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L_A allelic heterozygosity of the 5HTTLPR polymorphism is associated with higher cognitive function and lower interpersonal sensitivity

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The polymorphic region 5HTTLPR of the *SLC6A4* gene, encoding the serotonin transporter, is now conceptualized as having three primary allelic variants: L_A, L_G, and S. Of these alleles, only the L_A allele is high functioning with regard to promoter productivity (Hu *et al.*, 2005). Previous research of serotonergic polymorphisms has demonstrated associations with cognition and anxious personality traits (Lesch *et al.*, 1996; Payton *et al.*, 2005). We explored associations between these allelic variants and measures of cognition, anxiety, and interpersonal sensitivity.

Sixty-eight adults aged 55–90 years with an unequivocal diagnosis of atherosclerotic vascular disease provided informed consent approved by the University of Iowa Institutional Review Board. Cognitive function was assessed via the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Anxiety and interpersonal sensitivity measures were obtained from the Symptom Checklist-90-Revised. Participants were genotyped for the 5HTTLPR polymorphism using previously validated methods (Heils *et al.*, 1996). The A and G polymorphisms of the 5HTTLPR L allele were determined by direct sequencing after gel extraction. Patients were divided into groups on the basis of the total number of L_A alleles and heterozygosity at the L_A allele. Analysis of covariance explored relationships of interest, controlling for age, sex, and education.

No significant differences were seen in age, sex, or education between groups. Statistical analyses nonetheless controlled for age, sex, and education. Fifteen participants had no L_A alleles, 35 had one allele, and 19 participants were homozygous for the L_A allele.

Those heterozygous for L_A demonstrated significantly higher RBANS total scores ($F = 4.08$, d.f. = 1, $P = 0.048$, effect size 0.47), and further demonstrated higher scores on the RBANS subscale for attention ($F = 5.25$, d.f. = 1, $P = 0.025$, effect size 0.56). No further RBANS subscales demonstrated a significant association. No significant associations were found between the number of L_A alleles and RBANS total scale score or the attention subscale.

Symptom Checklist-90-Revised interpersonal sensitivity scores were significantly associated with the number of L_A alleles ($F = 2.72$, d.f. = 2, $P = 0.027$) and heterozygosity at the L_A allele ($F = 5.57$, d.f. = 1, $P = 0.021$, effect size 0.53). Anxiety scores were not significantly associated with genotype.

Our analysis demonstrates superior general cognitive functioning, better attention, and a lower level of interpersonal sensitivity in those heterozygous for the higher functioning, L_A allele of the 5HTTLPR polymorphism with a moderate effect size. The refined genotypic analysis of the 5HTTLPR polymorphism may delineate previous disparate findings regarding the influence of serotonin transporter polymorphisms.

The possibility of allelic heterozygosity conveying certain advantages may explain the diverse distribution of these alleles. Nearly 50% of our sample was heterozygous for L_A, a finding consistent with other studies (Hu *et al.*, 2005) and perhaps suggestive of some evolutionary advantage to such heterozygosity. Genetic heterozygosity in a promoter region may provide greater capacity for transcriptional modulation and convey further downstream advantages for functions served by serotonergic systems, including attention, cognition, and affective responses.

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