Preferential Transmission of Paternal Alleles at Risk Genes in Attention-Deficit/Hyperactivity Disorder

Ziarih Hawi, Ricardo Segurado, Judith Conroy, Karen Sheehan, Naomi Lowe, Aiveen Kirley, Denis Shields, Michael Fitzgerald, Louise Gallagher, and Michael Gill

Departments of Psychiatry and Genetics, Trinity College, Dublin

Family, twin, and adoption studies have demonstrated a significant genetic contribution to the etiology of attention-deficit/hyperactivity disorder (ADHD). Pharmacological, neuroimaging, and animal-model findings suggest imbalances in monoaminergic (dopaminergic, serotonergic, and noradrenergic) neurotransmission in ADHD. We have examined monoaminergic candidate genes for possible genetic association with ADHD in the Irish population, focusing particularly on genes of the dopaminergic and serotonergic systems. We have observed that several of these genes are associated with ADHD, including *DAT1, DBH, DRD4, DRD5,* and *5HT1B*. Here, we present what appears to be a systematic overtransmission of paternal alleles at candidate genes associated with ADHD. For the nine genes included in the analysis, the overall odds ratio for paternal transmission was 2, compared with 1.3 for maternal transmission (paternal vs. maternal $\chi^2 = 9.6$; $P = .0019$). Transmission to females, from either parent, was significantly stronger than to males. Possible reasons for this preferential transmission include imprinting and ascertainment bias, although results of further analyses show that the latter is unlikely.

Introduction

Attention-deficit/hyperactivity disorder (ADHD [MIM 143465]) is one of the most prevalent syndromes, which affects 2%–6% of school-age children. It is typically characterized by inattention, excessive motor activity, impulsivity, and distractibility. Individuals with ADHD have significant impairment in family and peer relations and in academic functioning and are at increased risk of drug abuse and dangerous behavior, such as reckless driving (Mannuzza et al. 1993; Nada-Raja et al. 1997). Family, twin, and adoption studies demonstrate the importance of genetic factors in predisposition to ADHD. Relatives of patients have a higher morbidity risk (25.3%) for the disorder compared with relatives of control individuals (4.6%) (Biederman et al. 1992). Heritability is estimated to be 39%–91% (Thapar et al. 1999). On the basis of symptom scores, ADHD was classified into three major subtypes: the combined (50%–75%), inattentive (20%–30%), and hyperactive (<15%) subtypes (Wilens et al. 2002).

Boys are more frequently affected with the disorder than are girls, with observed ratios that range from 2:1–4:1 in population-based surveys to 9:1 in clinical studies (Ford et al. 2003; Poeta and Rosa Neto 2004). Although well documented in the literature of ADHD, the causes of sex differences are unknown; however, a multiple-threshold model has been proposed. In this model, the cause of ADHD was assumed to be polygenic factors (more than one gene involved) in combination with environmental factors. In this context, individuals differ in the amount of liability that they have for the disorder. The development of the disorder depends on whether the individual exceeds a given threshold of liability (Rhee et al. 1999). According to this model, female probands would require a greater liability than would male probands. This model therefore predicts that the rate of the disorder would be higher in the relatives of female probands than those of male probands. Evidence to support the polygenic multiple-threshold model for ADHD was reported by Kashani et al. (1979) and Faraone et al. (1995). Girls with ADHD are less likely than boys to develop major depression, learning disabilities, conduct disorder, and oppositional defiant disorder (Biederman et al. 2002). This may result in boys being referred for assessment more frequently than girls. Furthermore, because the symptoms of inattention (more prevalent in girls) are more covert than those of hyperactivity and impulsivity (more common in boys), fewer girls than boys might be diagnosed with the disorder (Biederman and Faraone 2004).

Pharmacological, neuroimaging, and animal-model findings suggest the importance of imbalance in monoaminergic neurotransmission in ADHD. This has also been supported by recent genetic association studies

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Address for correspondence and reprints: Dr. Ziarih Hawi, Department of Genetics, Trinity College, Dublin 2, Ireland. E-mail: zhhawi@tcd.ie

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(Hawi et al. 2003). The focus of most molecular studies (association/linkage) has been on the genes of the dopaminergic and, to lesser extent, the serotonergic systems. However, genes relating to the noradrenergic and glutaminergic systems are also under investigation.

To date in our studies, we have investigated 17 candidate genes for ADHD, focusing on monoaminergic system genes, particularly dopaminergic and serotonergic (table 1). The results of these studies have been the subject of several publications that describe evidence for association at *DAT1* (MIM 126455), *DBH* (MIM 609312), *DRD4* (MIM 126452), *DRD5* (MIM 126453), *5HT1B* (MIM 182131), *SNAP25* (MIM 600322), and *TPH2* (MIM 607478) (see Daly et al. 1999; Brophy et al. 2002; Hawi et al. 2002; Lowe et al. 2004*a*; Sheehan et al. 2005).

It is evident that ADHD is a heterogeneous and genetically complex disorder, with several genes (each of minor or moderate effect) involved in the etiology of the syndrome. Overall, the literature supports *DRD4, DRD5,* and *DAT1* as susceptibility loci for ADHD (Faraone et al. 2001, 2005; Maher et al. 2002; Lowe et al. 2004*b*).

In our individual gene studies, we have observed what appears to be a consistent pattern of preferential paternal transmission of risk alleles to affected children with ADHD. In this work, we investigated our observations in a more systematic manner. In particular, we examined paternal versus maternal transmission for all studied genes in the Irish ADHD sample, for "associated" genes (see definition in the "Material and Methods" section), for transmission to male versus female children, and for transmission from "affected" (see definition in the "Material and Methods" section) versus unaffected parents.

Material and Methods

Subjects

A total of 179 Irish ADHD-affected nuclear families were included in the current study. The sample was ascertained and the diagnosis confirmed as described elsewhere (Kirley et al. 2004). In brief, consensus diagnoses were made in accordance with DSM-IV criteria. One or both parents of each child were interviewed using the Child and Adolescent Psychiatric Assessment. To fulfill DSM-IV criteria for symptom pervasiveness, information about ADHD symptoms at school was obtained from teachers through use of the Teacher Telephone Interview, which involved asking teachers about DSM-IV symptoms of ADHD and impairment shown in class. In addition, 155 Irish autistic nuclear families (probands and both parents) were recruited through schools and parent support groups. Subjects were assessed by use of the Autism Diagnostic Interview–Revised (Lord et al. 1989) and the Autism Diagnostic Observation Schedule–Generic (Lord et al. 2000) and were used as a comparative group, since autism (MIM 209850) exhibits a similar male:female ratio. Of the sample, 77% were affected with ADHD–combined type, whereas 15% met research

Table 1

TDT Analysis of Candidate Genes Examined in the Study Sample

System and Gene	No. of Examined Markers	χ^2	*P*
Dopaminergic:			
Dopamine receptor 1 (*DRD1*)	1	.17	.78
Dopamine receptor 2 (*DRD2*)	2	.57	.57
Dopamine receptor 3 (*DRD3*)	1	.1	.87
Dopamine receptor 4 (*DRD4*)	5	7.5	.008
Dopamine receptor 5 (*DRD5*)	5	11.1	.001
Dopamine transporter (*DAT1*)	5	1.2	.4
Catechol-O-methytransferase (*COMT*)	1	.06	.87
Tyrosine hydroxylase (*TH*)	1	4.4	.04
Dopamine beta hydroxylase (*DBH*)	4	1.2	.31
Dopa decarboxylase (*DDC*)	3	4.2	.098
Synaptosomal-associated protein 25 (*SNAP-25*)	7	2.7	.12
Serotonergic:			
Serotonin receptor 1B (*5HT1B*)	3	1.9	.2
Serotonin receptor 2A (*5HT2A*)	2	.64	.5
Serotonin transporter (*SERT*)	4	3.6	.08
Tryptophan hydroxylase 2 (*TPH2*)	8	12.1	.0006
Noradrenergic:			
Noradrenaline transporter (*NET*)	2	2.3	.17
Glutamatergic:			
N-methyl-D-aspartate receptor 2A subunit (*GRIN2A*)	1	.03	.9

criteria for ADHD–inattentive type, and 8% for ADHD–hyperactive-impulsive type.

Genotyping Methods

PCR-based genotyping of markers included in this study was conducted using the primer sequences and amplification conditions as described and referenced in table 2.

Transmission/Disequilibrium Test

The transmission/disequilibrium test (TDT) is a linkage and family-based association test (Spielman et al. 1993) designed to avoid errors in case-control studies that are due to population stratification. It compares the frequency of transmitted and nontransmitted alleles from parents heterozygous for a given polymorphism.

Definition of ADHD History–Positive Parents

Parents completed the Wender Utah Rating Scale (WURS) (Ward et al. 1993) to retrospectively determine the presence and extent of ADHD symptoms and behaviors during their childhood. WURS consists of a 25-item subscale in which a cutoff score of $\geqslant 36$ is 96% sensitive and specific for a retrospective diagnosis of childhood ADHD in someone now the parent of an affected child (Ward et al. 1993). A positive parental history of ADHD is therefore defined as a score of $\geqslant 36$ on the 25-item subscale of the WURS.

Definition of Associated Genes and Joint Analysis of Marker Data

Since we previously observed a preponderance of paternal transmission of risk alleles at several of the candidate genes examined, we decided to investigate whether this phenomenon is restricted to ADHD and the combination of genes examined. We defined the "risk" allele for a marker as the allele that demonstrated the highest transmitted:nontransmitted ratio in our full sample, regardless of whether the finding was statistically significant. If the TDT demonstrated overtransmission of the "risk" allele over the other allele(s) at a level of $P < .1$, that allele was classed as "associated." This threshold was set deliberately lenient to reduce the type II error rate and would be expected to lead to an underestimate of the size of parent-of-origin effects in our analysis. In addition, we included markers that have been confirmed (by several groups) to be associated with ADHD. We made the assumption that transmission of alleles at each gene is independent of transmission of alleles at other genes and therefore can be combined additively, to test a general paternal versus maternal hypothesis.

Table 2

Marker Names, PCR Primers, and Amplification Conditions

The table is available in its entirety in the online edition of *The American Journal of Human Genetics*.

Results

Markers at 9 (6 dopaminergic and 3 serotonergic) of the 17 genes examined passed the threshold (TDT $P < .1$ or associated in several samples) to be considered "associated" with ADHD (table 1): *DRD4, DRD5, DAT1, SERT, TPH2, TH, DDC, SNAP-25,* and *5HT1B*. When the data were stratified on the basis of sex of transmitting parent (table 3), paternal transmission showed, in general, larger odds ratios (ORs) than did maternal transmission. Nominally significant overtransmission of paternal alleles was seen at *DRD4, DRD5, DAT1, SERT,* and *TPH2,* and a trend was seen in the case of *TH, DDC, SNAP-25,* and *5-HT1B*. In contrast, no significant association at any of these genes was observed when maternal transmission was considered. This observation implies that association with ADHD is due principally to paternal overtransmission of the risk allele at nine independent loci. This cannot be accounted for by differences in sample size, since the number of maternal observations is comparable to the number of paternal observations across all loci.

When data from the "associated" alleles were combined (table 3), highly significant excess paternal transmission was observed ($\chi^2 = 41.6$; $P = 1.5 \times 10^{-10}$; OR = 1.94), whereas a marginally significant excess of transmission of maternal alleles was seen ($\chi^2 = 5.2$; $P = .026$; OR = 1.26).

We then tested the hypothesis that there was, overall, greater paternal versus maternal transmission for these genes, versus the null hypothesis that the ratio of transmitted:nontransmitted "risk" alleles is independent of the sex of the parent. The associated paternal versus maternal risk-allele transmissions were compared using a standard χ^2 test with 1 df. We found a highly significant difference, attributable to an excess transmission of paternal alleles compared with those of maternal origin ($\chi^2 = 9.6$ [1 df]; $P = .0019$; OR = 1.56) (table 3).

To examine whether the observed paternal overtransmission of the associated alleles might be due to a strong effect at a single locus, we conducted a simple sensitivity analysis (table 4). This was performed by removing one marker at a time and analyzing the remainder as described above. Significant differences between paternal and maternal transmissions remained for all analyses, with P values ranging from .013 (when *DAT1* was re-

Table 3

Paternal versus Maternal Transmission of ADHD-Associated Genes

	Transmission of ADHD-Associated Genes													
	Paternal							Maternal						
	TDT for							TDT for						
	Associated Allele		Other Alleles					Associated Allele		Other Alleles				
Gene (Marker)	T	NT	T	NT	χ^2	*P*	OR	T	NT	T	NT	χ^2	*P*	OR
DRD4 (−616)	40	23	23	40	4.6	.043	1.7	32	19	19	32	3.3	.09	1.7
DRD5 $(CA)_n$	57	29	29	57	9.1	.0034	2.0	54	36	36	54	3.6	.07	1.5
DAT1 (VNTR)	33	18	18	33	4.4	.048	1.8	23	30	30	23	.9	.41	.8
TH $(TCAT)_n$	21	12	12	21	2.5	.16	1.8	28	19	19	28	1.7	.24	1.5
DDC (4-bp ins)	7	2	2	7	2.8	.18	3.5	10	7	7	10	.53	.63	1.4
SNAP-25 (*MnlI*)	33	22	22	33	2.2	.18	1.5	28	33	33	28	.4	.6	.8
5HT1B (861G)	36	23	23	36	2.9	.11	1.6	29	23	23	29	.73	.46	1.3
SERT (*D17S1294*)	15	2	2	15	9.9	.002	7.5	9	10	10	9	.05	1.0	.9
TPH2 (*rs1843809*)	26	7	7	26	10.9	.001	3.7	23	12	12	23	3.5	.09	1.9
Combined TDT	268	138	138	268	41.6	1.5×10^{-10}	1.94	236	189	189	236	5.2	.026	1.26

Note.—Test of paternal versus maternal transmissions: $\chi^2 = 9.6$ (1 df); $P = .0019$; OR = 1.56. T = transmitted; NT = not transmitted.

moved) to .0011 (when *DRD4* was removed), which suggests that *DAT1* contributed more than any other marker to the combined analysis.

The same sets of analyses were repeated with the seven gene/markers "not associated" with ADHD (data not shown), to test whether increased paternal transmission might be a general phenomenon at all loci. The alleles tested were those that showed any increase in transmission over nontransmission (none happened to have equal frequencies for transmission and nontransmission). TDT analysis showed no significant differences in the transmission of the "risk" allele (as defined above) when paternal or maternal origin was considered separately or when compared with each other ($\chi^2 = 0.68$; $P = .41$).

As a further comparison with our data, we decided to examine genes associated with autism in a similar-sized sample of parent-child trios. Similar to ADHD, boys are more commonly affected with autism than are girls, with an average ratio of 3:1 (Fombonne et al. 2001). We tested the transmission of associated alleles by sex of parent in an autism sample (table 5) to see whether the observed preferential paternal transmission of the associated allele is a phenomenon related to ADHD alone. Three markers/alleles (located on different chromosomes) associated with autism (with use of the same criteria of an uncorrected TDT $P < .1$) were examined. In a combined analysis, remarkably similar excess transmissions were observed for alleles of paternal ($\chi^2 = 10$; $P = .002$) and maternal ($\chi^2 = 10.6$; $P = .0015$) origin. Comparison of paternal versus maternal transmissions showed no parent-of-origin effect ($\chi^2 = 0.01$ [1 df]; $P = .93$).

Discussion

It is evident from the data that there is a significant distortion in the transmission pattern of alleles associated with ADHD, dependent on the sex of the transmitting parent. This phenomenon seems to be ADHD specific and does not generalize to autism, another psychiatric condition with a high male:female ratio. It also appears to be specific to loci associated with the ADHD phenotype, since there is no suggestion of such an effect at alleles not associated with ADHD. There are several possible explanations for these observations.

First, it is necessary to consider whether biased sam-

Table 4

Sensitivity Analysis

	TDT for ADHD-Associated Genes					
	Paternal		Maternal			
Sample	T	NT	T	NT	χ^2	*P*
All[a]	268	138	236	189	9.6	.0019
No *DRD4* (−616)	228	115	204	170	10.6	.0011
No *DRD5* $(CA)_n$	211	109	182	153	9.2	.0024
No *DAT1* (VNTR)	235	120	213	159	6.1	.013
No *TH* $(TCAT)_n$	247	126	208	170	9.9	.0016
No *DDC* (4-bp ins)	261	136	226	182	9.0	.0026
No *SNAP-25* (*MnlI*)	235	116	208	156	7.3	.007
No *5HT1B* (861G)	232	115	207	166	9.8	.0017
No *SERT* (*D17S1294*)	253	136	227	179	6.9	.0085
No *TPH2* (*rs1843809*)	242	131	213	177	8.3	.0038

Note.—T = transmitted; NT = not transmitted.

[a] All nine ADHD-associated genes tested.

Table 5

Transmission of Genes Associated with Autism in the Irish Population

	Transmission of Autism-Associated Genes													
	Paternal							Maternal						
	TDT for							TDT for						
	Associated Allele		Other Alleles					Associated Allele		Other Alleles				
Gene (Marker)	T	NT	T	NT	χ^2	*P*	OR	T	NT	T	NT	χ^2	*P*	OR
SERT (ins/del)	21	11	11	21	3.1	.1	1.9	23	12	12	23	3.5	.09	1.9
ITGA4 (*rs3770112*)	32	16	16	32	5.3	.03	2	32	16	16	32	5.3	.03	2
EN2 (*rs3757846*)	26	17	17	26	1.9	.2	1.5	20	12	12	20	2	.2	1.6
Combined TDT	79	44	44	79	10.0	.002	1.8	75	40	40	75	10.6	.0015	1.9

Note.—Test of paternal versus maternal transmissions: $\chi^2 = 0.01$ (1 df); $P = .93$. T = transmitted; NT = not transmitted.

ple selection might account for the findings. Specifically, it could be suggested that the ascertainment of cases of ADHD might depend on the affection status of the parent who, first, brings the child to the attention of the clinical services and, second, agrees to participate in research and brings the child to a test site for assessment. If it is more likely that that parent would be the mother and if having ADHD herself would bias her against taking the steps described above to get her child into the research program, then the sample might be biased toward families in which mothers were unaffected and thus less likely to transmit associated alleles. To address this possibility, the first question to ask is whether the sample contains more affected fathers than affected mothers. Thirty percent of study parents were affected (as determined by the Wender rating scale), 35% of fathers and 25% of mothers ($\chi^2 = 3.82$; $P = .051$). Therefore, there is a trend of more affected fathers, but this is in keeping with the fact that ADHD is more prevalent in males. There is not the virtual absence of affected mothers that might have been anticipated under the hypothesis of ascertainment bias.

The second question is whether affected parents transmit alleles from associated genes more than do unaffected parents and whether this differs by sex of the transmitting parent. TDT analysis conducted on the number of transmissions analyzed by sex of transmitting parent and by parental history of ADHD shows combined ORs of 2.25 and 1.7 for history-positive and history-negative paternal transmissions, respectively ($\chi^2 = 1.5$; $P = .22$), and ORs of 1.35 and 1.2 for history-positive and history-negative maternal transmissions, respectively ($\chi^2 = 0.3$; $P = .6$). Transmissions from history-positive fathers were significantly greater than from history-positive mothers ($\chi^2 = 5.5$; $P = .02$), and transmissions from history-negative fathers were greater than from history-negative mothers, but not at a significant level ($\chi^2 = 3.16$; $P = .075$). These data suggest that the excess paternal transmission did not arise from data censoring, because of the bias toward inclusion of unaffected mothers in the sample. However, it should be noted that the method of determining history-positive parents, the WURS questionnaire, may not be a reasonable proxy measure of persistence of ADHD symptoms into adulthood.

Third, could imprinting be involved? Several investigators have observed significant sexual dimorphism in the incidence of psychiatric disorders. Although an increased incidence of autism, ADHD, and antisocial personality disorder is found in males, eating disorder, depression, panic disorder, and phobia are more prevalent in females (Craig et al. 2004). These findings suggest the possibility of a genomic mechanism (such as imprinting) as a contributing factor in these conditions. Imprinting involves the sex-dependent germ-cell epigenetic inactivation of a gene, which results in monoallelic expression in offspring that is parent-of-origin dependent (Murphy and Jirtle 2003). The functional impact of this mechanism can be striking, particularly on brain development. Keverne et al. (1996) suggested that genomic imprinting might facilitate a rapid nonlinear expansion of certain brain regions during development of psychiatric conditions, including ADHD.

Studies of chimeric embryos to assess the roles of the paternal genomes in brain development showed that the contribution of the parthenogenetic/gynogenetic (Pg/Gg duplicated maternal genome) cell to brain development was ~30%–40%, compared with 5% in the case of the androgenetic cell (Ag duplicated paternal genome) (Barton et al. 1991; Keverne et al. 1996). In addition, the distribution of Ag and Pg cells was found to accumulate in different regions in the brain. Whereas the Ag specifically accumulated in the forebrain, the Pg cells were found predominantly in the cortex and striatum. For control cells, a uniform distribution was observed throughout the brain region (Keverne et al.

Table 6

Parental Transmission by Sex of Child

	Results of Combined TDT for													
	Boys							Girls						
	Associated Allele		Other Alleles					Associated Allele		Other Alleles				
Transmission	T	NT	T	NT	χ^2	*P*	OR	T	NT	T	NT	χ^2	*P*	OR
Paternal	232	130	130	232	28.7	1.11×10^{-7}	1.8	39	11	11	39	15.7	9.02×10^{-5}	3.5
Maternal	210	169	169	210	4.4	.04	1.2	35	16	16	35	7.1	.01	2.2
Total TDT	442	299	299	442	27.6	1.83×10^{-7}	1.5	74	27	27	74	21.9	4.72×10^{-6}	2.7

Note.—Test of paternal versus maternal transmissions for boys: $\chi^2 = 5.8$ (1 df); $P = .016$; OR = 1.44. Test of paternal versus maternal transmissions for girls: $\chi^2 = 1.1$ (1 df); $P = .29$; OR = 1.6. Test of transmissions to boys versus transmissions to girls: $\chi^2 = 7$ (1 df); $P = .008$; OR = 1.85. T = transmitted; NT = not transmitted.

1996). This effect is likely due to the deficiency of paternally expressed genes and the double dosage of maternally expressed genes. Imprinted variants, regardless of their parent of origin, are involved in several diseases, including psychiatric and behavioral disorders such as Prader-Willi syndrome (PWS [MIM 176270]) and Angelman syndrome (AS [MIM 105830]). Patients with PWS inherit both copies of imprinted chromosome 15 from their mothers, whereas children who lack portions of maternal chromosome 15q or who possess two copies of paternal chromosome 15 were found to have mental retardation and suffer from seizures as a part of AS (Nicholls 1993; Keverne et al. 1996).

It is well recognized that imprinted genes tend (in general) to cluster in certain chromosomal regions. However, none of the ADHD-associated genes has been mapped to any of these regions. Since ADHD-associated genes map to many different chromosomes, it is unlikely, a priori, that all these genes are imprinted. It remains possible that a generalized disturbance of an imprinting mechanism is a feature of ADHD and that we are detecting linkage disequilibrium to multiple polymorphic methylation target sequences in at least some of the genes showing paternal overtransmission to ADHD-affected cases. However, we are not aware of any molecular evidence to support the involvement of genomic imprinting in ADHD, and the present study does not provide such evidence.

In moving aside from analyses of parental origin of risk alleles, it occurred to us that the method of combining data from multiple associated genes might enable us to test another hypothesis: the proposed differential genetic loading by sex of probands in a disorder with a male:female prevalence ratio such as ADHD. Sex differences in the prevalence of ADHD have been well documented, with boys more likely to develop ADHD than girls (ratio reaching 9:1). Cloninger et al. (1978) hypothesized that the sex differences in ADHD may be explained on the basis that girls require a greater genetic loading to manifest ADHD than do boys. This could be the result of either an inherent risk factor in being male or an inherent protective factor in being female. This hypothesis has been supported recently by Rhee and Waldman (2004). They found that DZ twins or siblings of girls with ADHD had a higher number of symptoms than did twins or siblings of boys with the disorder. In our sample, TDT analysis of transmission by the sex of the child with ADHD (table 6) showed highly significant overtransmission of associated alleles to both girls ($\chi^2 = 21.9$; $P = 4.7 \times 10^{-6}$; OR = 2.7) and boys ($\chi^2 = 27.6$; $P = 1.8 \times 10^{-7}$; OR = 1.5), which shows that girls require nearly twice the genetic loading of boys ($\chi^2 = 7$; $P = .008$; OR = 1.85). The strongest ORs are found for transmissions from fathers to daughters (OR = 3.6), and the weakest from mothers to sons (OR = 1.2). This further supports the hypothesis that more genetic loading is necessary for girls to develop ADHD.

A further option is that these findings could be due to type I error (false-positive result). In general, this may occur as a consequence of small sample size or as a result of sex or ethnic mismatch of patient and control groups. The failure to replicate several association findings in psychiatric disorders has been attributed, at least in part, to the above factors. However, the findings of this study are the results of TDT analysis (a linkage and family-based association) in which the nontransmitted alleles are used as an internal control to avoid population stratification (ethnic and/or sex mismatch). Furthermore, the ADHD-affected nuclear families of the present study are all of Irish origin except for one family in which the father is of Croatian origin. It is less likely, therefore, that these results are chance findings, especially since the examined population is relatively large and the findings appear to be consistent across many genes.

Finally, the findings of this study need to be replicated in other ADHD samples, which should be possible, given

the fact that many of the markers included in our study have also been found by several groups to be associated with ADHD.

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Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ADHD, *DAT1, DBH, DRD4, DRD5, 5HT1B, SNAP25, TPH2,* autism, PWS, and AS)

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