Candidate Genetic Pathways for Attention-Deficit/Hyperactivity Disorder (ADHD) Show Association to Hyperactive/Impulsive Symptoms in Children With ADHD

Janita Bralten, Barbara Franke, Irwin Waldman, Nanda Rommelse, Catharina Hartman, Philip Asherson, Tobias Banaschewski, Richard P. Ebstein, Michael Gill, Ana Miranda, Robert D. Oades, Herbert Roeyers, Aribert Rothenberger, Joseph A. Sergeant, Jaap Oosterlaan, Edmund Sonuga-Barke, Hans-Christoph Steinhausen, Stephen V. Faraone, Jan K. Buitelaar, Alejandro Arias-Vásquez

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Objective: As multiple genes with small effect size are assumed to play a role in attention-deficit/hyperactivity disorder (ADHD) disease etiology, considering multiple variants within the same analysis likely increases the total explained phenotypic variance, thereby boosting the power of genetic studies. We investigated whether pathway-based analysis could bring us closer to unraveling the biology of ADHD.

Method: We describe pathway as a predefined gene selection based on a well-established database or literature data. Common genetic variants in pathways involved in dopamine/norepinephrine and serotonin neurotransmission and genes involved in neurite outgrowth were investigated in cases from the International Multicentre ADHD Genetics (IMAGE) study. We performed multivariable analysis to combine the effects of single genetic variants within the pathway genes. Phenotypes were DSM-IV symptom counts for inattention and

hyperactivity/impulsivity (n=871) and symptom severity measured with the Conners Parent (n=930) and Teacher Rating Scales (n=916).

Results: Summing genetic effects of common genetic variants within the pathways showed significant association with hyperactive/impulsive (pempirical=0.007), but not inattentive symptoms (pempirical=0.73). Analysis of parent-rated Conners hyperactive/impulsive symptom scores validated this result (pempirical=0.0018). Teacher-rated Conners scores were not associated. Post-hoc analyses showed significant contribution of all pathways to the hyperactive/impulsive symptom domain (dopamine/norepinephrine pempirical=0.0004, serotonin pempirical=0.0149, neurite outgrowth pempirical=0.0452).

Conclusion: The current analysis shows association between common variants in 3 genetic pathways with the hyperactive/impulsive component of ADHD. This study demonstrates that pathway-based association analyses, using quantitative measures of ADHD symptom domains may increase the power of genetic analyses to identify biological risk factors involved in this disease.

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