
Editorial

The truth about genetic variation in the serotonin transporter gene and response to stress and medication†

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Summary
The question of whether a functional variant in the promoter of the serotonin transporter gene (5-HTTLPR) influences response to adversity and/or antidepressants has generated great interest and controversy. A review of the literature suggests that the issue is complicated by differences in methodology and sample ethnicity. When these confounders are accounted for, there probably is a real, if small, effect of 5-HTTLPR on response to both serotonin reuptake inhibitors and environmental adversity.

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The idea that individuals differ in their response to stress is commonplace and every clinician who has ever prescribed antidepressants knows that there is considerable variation in the extent to which patients with depression show a therapeutic improvement or develop unwanted effects. Similarly, the idea that genes might contribute to these types of individual differences is hardly contentious. It is somewhat surprising therefore that attempts to identify such sources of variation at a molecular level have provoked a good deal of debate and controversy, much of which, as exemplified by a paper in this issue of the Journal by Lewis et al., has been focused on the gene that encodes the serotonin transporter.

A polymorphism (common variant) in the promoter region of the serotonin transporter gene affecting expression was first reported by Lesch and colleagues in 1994. This is a so-called length polymorphism, 5-HTTLPR, that exists in two forms, a long allele (‘L’) containing a sequence of 43 base pairs and a short allele (‘S’) in which this sequence is deleted. The long form was shown to be associated with higher and the short form with lower expression of the gene product. Early reports suggested association between carrying the short form and depressive disorder, but there were subsequent failures of replication and the authors of the most recent meta-analysis conclude that, although there may indeed be a very small effect, the picture is clouded by publication bias. Indeed, much more interest has been concentrated, not on whether 5-HTTLPR has a main effect, but on whether it moderates the effects of adversity in provoking depressive symptoms and whether there is an interaction with response to antidepressants.

Interaction with adversity

In 2003, Caspi and colleagues published a report in the journal Science that has since become one of the most talked about papers in psychiatry and has been cited over 2000 times. They reported that, in a cohort of young men and women aged 26 from Dunedin, New Zealand, individuals with one or two copies of the short allele of the 5-HTTLPR exhibited more depressive symptoms, diagnosable depression and suicidality following stressful life events than individuals homozygous for the long allele. Subsequently, Eley et al. published a partial replication in which there was a significant genotype–environmental risk interaction for 5-HTTLPR in female (but not male) adolescents, with the effect being in the same direction as in the Caspi et al. study. Many other studies, some supportive, and some negative, have followed and in 2009 two meta-analyses were published, where both sets of authors concluded that the overall evidence did not in fact favour the existence of an interaction between 5-HTTLPR and stressful life events in depression. However, neither meta-analysis took into account the substantial heterogeneity in methodology of the studies reviewed which, as we had earlier pointed out, had systematic effects on the results.

Specifically, negative studies tended to have used brief self-report measures of adversity rather than semi-structured interviews or more objective evidence, such as third-party reports. Negative studies also appeared to be associated with the age of individuals, with studies on older adults or adolescents, particularly boys, tending not to show an interaction effect, consistent with the early study by Eley and colleagues.

We subsequently performed an updated systematic review and found 34 published studies on the interaction between 5-HTTLPR and adversity (as opposed to 5 and 14 studies scrutinised in the two ‘negative’ 2009 meta-analyses). We found that 17 of these replicated the original Caspi et al. finding of environment interaction – that is, those carrying the short 5-HTTLPR allele have higher rates of depression or depressive symptoms following life events than those who only carry the long allele. We classified eight studies as partial replications (including that of Eley et al.) where there was an interaction only in females or only with a subset of types of adversity and nine were non-replications. We found a statistically significant relationship between the method used to measure environmental adversity, and the outcome of the study, in that all studies that used objective indicators or semi-structured interviews replicated the environment interaction and all non-replications used brief self-reports. There was also a statistically significant preponderance of non-replications or partial replications in adolescent samples. For reasons that were...
not apparent, we also found that the negative meta-analyses preferentially included studies that used self-report measures of adversity.

There has now been a third meta-analysis which took a more inclusive approach, combining findings at the level of significance tests rather than raw data. This was positive overall and was most highly significant for a moderating effect of 5-HTTLPR on depression in relation to childhood maltreatment and medical illness rather than recent life events. This meta-analysis has confirmed a hypothesis previously proposed by Brown & Harris that the moderating effect of 5-HTTLPR is relatively specific to childhood maltreatment. It has also confirmed our previous finding that the negative results of some studies can be explained by the use of brief self-report instruments to assess stress and that the positive genotype–environment is very unlikely to be due to publication bias.

An additional source of variability might be a single-base substitution (rs25531, A/G) in the long form of 5-HTTLPR that appears to have functional significance. Hu et al. found that lG behaves equivalent to the low-expressing s allele and therefore studies that include many l alleles within s/l and l/l genotypes may underestimate the effect of 5-HTTLPR. This was confirmed by Zalsman et al. who investigated the association of 5-HTTLPR with stressful life events and severity of depression in Caucasian participants, genotyped for lG, lA and s. They found that lower-expressing alleles (lG and s) independently predicted greater depression severity compared with the higher-expressing lA allele, and that lower-expressing alleles increased the impact of life events on severity of depression. The authors found that 10.5% of the l alleles were the lower-expressing lG allele that otherwise would have been treated as the higher-expressing l allele.

**Response to antidepressants**

Since the serotonin transporter is the presumed site of action of selective serotonin reuptake inhibitor (SSRI) antidepressants, it is unsurprising that polymorphisms in the serotonin transporter gene have been seen as prime candidates for pharmacogenetic studies of antidepressants. A paper by Lewis et al. in this issue of the Journal, on the GENPOD study, is the latest such investigation and fails to provide any support for the hypothesis that the 5-HTTLPR genotype is associated with response to citalopram or indeed to the selective noradrenergic anti-depressant, reboxetine. Previously, our own investigation on the moderating effect of 5-HTTLPR based on the multisite European GENDEP study also compared an SSRI, escitalopram, with a serotonin transporter, reboxetine. Interestingly, humans are not the only mammals that have a common functional variant in the promoter region of their serotonin transporter gene. Rhesus macaque monkeys also have a serotonin promoter polymorphism with long (more active) and short (less active) alleles. Macaques can be stressed early in life by being separated from their mothers and reared instead with a peer group. Their resultant ‘anxiety’ can be assessed both behaviourally and by measuring adrenocorticotropic hormone (ACTH) and cortisol levels at baseline and during separation stress. When such a study was performed on monkeys of known 5-HTTLPR genotypes the findings were somewhat analogous with the findings on adversity in humans. There was a separation × rearing × 5-HTTLPR interaction, such that animals reared with peers who carried a short 5-HTTLPR allele had higher ACTH levels during separation than did the other animals studied.

Rodents do not have a similar polymorphism but the effect of having a short allele early in development can be mimicked by giving them SSRIs as pups or by complete or partial ‘knockout’ of the serotonin transporter gene. Such disruptions also lead to exaggerated stress responses in animals with low or absent serotonin transporter activity compared with normal mice of the same strain.

Two types of relevant experiment have been performed in human volunteers and in volunteers who have recovered from depression. In the first, healthy volunteers are exposed to stimuli such as fearful faces during functional brain magnetic resonance analysis, found no effect of 5-HTTLPR on response to citalopram. However, this was carried out on a mixed-ethnicity sample. When a subsequent analysis was performed, dividing up the participants according to ethnic origin, a moderating effect of 5-HTTLPR on improvement of depressive symptoms in response to citalopram was indeed found, but only among White non-Hispanics. Ethnicity has also been a confounding factor in other analyses. A meta-analysis of 15 mainly fairly small studies, but with a combined total of 1435 individuals, showed that long-allele carriers were more likely to respond to SSRI antidepressants and/or enjoy a remission than short-allele homozygotes. Again the effect was only in Europeans and was not present in Korean and Japanese populations included in the meta-analysis.

One possible explanation of these ethnic differences could lie in the other common variants in the serotonin transporter gene that are thought to have functional effects.

One of these, a single nucleotide polymorphism (SNP) called rs202933 in the first intron of the gene, had a small but significant effect on response to both escitalopram and nortriptyline in the GENDEP study and is known to have a large variation in allele frequency between populations. Variation in this SNP, which was not tested in the GENPOD study, is unlikely to explain GENDEP/GENPOD differences as both studies were exclusively of White Europeans, but it might explain some of the differences in other studies of Europeans versus non-Europeans.

An additional complexity is that an analysis of the GENDEP study taking self-rated life events into account showed that adversity in the 6 months before treatment interacted with 5-HTTLPR genotype in predicting response to antidepressants. This perhaps suggests that the 5-HTTLPR genotype has in fact a rather broad role as a marker of emotional reactivity and we can now turn to consider the experimental evidence relating to this more general hypothesis.

**Experimental evidence of 5-HTTLPR effects on stress response**

Interestingly, humans are not the only mammals that have a common functional variant in the promoter region of their serotonin transporter gene. Rhesus macaque monkeys also have a serotonin promoter polymorphism with long (more active) and short (less active) alleles. Macaques can be stressed early in life by being separated from their mothers and reared instead with a peer group. Their resultant ‘anxiety’ can be assessed both behaviourally and by measuring adrenocorticotropic hormone (ACTH) and cortisol levels at baseline and during separation stress. When such a study was performed on monkeys of known 5-HTTLPR genotypes the findings were somewhat analogous with the findings on adversity in humans. There was a separation × rearing × 5-HTTLPR interaction, such that animals reared with peers who carried a short 5-HTTLPR allele had higher ACTH levels during separation than did the other animals studied.

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Two types of relevant experiment have been performed in human volunteers and in volunteers who have recovered from depression. In the first, healthy volunteers are exposed to stimuli such as fearful faces during functional brain magnetic resonance
imaging (fMRI) when they typically show activation of the amygdala and associated regions. Hariri et al.24 showed that those individuals with one or two copies of the short allele of 5-HTTLPR showed greater amygdala neuronal activity, as assessed by blood oxygen level dependent fMRI, in response to fearful stimuli compared with individuals homozygous for the long allele. It has also been shown that short-allele homozygotes, more than other genotype subgroups, showed significantly greater positive functional connectivity between right amygdala and right fusiform gyrus and between right fusiform gyrus and right ventrolateral prefrontal cortex in response to prototypically fearful faces.25 In the second type of study, individuals have a low mood induced by giving them an amino acid mixture without tryptophan, which depletes them of this amino acid. One such study looked at women with or without a family history of depression who were genotyped for 5-HTTLPR. All women showed a reduction in plasma tryptophan levels but the most pronounced reduction in mood was in women who had both a family history of depression and who were homozygous for the short allele. Women who were long-allele homozygotes did not develop depressive symptoms, irrespective of family history.26

Taken together, these experimental studies reveal mechanisms of greater sensitivity to the environment that likely mediate the relationship between adversity and psychopathology, observed in the epidemiological studies.21 22

### Conclusions

Both the moderating effect of the serotonin transporter gene on antidepressant response and the alleged relationship between 5-HTTLPR genotype and depressive symptoms following life events have provoked controversy, most recently exemplified by Lewis et al.’s paper on the GENPOD study in the current issue of the Journal.1 We have argued that there are systematic effects that characterise the negative studies in the life events area and that when the problems resulting from low power and/or mixed ethnicity are taken into account there probably is a real, if small, effect of 5-HTTLPR on response to SSRIs. We agree with Lewis et al. that testing for 5-HTTLPR genotype on its own is not likely to be clinically useful but it might, however, form part of a battery of tests that does turn out to have predictive utility. Finally, we are not just dealing with a body of evidence concerning 5-HTTLPR that is restricted to antidepressant response and response to life events. There is also a whole set of animal and human experiments that consistently point in the same direction in which possession of one or more short alleles is associated with greater reactivity to stress. The truth is that there are just too many straws travelling in the same direction for us not to know which way the wind is blowing.

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**References**


Genetic variation in the serotonin transporter gene


The Great Asylums of Scotland

Tom Pow

The great asylums of Scotland, cloistered like the proud abbeys we tore down brick by brick. Yet harder to love. They docked at the edge of our towns like relations with whom we felt ill at ease. Ones who kept themselves to themselves. Their farms. Their laundries. Their water supplies. We stand in their portals, our eyes drawn down the tree-lined avenues to the prospect of distant hills. Country houses? Hydros? Oh, what shall we do with them? – the great asylums of Scotland, still with us, as keen to serve as the day they were built.

A fleet for their time they set out, freighted with hope and grand design. Look at them now, scuttled on the ocean floor. Light floods them. Along their corridors, doors flap open on empty cabins with nothing to hide. In attic rooms the sky’s light pours over a tide-wrack of maps, plans, records – a grid to lay over a waste of rage, grief, anger and pain. None of that will make a cairn. In these, the great asylums of Scotland, always it is evening about to fall. The heavy doors are closing in on us all. and the counting begins. But coming through the frayed web of darkness are slants of light: greenness, firstness, hope. What is to be done with a two-faced legacy such as this? Multi-occupancy – that’s the answer! Flatpacks to the gentlemen’s quarters, IKEA to the boardrooms. Four by fours draw up before the great asylums now. They’re made for them, framed by chestnut trees, like adverts. Inside the auction hall – the stillness of graveyards, the discretion of private affairs. Oh how beautiful are the crafted dovetails in the wardrobes no one wants. They sulk like small monuments history has ignored. So much gloom. ‘I wouldn’t want any of it in my house,’ someone says. ‘Not knowing where it’s come from.’ As if objects soak up instability like nicotine. If so, not only so – for writing up the staircase in Crichton Hall are oak leaves, carved not by craftsmen from Antwerp, but by men tramping over winter fields from Dalton using a water pipe as guide. Run your hands over the leaves and you’ll feel their approval for their new asylum. Though of the mad, little could be salvaged – not one knitted pullover, not one apron – for these craftsmen, the trade in lunacy was a godsend. The melancholy we mourn they transformed into bread, milk, sunlight.

Tom Pow was writer in residence at the Edinburgh International Book Festival 2001–2003 and poet in residence at StAnza, Scotland’s poetry festival. He is senior lecturer at Glasgow University, Crichton Campus, Dumfries. This poem is from his collection Dear Alice – Narratives of Madness (Salt, 2008), a poetic response to the Crichton Royal, Dumfries. Reproduced with permission from Salt Publishing Limited. © Tom Pow

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