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Ethnic differences in BDNF Val66Met polymorphism

The article by MacGregor Legge *et al*[1] focused on brain derived neurotrophic factor's (BDNF's) Val66Met polymorphism contribution to major depressive disorder and sought to determine whether the same neural effects would be observed in healthy individuals. There was a specific focus on cortical thickness in the amygdala, prefrontal regions of the anterior cingulate cortex and middle frontal and orbitofrontal cortices. The study focused on 79 patients with diagnosed major depressive disorder and 74 control participants, all of White European ancestry. The main effects were of Met carrier status on cortical thinning in the caudal middle frontal cortex in patients with major depressive disorder and controls. The polymorphism in the caudate middle frontal cortex was greater and no significant interaction was found in the amygdala.

One limitation not covered by the authors was the lack of ethnic diversity among the sample population. One previous study[2] investigated the BDNF polymorphism in an exclusively Mexican American experimental and control population and found it also to be associated with major depressive disorder. However, previous studies have found that the polymorphism has allele frequencies dependent on ethnic background. In White populations, the Val allele is found to be the most common and the frequency of the Met allele is 25% to 32%.[3,4] In Asian populations the Met allele is more frequent, about 40% to 50%.[5–7] As MacGregor Legge *et al* found that the Met allele had the greatest effect on major depressive disorder, one would assume it would be of paramount importance to examine how differing frequencies affect the occurrence of the disorder. Pivac *et al*[8] in their study on ethnic differences in BDNF Val66Met polymorphism in a Croatian and Korean non-clinical sample found that polymorphisms and mood disorders may be dependent on ethnicity.

Searches for studies of the BDNF polymorphism in African–Carribbean and other ethnicities obtained no results. As generalisable conclusions cannot be drawn on the varying effects of the BDNF polymorphism on major depressive disorder or any major psychiatric illness in different ethnic groups, further examination into this topic would be significant.

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5 Choi MJ, Kang RH, Lim SW, Oh KS, Lee MS. Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. *Brain Res* 2006; **1118**: 176–82.

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Authors' reply: We thank Yeebo for this comment on our paper, raising an important point that the frequency of genetic polymorphisms tends to vary between different ethnic groups. In our study, we had sought to investigate the association of the BDNF Val66Met polymorphism with imaging phenotypes in the context of major depressive disorder, rather than an investigation of an association for the polymorphism with major depressive disorder. As Yeebo states that we had sought 'to determine whether the same neural effects would be observed in healthy individuals', we would like to clarify that we had investigated whether the effects of the polymorphism on specific brain regions in healthy individuals would also be observed in the same brain regions in individuals with major depressive disorder.

Yeebo's general comment on the differing frequency of the genetic polymorphisms between different ethnic groups has long been a source of difficulty in allelic association studies because – unless there is careful ethnic matching of cases and controls – spurious results can arise, including both false-positive and false-negative findings. For this reason, we had restricted our study to individuals of White European origin.

Yeebo draws attention to the possibility that the association between the BDNF Val66Met polymorphism and major depressive disorder is specific to certain ethnic groups, and this raises another but slightly different interesting issue. Disease associations with polymorphisms arise either because the polymorphism itself plays a causal role or because it is in linkage disequilibrium with another variant that has a causal role. The degree of linkage disequilibrium between adjacent polymorphisms is in general approximately proportional to their distance apart but is also dependent on other factors including allelic frequency, so ethnic differences in observed linkage disequilibrium may arise. It has usually been assumed that because the BDNF Val66Met polymorphism is functional, its role in depression is likely to be causal. If the association between this polymorphism and major depressive disorder were found to vary between different ethnic groups, this would be attributable to either different Met allele frequencies between the ethnic groups or the Val66Met polymorphism being in linkage disequilibrium with another variant in BDNF that has a causal role in major depressive disorder.[1]

There are also publicly available data on the Single Nucleotide Polymorphism Database (www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6265) which indicate that in African and African American populations, the frequency of the Met allele seems to