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·Correspondence·

# Authors' response to "Maternal age as a potential explanation of the role of the L allele of the serotonin transporter gene in anxiety and depression in Asians"

Haixia Long[1,2], Bing Liu[1,2], Bing Hou[1,2], Chao Wang[3], Jin Li[1,2], Tianzi Jiang[1,2,3,4]

[1]*Brainnetome Center,* [2]*National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China*

[3]*Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China*

[4]*Queensland Brain Institute, University of Queensland, Brisbane, QLD 4072, Australia*

Corresponding author: Tianzi Jiang. E-mail: jiangtz@nlpr.ia.ac.cn



In the letter to the editor, Dr. Comings *et al*. proposed a potential explanation of our findings that the L allele rather than S allele of 5-HTTLPR was associated with higher anxiety levels and reduced amygdala-prefrontal cortex (PFC) connectivity in Han Chinese[1], which demonstrated an 'allele reversal' in the genetics of the 5-HTTLPR gene in Asians *versus* Caucasians. The authors alleged that this 'allele reversal' might simply result from maternal age and suggested that we test this on our datasets. Unfortunately, we cannot because maternal age information was not included in our sample. However, from the following evidence we can conclude that this explanation cannot be applied to our findings[1]. First, the main evidence used is the authors' previous study on an association of the DRD1 gene with OCD scores in individuals with Tourette syndrome/ADHD, which is completely different from our study[1] because the diagnostic status might influence the association analysis between maternal age and platelet serotonin level. So the conclusion from their study cannot be applied to our findings. The authors also used an unpublished study of 5-HTTLPR genotyping on 98 subjects to support their interpretation. But this evidence is unreliable because there is too much uncertainty in such a small sample. For example, in that study it is not known whether the participants are from a healthy population, patients, or a mixture of both, what diseases they have (if any), and whether they are Asian or Caucasian. Second, there is no clear criterion that defines old maternal age, because the effect of maternal age is considered as a continuum rather than a cut-off. Moreover, the age of women having their first child varies across countries rather than ethnicity. From OECD Family Database (2014, Paris, www.oecd.org/social/family/database) and the work of Matthews and Hamilton[2], the mean maternal age at the birth of the first child in Japan falls between those in Germany and the USA. And individuals are relatively equally distributed throughout different maternal age groups in a large Chinese cohort: 4324 with a maternal age <25 years, 3550 between 25 and 29 years, and 3433 with a maternal age >29 years[3]. Thirdly, previous studies in Japan and Korea also showed that the L allele rather than S allele of 5-HTTLPR is associated with depression and higher amygdala activity during an emotional processing task and in the resting-state[4-9], while the S allele is linked to this effect in Caucasians[10-16]. More importantly, the allele distribution of 5-HTTLPR variants is significantly different between Asians and Caucasians, with a higher S allele frequency in the former[13]. Because previous imaging genetics studies on 5-HTTLPR also did not take maternal age into account, based on the same criteria, our current and further studies show that the L allele is associated with reduced amygdala-PFC connectivity and default-mode network connectivity[1, 17], which is contrary to the findings in Caucasians[18-20].

In summary, maternal age is not a driving factor for ethnic difference in the effect of 5-HTTLPR based on the current evidence, though it might be a factor that needs to be considered in future studies. Such studies in a large, multi-ethnic sample are needed to investigate the association between 5-HTTLPR, depression/anxiety, neural circuits, and maternal age. In particular, further studies can directly examine the effect of 5-HTTLPR on the anxiety/depression score and neural circuits in Asian and Caucasian populations with matched maternal ages, which can help us to understand whether there is a fundamental Asian-Caucasian difference or just the influence of maternal age. More research will likely provide multiple perspectives.

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