significance taking into account all sources of multiple testing (e.g. phenotypes, genotypes, environments, covariates, subgroups).
- It is a meta-analysis of several or many studies addressing the same genetic variant and/or environmental variable and the same behavioral outcome.

We also recommend that authors follow the STREGA reporting guidelines (Little et al. 2009), paying particular attention to appropriate corrections to significance criteria for multiple testing and to disclosure of all analyses conducted with the same data sets.

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We hope that by adopting these recommendations, *Behavior Genetics* will continue to publish papers that advance our knowledge and understanding of genetics and behavior.

## References

- Duncan L, Keller MC (2011) A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. doi:[10.1176/appi.ajp.2011.11020191](https://doi.org/10.1176/appi.ajp.2011.11020191)
- Ioannidis JP (2005) Why most published research findings are false. *PLoS Med* 2(8):e124
- Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N. (2009) Strengthening the reporting of genetic association studies (STREGA): an extension of the STROBE Statement. *Hum Genet* 125(2):131–151. Available online at: <http://www.springerlink.com/content/8265g7w571722251/fulltext.pdf>. Accessed 14 September 2011
- Sullivan PF (2007) Spurious genetic associations. *Biol Psychiatry* 15(61):1121–1126