Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression

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The hypothesis that the S allele of the 5-HTTLPR serotonin transporter promoter region is associated with increased risk of depression, but only in individuals exposed to stressful situations, has generated much interest, research and controversy since first proposed in 2003. Multiple meta-analyses combining results from heterogeneous analyses have not settled the issue. To determine the magnitude of the interaction and the conditions under which it might be observed, we performed new analyses on 31 data sets containing 38 802 European ancestry subjects genotyped for 5-HTTLPR and assessed for depression and childhood maltreatment or other stressful life events, and meta-analysed the results. Analyses targeted two stressors (narrow, broad) and two depression outcomes (current, lifetime). All groups that published on this topic prior to the initiation of our study and met the assessment and sample size criteria were invited to participate. Additional groups, identified by consortium members or self-identified in response to our protocol (published prior to the start of analysis) with qualifying unpublished data, were also invited to participate. A uniform data analysis script implementing the protocol was executed by each of the consortium members. Our findings do not support the interaction hypothesis. We found no subgroups or variable definitions for which an interaction between stress and 5-HTTLPR genotype was statistically significant. In contrast, our findings for the main effects of life stressors (strong risk factor) and 5-HTTLPR genotype (no impact on risk) are strikingly consistent across our contributing studies, the original study reporting the interaction and subsequent meta-analyses. Our conclusion is that if an interaction exists in which the S allele of 5-HTTLPR increases risk of depression only in stressed individ-

uals, then it is not broadly generalisable, but must be of modest effect size and only observable in limited situations.Molecular Psychiatry advance online publication, 4 April 2017; doi:10.1038/mp.2017.44.
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