Dimorphic association of dopaminergic transporter gene variants with treatment outcome: Pilot study in Indian ADHD probands

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Abstract

Background
Scholastic under achievement, poor decision making and lack of self-regulation are major disadvantages in probands with Attention Deficit Hyperactivity Disorder (ADHD). Since contribution of neurotransmitters, chiefly dopamine (DA)/norepinephrine (NE) have been indicated in the etiology, medications have been developed targeting these neurotransmitters. However, due to variation in response and side effects, treatment is often discontinued. We aimed at understanding the role of DA/NE system gene variants, rs28363170, rs3785143, rs1611115 and rs4680, in medication response. ADHD probands diagnosed after the Diagnostic and Statistical Manual for Mental Disorders-IV were evaluated by the Conners' Parent Rating Scale-revised (CPRS-R). Peripheral blood collected from drug naïve probands was used for genomic DNA isolation and analysis of gene variants. Probands were prescribed either Methylphenidate (MPH) or Atomoxetine (ATX) and post-treatment outcome was assessed using the CPRS-R as well as Drug Side Effect Rating Scale.

Results
While significantly reducing behavioral problems ($\chi^2 = 8.05$, p = 0.005), MPH treatment resulted in more pronounced side effects as compared to ATX. rs28363170 and rs3785143 variants affected MPH and ATX induced improvement in traits differently (Cohen's $d > 0.80$). Quantitative trait analysis also revealed significant differential role of rs28363170/rs3785143 in medication response (add value > 8.0, 95% CI 1.11–16.11).

Conclusion
This pioneering study on Indian ADHD probands indicates that rs28363170 and rs3785143 could be major modulators for treatment outcome; while MPH may be more beneficial in the presence of rs28363170 10R and rs3785143 T variants, ATX treatment may provide relief in presence of rs28363170 9R and rs3785143 C variants.