Regulating the Regulators in Attention-Deficit/Hyperactivity Disorder: A Genetic Association Study of microRNA Biogenesis Pathways.


Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent complex psychiatric disorders in children as well as adults. ADHD impacts not only the affected individuals but also their families and social and professional networks. The clinical and diagnostic criteria for ADHD remain imprecise, in part, due to lack of robust biomarkers. ADHD comprises multiple subsets of diseases that present a shared set of downstream clinical findings while displaying extensive molecular heterogeneity. This calls for innovation in diagnostic strategies that can help establish an ADHD diagnosis unequivocally as well as guiding precision medicine in this common mental health disorder. No study has examined, to the best of our knowledge, the upstream regulation of miRNAs that impact the downstream final ADHD phenotype. The latter focus on putative genetic biomarkers that regulate the regulators and can be tested empirically, for example, through genetic association analyses of the biogenesis pathways for miRNAs that impact the ADHD phenotype. Hence, we report here polymorphic variation in 10 miRNA biogenesis pathway candidate genes, including RNASEN, DGCR8, XPO5, RAN, DICER1, TARBP2, AGO1, AGO2, GEMIN3, and GEMIN4, in a large sample from the Eastern Mediterranean region (N = 355; 191 cases and 164 controls). We found that AGO1 rs595961 was significantly associated with ADHD susceptibility (p < 0.05). While polymorphic variation in other miRNA biogenesis pathway genes did not display a significant association in the present sample, the observations reported herein on miRNA biogenesis variation offer a new avenue of research for innovation in biomarker discovery concerning ADHD and other complex psychiatric diseases with major global health burden.