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Parent-of-origin effects in attention-deficit hyperactivity disorder

Lisa M. Goos [a,*], Payam Ezzatian [b], Russell Schachar [a]

[a] Department of Psychiatry, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8
[b] Department of Psychology, University of Toronto, Toronto, Ontario, Canada

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Abstract

The goal of the present study was to investigate parent-of-origin effects in attention-deficit hyperactivity disorder (ADHD). Parent-of-origin effects in ADHD may be due to differences in the relative quantity of risk factors transmitted by each parent. Alternatively, parent-of-origin effects may be produced by qualitative differences in the risks transmitted, such as those carried on the sex chromosomes or regulated by genomic imprinting. 60 children with maternal-only history of ADHD and 131 children with paternal-only history of ADHD were compared on three domains for which prior evidence suggested parent-of-origin effects may exist: core symptoms, disruptive behaviours and depression. Dependent variables were derived from previously validated, age-appropriate and standardized parent and teacher interviews and questionnaires. Depression levels were rated using the *Child Depression Inventory*. Consistent with previous research and the predictions derived from threshold models of ADHD etiology, the maternal history group received higher ratings of behavioural disorder (ADHD, conduct disorder and oppositional symptoms) than the paternal history group. Parent-of-origin effects were also observed for depression, with the paternal history group rating themselves as significantly more depressed than children in the maternal history group, particularly girls. Heightened paternal transmission relative to maternal is suggestive of genomic imprinting, and the interaction with proband sex indicates the involvement of the sex chromosomes or sex-specific physiological or hormonal factors. Interpretations of these data in terms of environmental and genetic factors, including epigenetic and sex-linked hypotheses, are explored.

Keywords: Genomic imprinting; Sex differences; Depression; Inheritance; Behavioral disorders

1. Introduction

1.1. ADHD is heterogeneous in symptoms and cause

Attention-deficit hyperactivity disorder (ADHD) is one of the most common mental health disorders of childhood, affecting approximately 3–7% of all school age children (Swanson et al., 1998). Characterized by impairing levels of inattention and/or hyperactivity–impulsivity (American Psychiatric Association, 1994; Leo et al., 2003), ADHD is also associated with high levels of psychiatric comorbidity (Biederman et al., 2005), including disruptive behaviour disorders such as conduct (CD) and oppositional defiant disorder (ODD) (Burke et al., 2005; Dick et al., 2005; Volk et al., 2005), and emotional problems including depression and anxiety (Biederman et al., 1986).

Although ADHD is highly heritable, a variety of genetic and non-genetic risk factors contribute to ADHD, and no single causal factor has been found in all diagnosed children (Faraone et al., 2005; Jensen et al., 1997; Max et al., 1998, 2003). It is most likely that multiple underlying

* Corresponding author.
E-mail address: lisa.goos@sickkids.ca (L.M. Goos).

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genes, each contributing varying degrees of liability to the disorder, contribute to the core phenotype and associated comorbidities (Mill et al., 2005; Rhee et al., 1999; Slutske et al., 1997).

When groups of ADHD probands are selected for study, this phenotypic and etiological heterogeneity can hamper our ability to detect influences of small effect size. Subsequently, the identification of more homogeneous subgroups within ADHD populations has become the method of choice for advancing our study of this disorder. This method has been fruitfully applied using comorbidities (Biederman et al., 1991; Faraone et al., 1991), cognitive abilities (Crosbie and Schachar, 2001), DSM subtype (Chhabildas et al., 2001; Murphy et al., 2002; Schmitz et al., 2002), and proband sex (Biederman et al., 2002; Faraone et al., 2001; Graetz et al., 2005) as grouping variables, among others. In the present study, children were grouped according to parental history of the disorder.

1.2. Why is parental origin important?

While often considered functionally equivalent, parents may differ in the relative quantity of risk factors they transmit, and may also transmit qualitatively different risks. These differences may result in parent-of-origin effects in the phenotypic manifestation of ADHD, with the offspring of affected mothers differing from the offspring of affected fathers. Parent-of-origin effects may be due to environmental factors, genetic factors, or a combination of the two. Modeling of behaviour by parents and aspects of the environment that are consequent to parental ADHD may result in the apparent transmission of traits from one parent versus the other. Parent-of-origin effects that are biological in nature may be due to chromosomal or hormonal factors, sex differences in the accumulation of risk, or epigenetic phenomena such as genomic imprinting, in which genes from the mother and the father have differential patterns of expression in their offspring. In addition, parent-of-origin effects may be mediated by the sex of the affected offspring, producing sex-of-parent by sex-of-offspring interactions in symptom manifestation. In previous studies, differences between boys and girls with ADHD or variations in familial risk may have been obscured because parental sex was not taken into account.

The polygenic multiple threshold model of ADHD etiology posits that males and females differ in the burden of genetic and environmental risk factors required to produce clinically significant symptoms, with females requiring more (Rhee et al., 1999). According to this model, the considerable sex difference in the prevalence of ADHD (9 males to 1 female in clinical populations, American Psychiatric Association, 1994), is due to females' lower likelihood of expressing ADHD symptoms relative to males' for a given level of cumulative risk.

The study of ADHD in girls has produced some data in support of the polygenic multiple threshold model. For example, the siblings of affected girls have a greater number and more severe ADHD symptoms than do siblings of affected boys (Gaub and Carlson, 1997), and multiplex families with an affected girl are more likely to have at least one parent with ADHD than are families with only affected boys (Smalley et al., 2000). When the tenets of the threshold model are carried through to adulthood, it suggests female probands will convey a greater quantity of risk to their children than affected males (Faraone et al., 1995; Rhee et al., 1999). This predicts increased prevalence of ADHD in the population of children of ADHD mothers versus fathers, but it may also be an important factor mediating phenotypic variability in clinical samples.

Distinct from sex differences in the quantity of risk factors transmitted from parent to child, qualitatively different genetic contributions may also play a role. For example, parents make unique genetic contributions to their offspring via the sex chromosomes: The Y chromosome is only transmitted from fathers to sons; the paternal X chromosome goes only to daughters, while sons carry only the maternal X. In addition to these chromosomal events, an epigenetic regulatory process called genomic imprinting may play a role in the etiology of ADHD.

Genomic imprinting is the differential expression of a gene on the basis of parental origin. In all humans as well as other mammals, a certain subset of genes are only active when inherited from the father, while a different set are only active when inherited from the mother. Although rarely studied to date, there is some evidence to suggest it plays a role in the genetic etiology of ADHD. Hyperactivity in mice was the first behavioural effect of imprinted genes ever recorded (Cattanach and Kirk, 1985), and a number of human neurological disorders show phenotypic variation based on the parent-of-origin, which is considered indicative of genomic imprinting (Hall, 1997). These include autism (Cook et al., 1997) and schizophrenia (Ottman et al., 1988) as well as disorders that commonly occur in conjunction with ADHD, such as Tourette's syndrome (Lichter et al., 1995) and bipolar affective disorder (BPAD, McMahon et al., 1995). Familial studies indicate that at least some common genetic factors contribute to both ADHD and depression (Mick et al., 2003), including BPAD (Biederman et al., 1991; Faraone and Biederman, 1997), likely due to dysfunction in dopamine neurotransmitter systems (Barr et al., 2001; Jucaite et al., 2005; Misener et al., 2004;