ADHD and DAT1:

Further evidence of paternal over transmission of risk alleles and haplotype

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Abstract:
We [Hawi et al. (2005); Am J Hum Genet 77:958–965] reported paternal over-transmission of risk alleles in some ADHD-associated genes. This was particularly clear in the case of the DAT1 3′-UTR VNTR. In the current investigation, we analyzed three new samples comprising of 1,248 ADHD nuclear families to examine the allelic over-transmission of DAT1 in ADHD. The IMAGE sample, the largest of the three-replication samples, provides strong support for a parent of origin effect for allele 6 and the 10 repeat allele (intron 8 and 3′-UTR VNTR, respectively) of DAT1. In addition, a similar pattern of over-transmission of paternal risk haplotypes (constructed from the above alleles) was also observed. Some support is also derived from the two smaller samples although neither is independently significant. Although the mechanism driving the paternal over-transmission of the DAT risk alleles is not known, these finding provide further support for this phenomenon.

Keywords: ADHD; DAT1; parent of origin effect; VNTR

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly heritable behavioural condition affecting 2-6% of children worldwide that is characterized developmentally inappropriate levels of inattention, hyperactivity and impulsivity. The exact aetiology of the disorder is not well characterized but consists of a combination of genetic and environmental factors. The emerging literature from pharmacological, animal model, molecular and neuroimaging studies indicate the importance of catecholamine dysregulation (particularly dopaminergic) in the pathogenesis of ADHD. Methylphenidate is the most widely used psychostimulant for the treatment of ADHD. The site of action of this drug is to block the dopamine transporter and consequently increase the amount of dopamine in the synaptic cleft.

A genetic association between ADHD and the 10 repeat allele of a variable number of tandem repeat (VNTR) polymorphism within the 3'untranslated region of the dopamine transporter gene (DAT1), was first reported by Cook et al .[1995]. Subsequent studies reported inconsistent findings with some (but not all) supportive of the association. Four meta analyses have been conducted on the published reports; three of which [Maher et al., 2002., Faraone et al., 2005., and Yang et al., 2007] provided only weak evidence that DAT1 is an ADHD risk gene of minor effect (OR=1.1-1.27), with the third not supportive (Li et al 2006). However they did find significant evidence of heterogeneity because of greater evidence for positive association results from family based studies and European studies compared to case-control studies and Asian studies. Not included in these meta analyses are several recent studies some supporting the DAT1 association with ADHD [Kopecková et al., 2008] and some not [Wohl et al., 2008].

Furthermore, two recent reports from the same group [Brookes et al., 2006a and Brookes et al., 2006b] report association between ADHD and allele 6 of a VNTR mapped to intron 8 of DAT1. This association was first reported on two separate ADHD samples (English and Taiwanese) [Brookes et al., 2006a] and was subsequently replicated, although with a smaller effect size, in the International Multi Centre ADHD Genetics (IMAGE) project sample [Brookes et al., 2006b]. Furthermore, they observed a significant association between ADHD and a common haplotype made up of allele 6 of the intron 8 variant and the 10-repeat allele of the 3'un-translated VNTR [Asherson et al., 2007] in all three datasets.

Inconsistency in association findings at DAT1 could be due to a very small effect size of the associated alleles, clinical or genetic heterogeneity, or other confounding factors such as epigenetic effects. In ADHD, boys are more frequently affected than girls with ratios ranging from 2:1 to 4:1 in population based surveys, to 9:1 in clinical studies. The exact reasons for the gender differences in ADHD are not known, although in the general population there is an overall higher level of ADHD symptoms among males and twin studies suggest no differences in the genetic influences on the two genders. We previously [Hawi et al., 2005] reported over transmission of ADHD associated risk alleles at several gene loci to affected offspring from fathers compared to mothers. This was evident for variants at several dopaminergic genes particularly DAT1. However, in two subsequent studies a parent of origin effect was not observed [Kim et al., 2007 and Luca et al., 2007]. In a third study, Anney et al. [2007] examined the overall and gene-specific parent of origin effect in 554 independent SNPs

across 47 ADHD candidate genes. No overall parent of origin effect in the IMAGE sample (χ^2 =1.82, P = 0.117) was observed. However, three genes, the dopamine decarboxylase (DDC), Tryptophan Hydroxylase TPH2, and noradrenergic transporter (SLC6A2) showed nominal association (P<0.01) with ADHD combined subtype when restricted to maternal or paternal transmission only.

In the current investigation, we further examine the parent of origin hypothesis at DAT1 (paternal over transmission of ADHD associated alleles) in three independent samples. The first is a newly ascertained Irish ADHD sample (52 full trios). The second is an English ADHD sample (63 full trios) and the third is a multicentre collaborative IMAGE sample consisting of 1,084 trios. In addition, we have typed our original Irish sample to include the intron 8 VNTR and analysed this variant individually and in a haplotype with the 3' VNTR.

Material and Methods

Irish sample 1.

178 (170 full trios and 8 duos) ADHD nuclear families were recruited throughout Ireland and have been used to investigate several candidate genes. Cases and available parents were recruited from child psychiatric clinics and schools in west County Dublin and from the Hyperactive and Attention Deficit Children's Support Group of Ireland. Consensus diagnoses were made according to DSM-IV ADHD or UADD either with or without comorbidity. These diagnoses were based on all available clinical information and the Child Behaviour Checklist (CBCL), the Conners Parents and Teachers Rating Scales, and the Comprehensive Teachers Rating Scale (ACTeRS).

Irish sample 2.

52 trios were included in the current study as part of a larger sample of 108 nuclear families of children with ADHD participating in a naturalistic, pharmaco-genetic study of stimulant response in ADHD. The children recruited for the pharmacogenetic study shared identical inclusion and exclusion criteria as well as diagnostic criteria as the Irish sample I (see above). The key differences between the two samples are that the children in the pharmacogenetic study were stimulant naïve as a selection criterion and they were also younger in age (4-15 y vs. 5-17 y).

English Sample

This sample is collected from several child psychiatric clinics in the United Kingdom. It consists of 63 parent proband trios and 44 mother-Child duos. Probands are Caucasians with an age range between 5-15 y old. All proband fulfil the DSM-IV diagnostic criteria for ADHD. Cases were diagnosed using the child and the adolescent Psychiatric assessment (CAPA). More clinical and diagnostic details can be found in [Kent et al., 2002].

The IMAGE sample

IMAGE families were identified through ADHD probands attending outpatient clinics at the data collection sites in 7 European countries and Israel. It consists of 1034 nuclear families with probands and their siblings were aged 5–17 y at the time of entry into the study. DNA was obtained from ADHD individuals and one or both biological parents for DNA. The probands are clinically diagnosed with DSM-IV combined subtype. More details can be found in Brookes et al (2006).

VNTR genotyping and data analysis

DNA amplification and genotyping of intone 8 VNTR was performed as described by Brooke et al (2006) while the 3' untranslated VNTR was accomplished as described by Cook et al, 1995. Transmission disequilibrium analysis of individual and haplotypes analyses were conducted using

the program UNPHASED (http://portal.litbio.org/menu-bin/GLUE/glue.pl).

Imprinting testing

HapMap CEU lymphoblast cell lines were maintained in RPMI 1640 media supplemented with 15% FBS at 37°C and 5% CO_2. RNA was extracted from ~10^6 cells using the RNeasy extraction system (Qiagen) as recommended by the manufacturers. A total of 1µg of RNA was reversed transcribed using the Quantitect RT system (Qiagen). Genotyping of cDNA from 22 HapMap cell lines heterozygous for the SNP rs11564774 (mapped to the 3-UTR of the DAT1 gene) was conducted using Applied Biosystems Taq man assay.

Results

TDT analysis of the intron 8 shows a small but insignificant increase in the transmission of allele 6 to ADHD cases in the first Irish sample (χ^2=1.45, p=0.2, OR=1.25), the English (χ^2= 2.3, p= 0.12, OR=1.69) but not in the second Irish sample (χ^2= 0.1, p= 0.74, OR=1.1).

Analysis by the sex of transmitting parents is presented in Table 1. The first Irish sample shows preferential transmission of paternal alleles at the 3' UTR VNTR as previously published (Hawi et al, 2005). For this sample, the Intron 8 variant showed no POO effect. The second Irish sample shows no significant POO effect for either marker. The English sample however, showed a significant over transmission of the 10 repeat allele from mothers to ADHD cases (χ^2=7.7, p=0.005, OR= 4.7). In contrast to these findings, the IMAGE sample, by far the largest, showed a significant paternal over transmission of both allele 6 of intron 8 VNTR χ^2= 4, p=0.045, OR=1.26) and the UTR 10 repeat allele χ^2= 8.8, p=0.003, OR=1.4). Combined analysis (Table 2) of all samples strengthens the OR of the paternal over transmission of the 6 repeat allele of intron 8 VNTR (χ^2= 5.4, p=0.02, OR=1.27) and the 10 repeat allele (χ^2= 12.2, p=0.0005, OR=1.41).

Linkage disequilibrium (LD) analysis using parental (with no history of ADHD) genotypes was performed by the program Haploview and showed a significant LD between the two analyzed VNTRs (D'=0.65; r^2 = 32). Haplotype analysis according to the parent of origin using the program UNPHASED (http://portal.litbio.org/menu-bin/GLUE/glue.pl) is presented in Table 3.

TDT analysis of parental transmission of the putative 6-10 risk haplotype shows significant paternal over transmission in the first Irish ADHD sample (χ^2= 4.8, p=0.03, OR=1.8), and in the IMAGE sample (χ^2=9.5, p=0.002, OR=1.4). Furthermore, combined analysis increases the strength of the paternal over transmission of the risk haplotype to ADHD cases (χ^2= 14.5, p=0.00014, OR=1.45) compared to the maternal (χ^2=0.19 p=0.66, OR=1.04). This difference is significant at χ^2= 5.7, p=0.017.

If imprinting operates on DAT1, mono allelic expression is expected from heterozygous individuals for the SNP rs11564774. However, bi-allelic expression was observed in all 22 cell lines tested indicating that DAT1 is not imprinted in lymphoblast.

Table 1: Paternal TDT analysis of DAT1Individual markers in four ADHD samples

A: Paternal	Irish 1					Irish 2.					English					IMAGE				
Intron 8 alleles	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR
4	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	1	1	0	1	1
5	25	29	0.3	0.6	0.9	11	7	0.9	0.3	1.6	7	11	0.9	0.3	0.6	126	161	4.3	0.04	0.78
6	29	25	0.3	0.6	1.16	7	11	0.9	0.3	0.6	11	7	0.9	0.3	1.6	162	128	4	0.045	1.26
7	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	1	0	1.4	0.24	-
0																				
3-UTR alleles																				
8	0	4	5.5	0.01	-	0	2	2.8	0.1	-	ND	-	-	-	-	3	1	1	0.3	3
9	16	31	4.9	0.03	0.5	9	8	0.06	0.8	1.1	7	7	0	1	1	135	190	9.4	0.002	0.7
10	35	17	6.4	0.01	2.1	9	9	0	1	1	7	7	0	1	1	194	140	8.8	0.003	1.4
11	1	0	1.24	0.24	0.24	1	0	1.4	0.24	-	ND	-	-	-	-	11	18	0.02	0.9	0.6
B: Maternal																				
Intron 8 alleles	T	NT	χ2	p-value	OR	T	NT	χ2	p-value	OR	T	NT	χ2	p-value	OR	T	NT	χ2	p-value	OR
4	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-					
5	19	28	1.7	0.2	0.7	10	8	0.2	0.6	1.35	5	10	1.7	0.2	0.5	136	146	0.3	0.5	0.9
6	28	19	1.7	0.2	1.5	8	10	0.2	0.6	0.8	10	5	1.7	0.2	1.5	147	136	0.4	0.5	1.1
7	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	0	1	1.4	0.24	-
0																				
3-UTR alleles																				
6	ND					ND					ND					0	3	4.1	0.04	-
7	ND					ND					ND					1	0	1.4	0.24	-
8	1	1	0	1	1	1	0	1.4	0.24	-	ND	-	-	-	-	1	0	1.4	0.24	-
9	26	22	0.3	0.6	1.2	8	7	0.06	0.8	1.1	3	14	7.7	0.005	0.2	158	170	0.4	0.5	0.9
10	23	28	0.5	0.5	0.8	7	9	0.3	0.6	0.8	14	3	7.7	0.005	4.7	176	166	0.6	0.5	1.04
11	1	0	1.4	0.24	-	ND	-	-	-	-	ND	-	-	-	-	14	15	0.03	0.8	0.9

Hap=Haplotype, T= Transmitted, NT= Untransmitted, ND= Not detected

Table 2: Parental TDT analysis of DAT1 individual markers in the combined samples totalled.

	Paternal					Maternal				
A: Intron 8 alleles										
	T	NT	χ^2	p	OR	T	NT	χ^2	p	OR
4	1	1	0	1	1	4				
5	165	211	5.6	0.017	0.78	170	192	1.34	0.25	0.88
6	212	167	5.36	0.02	1.27	193	170	1.13	0.23	1.14
7	1	0	1.38	0.24	-	0	1	1.38	0.24	-
B: 3-UTR alleles										
6	0	0	-	-	-	0	3	4.159	0.04	-
7	0	0	-	-	-	1	0	1.386	0.24	-
8	3	7	1.65	0.20	0.42	3	1	1.046	0.31	3
9	167	235	11.60	0.0007	0.71	195	213	0.7944	0.37	0.9
10	244	173	12.20	0.0005	1.41	220	202	0.768	0.38	1.09
11	20	19	0.02	0.87	1.05	15	15	0	1	1

Table 3: Parental analysis of DAT1 Haplotype in three ADHD samples

	Irish 1.					Irish 2					English					IMAGE				
A: Paternal																				
Hap	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR
4-9	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	1	1	0	1	1
5-6	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	1	1	0	1	1
5-8	0	1	1.4	0.2	-	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-
5-9	15	18	0.3	0.6	0.8	7	4	0.8	0.4	1.75	6	6	0	1	1	91	122	4.5	0.03	0.8
5-10	6	7	0.08	0.8	0.9	0	5	6.9	0.008	-	1	4	1.9	0.17	0.25	45	42	0.1	0.7	1.1
5-11	1	0	1.4	1	-	ND	-	-	-	-	ND	-	-	-	-	1	2	0.3	0.6	0.5
6-8	0	3	4.2	0.04	-	0	1	1.4	0.2	-	ND	-	-	-	-	3	1	1.05	0.3	3
6-9	6	15	4	0.04	0.4	1	3	1	0.3	0.3	2	2	0	1	1	67	97	5.5	0.019	0.7
6-10	35	19	4.8	0.03	1.8	11	7	0.9	0.3	1.6	10	7	0.53	0.5	1.4	201	144	9.5	0.002	1.4
6-11	1	0	1.4	0.02	1.8	1	0	1.4	0.2	-	ND	-	-	-	-	16	17	0.03	0.9	0.9
7-10	ND	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	1	0	1.4	0.2	-
B: Maternal																				
Hap	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR	T	NT	χ^2	p-value	OR
4-9	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-
5-6	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	0	3	4.1	0.04	-
5-8	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-
5-9	12	19	1.6	0.2	0.6	7	5	0.3	0.6	1.4	3	7	1.6	0.2	0.4	107	96	0.6	0.4	1.1
5-10	7	8	0.06	0.8	0.9	2	0	2.7	0.096	-	2	0	2.7	0.1	-	43	51	0.7	0.4	0.8
5-11	1	0	1.4	0.24	-	1	0	1.4	0.24	-	ND	-	-	-	-	0	1	1.4	0.24	-
6-8	1	0	1.4	0.24	-	-	-	-	-	-	ND	-	-	-	-	1	0	1.4	0.24	-
6-9	19	7	5.7	0.016	2.7	4	3	0.14	0.7	1.3	2	5	1.3	0.25	0.4	63	77	1.4	0.24	0.8
6-10	20	26	0.8	0.4	0.7	5	11	2.3	0.12	0.5	9	4	2	0.2	2.3	184	168	0.7	0.4	1.1
6-11	ND	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	12	13	0.04	0.8	0.9
7-10	ND	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	0	1	1.4	0.24	-

Haplotype, T= Transmitted, NT= Untransmitted, ND= Not detected

Discussion

The IMAGE sample, the largest of the three replication samples, provides strong support for a parent of origin effect with allele 6 and the 10 repeat allele (intron 8 and 3 UTR VNTR respectively) of DAT1. In addition, a similar pattern of over transmission of paternal risk haplotypes (constructed from the above alleles) was also observed. Some support is also derived from the two smaller samples although neither is independently significant, probably due to sample size.

Since first reported (Cook et al, 1995), association with DAT 1 has been observed in some but not all samples. A random-effects model meta-analysis applied to family-based association studies between ADHD and DAT1 shows that the effect size of the DAT 1 variant is very small with ORs of 1.13 and 1.17 respectively [Faraone et al., 2005; Yang et al., 2007]. A parent of origin effect would have the result of diluting the overall association. Combining the results of all four samples from the present report for the risk haplotype suggests the presence of a parent of origin effect with an OR of 1.45 for paternal transmissions (χ^2=14.5, p=0.00014) and an OR of 1.04 for maternal transmission (χ^2=0.19, p=0.66). Comparison of ORs shows a significant parent of origin effect (χ^2= 5.7, p=0.017).

Restricting our analysis to combined subtype ADHD cases, as in the case of the IMAGE ADHD sample, enhanced our findings and shows significant paternal over transmission of both allele 6 of intron 8 (χ^2=7, p=0.008,OR=1.32) and the 10 repeat allele of the 3'VNTR (χ^2=12.5, p= 0.0004,OR=1.43), and for the haplotype of these two variants (paternal χ^2=15.3, p=0.000093,OR=1.48 ; maternal χ^2=0.98, p= 0.32,OR=1.1).

We [Hawi et al., 2005] previously hypothesized a possible imprinting mechanism operating at several associated genes in ADHD. This general hypothesis has not received support from other studies [Kim et al., 2007; Anney et al., 2007; Luca et al., 2007] but it remains a possibility that such mechanisms operate at certain genes only, such as DAT1. DAT1 is known to be expressed in the brain as well as in various other tissues including lymphocytes. We examined 22 HapMap cell lines that were heterozygous for the SNP rs11564774, an expressed SNP mapped to exon 15 of DAT1. Using quantitative PCR we showed no evidence of mono allelic expression in these individuals as might be expected if there was imprinting at DAT1. However, this does not rule out a partial allelic imbalance or a tissue specific or functional effect [Fukuda et al., 2006; Jinno et al., 1994]. This is difficult to examine in the absence of brain tissue from ADHD cases. Finally, there remains the possibility that our findings might be due to chance and further similar studies are required to confirm.

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