Interaction of Dopamine Transporter Genotype with Prenatal Smoke Exposure on ADHD Symptoms

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Objective To demonstrate that children homozygous for the 10-repeat allele of the common dopamine transporter (DAT1) polymorphism who were exposed to maternal prenatal smoke exhibited significantly higher hyperactivity-impulsivity than children without these environmental or genetic risks.

Study design We performed a prospective longitudinal study from birth into early adulthood monitoring the long-term outcome of early risk factors. Maternal prenatal smoking was determined during a standardized interview with the mother when the child was 3 months old. At age 15 years, 305 adolescents participated in genotyping for the DAT1 40 base pair variable number of tandem repeats polymorphism and assessment of inattention, hyperactivity-impulsivity, and oppositional defiant/conduct disorder symptoms with the Kiddie-Sads-Present and Lifetime Version.

Results There was no bivariate association between DAT1 genotype, prenatal smoke exposure and symptoms of attention deficit hyperactivity disorder. However, a significant interaction between DAT1 genotype and prenatal smoke exposure emerged ($P = .012$), indicating that males with prenatal smoke exposure who were homozygous for the DAT1 10r allele had higher hyperactivity-impulsivity than males from all other groups. In females, no significant main effects of DAT1 genotype or prenatal smoke exposure or interaction effects on any symptoms were evident (all $P > .25$).

Conclusions This study provides further evidence for the multifactorial nature of attention deficit hyperactivity disorder and the importance of studying both genetic and environmental factors and their interaction. *(J Pediatr 2008;152:263-9)*

Attention deficit hyperactivity disorder (ADHD) is the most common, often persistent behavior disorder in childhood, with rates of 3% to 5% among school-aged children.[1] ADHD, a severe impairment of psychological development resulting from a high level of inattention, restlessness, and impulsivity and is associated with severe social consequences and substantial health care costs.[2]

The exact etiologic pathways of ADHD are still unknown, but a considerable heritability with genetic factors contributing 65% to 90% of the phenotypic variation in the population is beyond dispute.[3] Many molecular genetics studies found associations with various dopamine genes, including the human dopamine transporter (DAT1) gene.[4-6] The DAT1 gene has a polymorphic 40 base pair (40 bp) variable number of tandem repeats (VNTR) sequence located in the 3′-untranslated region (3′ UTR) on chromosome 5p15.3.[7] This polymorphism varied between 3 and 13 copies, of which the common 10-repeat allele was associated with an increased expression of the transporter.[8-10]

However, association studies on DAT1 polymorphisms and ADHD yielded conflicting results.[11-13] One reason for this inconsistency may be that environmental factors associated with ADHD, such as prenatal and perinatal complications, low birth weight, and prenatal exposure to different drugs,[3,14,15] may moderate the gene effect. Smoking in pregnancy was a risk factor for long-term intellectual and development disabilities in the offspring in general,[16-18] and for ADHD in particular.[14,19,20] Behavior genetics studies suggest a role for gene-environment interactions,[21] and it is hypothesized that fetal adaptation to an unfavorable intrauterine environment might increase susceptibility to chronic diseases or disorders.[14] Kahn et al[22] investigated the independent and joint effects

3′-UTR	3′ Untranslated region	DSM	Diagnostic and Statistical Manual of Mental Disorders
ADHD	Attention-deficit/hyperactivity disorder		
CD	Conduct disorder	ODD	Oppositional defiant disorder
DAT1	Dopamine transporter polymorphism		

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of the common DAT1 polymorphism and maternal prenatal smoking on behavior problems among 5-year-olds in a prospective longitudinal study. Children with 2 copies of the high-risk 10-repeat allele of DAT1 (homozygous: DAT +/+) were compared with all other children (heterozygous: DAT+/− or homozygous for the 9-repeat allele: DAT −/−). The children with prenatal smoke exposure and DAT +/+ had significantly more hyperactive-impulsive ($P < .01$) and oppositional symptoms ($P < .001$) than all other groups. Additionally, among children with DAT +/− or −/−, prenatal smoke exposure was associated with higher oppositional scores compared with those without prenatal tobacco exposure.

Notwithstanding the fact that the biologic mechanisms underlying this gene-environment interaction are still not well understood, the study by Kahn et al[22] is one of a small number of studies in human beings to date that have ascertained that environmental factors moderate the effect of genes on ADHD, representing a first step in need of replication. Brookes et al[23] examined the interaction of DAT1 and maternal substance use during pregnancy, a gene-environment interaction for tobacco use was not confirmed. Neuman et al[24] showed no significant interaction for the DSM-IV ADHD phenotype between prenatal smoking and the DAT1 10-repeat allele. However, the odds for a diagnosis of ADHD were 1.8 times greater in twins whose genotype at the DAT1 contained the 9-repeat allele and whose mother smoked during pregnancy.

Given the conflicting results of these studies and the relevance of understanding this gene-environment interaction as a possibility for prevention of ADHD, this study attempts to further examine the association between prenatal smoking and the DAT1 gene with ADHD and ODD/CD symptoms in a longitudinal study monitoring children from a high-risk community sample.

METHODS

Sample

This investigation was conducted as part of the ongoing Mannheim Study of Risk Children, a prospective longitudinal study from birth into early adulthood following the long-term outcome of early risk factors. A total of 384 infants from the Rhine-Neckar region of Germany born between 1986 and 1988 were recruited consecutively according to a 2-factorial design intended to enrich and control the risk status of the sample. To control for confounding effects of family environment and infant medical status, only firstborn children with singleton birth, German-speaking parents, and no severe physical handicaps, obvious genetic defects, or metabolic diseases were included. The children were primarily white and from a disadvantaged family background. Additional details on this sample have been reported previously.[25,26] Assessments were conducted at regular intervals from the age of 3 months onward. The current investigation included 305 adolescents (146 male, 159 female) who participated in the 15-year assessment and for whom genetic data were available. Of the original sample of 384 participants, 18 (4.7%) were excluded because of severe handicaps (neurologic impairment or IQ < 70), 26 (6.7%) were dropouts, and 35 (10.4%) refused to participate in blood sampling. The study was approved by the ethics committee of the University of Heidelberg, and all participants gave their written informed consent.

Assessment

Assessment of psychiatric disorders in 15-year-olds was conducted with the Schedule for Affective Disorders and Schizophrenia in School Age Children K-SADS-PL (Kiddie-Sads-Present and Lifetime Version) by Kaufman et al. The K-SADS is a widely used structured diagnostic interview completed independently by parents and adolescents. The assessment tool was recently translated into German[27] and a considerable body of reliability and validity data has been published for the English version. Informants were asked about the presence or absence of symptoms during the 12-month period before assessment. Symptoms were rated on a 3-point scale (0 = absent, 1 = present below threshold, 2 = present above threshold), and, after dichotomization (0 vs 1, 2), were counted if they were endorsed by either the parent or the adolescent. Symptoms of ADHD and oppositional defiant/conduct disorder (ODD/CD) were assigned to domains as given in DSM-IV, and the number of symptoms present was calculated. Three symptom scores indexing severity of inattention (9 items, M = 1.82, SD = 2.67, α = .9), hyperactivity-impulsivity (9 items, M = 1.13, SD = 2.14, α = .88), and ODD/CD symptoms (23 items, M = 3.5, SD = 3.97, α = .86) were formed (all α from this study). ADHD symptom scores were strongly correlated (r = .75, $P < .0001$), and correlations with ODD/CD symptoms were moderate (inattention: r = .51; hyperactivity-impulsivity: r = .57, all $P < .001$).

Maternal prenatal smoking was determined during a standardized interview with the mother at the 3-month assessment. Eighty-two (26.9%) of the mothers who reported any regular smoking during pregnancy were assigned to the prenatal smoking group. Postnatal smoking of the parents was recorded within the framework of a standardized interview conducted with the mother at all assessment waves. A postnatal smoking score was formed counting the number of time points during child development at which the mother or father reported regular smoking.

Psychosocial adversity was assessed according to an "enriched" family adversity index as proposed by Rutter and Quinton.[28] The index measures the presence of 11 adverse family factors, covering characteristics of the parents, the partnership, and the family environment during a period of 1 year before birth (M = 1.96; SD = 2.05; range, 0-7). A description of the study sample and definitions of the index items are presented in Table I (available at www.jpeds.com). Information was derived from a standardized parent interview conducted at the 3-month assessment.