Family-based association study of DRD4 gene in methylphenidate-responded Attention Deficit/Hyperactivity Disorder.

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Abstract

The 48-basepair (48-bp) variable number tandem repeat (VNTR) polymorphism in exon 3 of the dopamine receptor D4 gene (DRD4) is implicated in the aetiology of attention-deficit/hyperactivity disorder (ADHD). In particular, ADHD in European-ancestry population is associated with an increased prevalence of the 7-repeat (7R) allele of the exon 3 VNTR. However, it is intriguing to note that the 7R allele has been found to be of very low prevalence in the Chinese general population. In a previous case-control study, our research team had found that the 7R allele was similarly absent in Chinese ADHD children in Hong Kong. Instead, there was an increased prevalence of the 2R allele in Chinese ADHD children. Interestingly, in Asian samples, the 2R allele had been found to be an evolutionary derivative of the 7R allele with equivalent biochemical functionality. So, the finding of an association between ADHD and 2R allele in Chinese population does not exactly contradict the original 7R allele finding in European-ancestry population. However, given the potential pitfall of population stratification in the previous case-control design, this current study tested the 2R allele and ADHD association using a methodologically more rigorous family-based approach on 33 Chinese ADHD probands who had favourable clinical responses to stimulant medication (methylphenidate). Haplotype Relative Risk (HRR) analysis and Transmission Disequilibrium Test (TDT) both showed a significant preferential transmission of the 2R allele from the biological parents to ADHD probands (pone-tailed = 0.038, OR = 2.04; pone-tailed = 0.048, OR = 2.29, respectively). A second hypothesis speculates that it is the deviation, including 7R and 2R alleles, from the conserved ancestral 4R allele which confers risk to ADHD. Thus, a preferential transmission of non-4R alleles, against the 4R allele, from biological parents to their ADHD probands is predicted. Both HRR analysis and TDT confirmed such prediction (pone-tailed = 0.029, OR = 2.07; pone-tailed = 0.032, OR = 2.43, respectively). This study re-confirmed the original finding of a previous study that in the Chinese population, the 2R allele of the DRD4 exon 3 VNTR was related to ADHD. This endorses the general thesis that DRD4 exon 3 VNTR polymorphism is related to ADHD, despite that the exact length or number of repeats of the associated alleles varies across ethnicity. This, in turn, supports the dopamine dysregulation theory of ADHD.