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Editorial

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

Peter McGuffin, Shaza Alsabban and Rudolf Uher

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.

Declaration of interest
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Peter McGuffin (pictured) is Director, Shaza Alsabban is a PhD student and Rudolf Uher is a clinical lecturer at the MRC Social Genetic and Developmental Psychiatry (SGDP) Centre at the Institute of Psychiatry, King's College London.

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*,[1] 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.[2] 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,[3] but there were subsequent failures of replication and the authors of the most recent meta-analysis[4] 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[5] 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*[6] 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[7,8] 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,[9] 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.[6]

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).[10] We found that 17 of these replicated the original Caspi *et al*[5] 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*[6]) 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

†See pp. 464–471, this issue.

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.[11] 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[12] 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*[13] found that l_G behaves equivalent to the low-expressing s allele and therefore studies that include many l_G alleles within s/l and l/l genotypes may underestimate the effect of 5-HTTLPR. This was confirmed by Zalsman *et al*[14] who investigated the association of 5-HTTPLR with stressful life events and severity of depression in Caucasian participants, genotyped for l_G, l_A and s. They found that lower-expressing alleles (l_G and s) independently predicted greater depression severity compared with the higher-expressing l_A 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 l_G 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*[1] 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 antidepressant, 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 mainly noradrenergic drug, nortriptyline.[15] In contrast with Lewis *et al*, we found that the polymorphism moderated the response to escitalopram (but not nortriptyline) with long-allele carriers improving more than short-allele homozygotes. We also found a significant threeway interaction between 5-HTTLPR, drug and gender, indicating that the effect was concentrated in men treated with escitalopram. The GENPOD study did not have sufficient power to rule out a small effect but the authors argued that their results make it unlikely that 5-HTTLPR genotype has a sufficiently large effect to form the basis of a clinically useful test.

It is worth considering these differing results against the background of other studies. GENDEP and GENPOD are two of the largest pharmacogenetic studies of antidepressants to date but are exceeded in size by the multisite US STAR*D study. This was not designed primarily as a pharmacogenetic study but two pharmacogenetic analyses have been performed. The first pharmacogenetic analysis of the STAR*D study, like the GENPOD 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.[16] Again the effect was only in Europeans and was not present in Korean and Japanese populations included in the meta-analysis.[17,18] 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 rs2020933 in the first intron of the gene, had a small but significant effect on response to both escitalopram and nortriptyline in the GENDEP study[15] 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.[19] 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.[20] 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.[21–23]

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.[23]

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.

Peter McGuffin, MB, PhD, FRCP, FRCPsych, FMedSci, **Shaza Alsabban**, MSc, **Rudolf Uher**, MD, PhD, MRCPsych, MRC SGDP Centre, Institute of Psychiatry, King's College London, UK

Correspondence: Peter McGuffin, MRC SGDP Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK. Email: peter.mcguffin@kcl.ac.uk

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Poems by doctors

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 dovetailes 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 traipsing 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 transfromed 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.

Chosen by Femi Oyebode.

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