

Letter to the Editor

Maternal age as a potential explanation of the role of the L allele of the serotonin transporter gene in anxiety and depression in Asians

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We were intrigued by the results of Long *et al.*^[1] indicating that the L allele of the 5-HTTLPR (serotonin transporter) gene was associated with anxiety and depression in Asians while in Caucasians the reverse is true. Does this mean that there is some fundamental difference in the genetics of the 5-HTTLPR gene in Asians versus Caucasians causing an 'allele reversal' due to some unknown east-west difference, or is there a simpler alternative explanation such as a hidden third variable that needs to be considered?

In 2006 we reported on a similar 'allele reversal' on the association of the *DRD1* gene and OCD scores in individuals with Tourette syndrome/ADHD^[2]. The important third variable was maternal age or more specifically maternal age at the birth of the mother's first child. The sample was dichotomized on the basis of maternal age at the time of the birth of the first child. In the ≤ 25 year the highest scores were significantly associated with the 2 allele of the *DdeI* polymorphism while in the ≥ 26 year group the highest scores were significantly associated with the 1 allele. Other similar examples were given.

Since we had maternal age and platelet serotonin levels on 300 of our Tourette syndrome/ADHD subjects we examined this interaction. In the younger maternal age group the mean platelet serotonin level was 77 ng/mL while in the older maternal age group the mean platelet serotonin was 62.7 ng/mL, $P = 0.031$. Lower platelet serotonin levels are known to be associated with depression^[3].

We had 5-HTTLPR genotyping on 98 subjects. The SS

genotype was associated with low serotonin levels in the younger maternal age group, while in the older maternal age group the LL genotype was associated with low platelet serotonin levels ($P = 0.045$).

While these are preliminary and exploratory results based on data we had available in our laboratory and clearly need replication on larger samples, they do suggest an explanation for the apparent 'allele reversal' in Asians relevant to the role of the L allele of the 5-HTTLPR gene in depression and anxiety. Namely, the association of the L rather than the S allele may be due to a lower maternal age of the Asian subjects in the Long *et al.*^[1] sample, not to any fundamental differences in the genetics of the 5-HTTLPR gene. If data on maternal age are available it would be easy to test if maternal age was associated with allele reversal in their sample.

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