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■ **Abstract** *Objective* The developmental trajectory of attention-deficit hyperactivity disorder (ADHD) is variable. Utilizing a longitudinally assessed sample, we investigated the contribution of susceptibility gene variants, previously implicated through pooled or meta-analyses, to the developmental course of Attention-Deficit Hyperactivity Disorder over time. *Methods* 151 children (aged 6–12) who met diagnostic criteria for ADHD were assessed using research diagnostic interviews during childhood and 5 years later in adolescence. Severity was defined as total number of ADHD symptoms at baseline and reassessment. Association with variants at *DRD4*, *DRD5*, and the dopamine transporter gene, *DAT* was analyzed using linear regression. *Results* As expected, affected individuals showed a decline in ADHD severity over time. The *DRD4* 48 bp VNTR 7-repeat and *DRD5* CA(n) microsatellite marker 148 bp risk

alleles were associated with persistent ADHD. Those possessing the *DRD4* 7 repeat risk allele showed less of a decline in severity at reassessment than those without the risk allele. *Conclusions* Those carrying the *DRD4* 7 risk allele showed greater symptom severity at follow-up and less ADHD reduction over time. These findings support the hypothesis that some susceptibility genes for ADHD also influence its developmental course.

■ **Key words** ADHD – longitudinal – *DRD4* – *DRD5* – *DAT1*

Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly disabling neurodevelopmental disorder affecting between 2 and 5% of the school aged population [5, 15]. Associated with a number of negative out-

comes including poor academic performance as well as impaired peer and family relationships, [3] ADHD is one of the most common reasons for referral to specialist Child Mental Health Services [23]. Most studies show some symptom decline over time, although the clinical diagnosis of ADHD is recognized to persist from childhood into adolescence and even

adulthood in some individuals [10, 14]. ADHD persisting beyond childhood has been shown to be associated with increased negative sequelae including antisocial behavior, and lower academic and occupational achievement levels [14]. Thus, the developmental course of ADHD has important clinical implications. However little is known about the etiological factors contributing to change in ADHD severity over time [34].

There is a substantial genetic contribution to ADHD, with twin studies reporting heritability estimates of between 60 and 80% [35]. Molecular genetic studies aimed at identifying risk gene variants for the disorder have yielded a number of replicated findings. The most widely replicated association is for a 48 bp variable number tandem repeat (VNTR) variant within the Dopamine D4 Receptor Gene (*DRD4*) [12, 13, 24, 26]. The second most robustly replicated finding in pooled analyses is to a simple repeat sequence polymorphism (a CA(n) microsatellite marker) flanking the Dopamine Receptor D5 Gene (*DRD5*) [24–26]. There are also replicated association study findings for a 480 bp VNTR in the 3' UTR (untranslated region) of the Dopamine transporter Gene (*DAT1*, also known as *Slc6a3*). However, the findings with *DAT1* are less consistent, with one meta-analysis yielding a small but significant association [13] and four other meta-analyses reporting no association [6, 24, 26, 30].

It has long been recognized that ADHD is a clinically varied disorder, differing in the predominance of symptom dimensions, comorbid disorders, and the clinical course over time [3]. Longitudinal twin studies have shown a strong genetic contribution to ADHD symptom persistence [20, 22, 28, 29, 31]. As a result of these findings, it has been suggested that genes influencing ADHD susceptibility may also play a role in its temporal course [34]. ADHD which persists into adolescence and adulthood has been demonstrated to be more familial than ADHD restricted to childhood [20]. It has also been suggested that samples with a persistent form of ADHD might reduce phenotypic and possibly genetic heterogeneity, thereby increasing statistical power to detect susceptibility gene variants associated with the disorder [11].

We set out to test these hypotheses by using the most robustly associated ADHD susceptibility gene variant detected so far, namely the *DRD4* 7 repeat allele. Specifically, we postulated that this allele would predict a worse developmental course in terms of ADHD symptom severity, defined as the total number of ADHD symptoms present. We also conducted exploratory analyses of these associations for the somewhat less well-established genetic risk factors *DRD5* and *DAT1*. Finally, allele frequencies for those

with baseline and “persistent” ADHD were compared to those of controls.

Method

British Caucasian children aged between six and twelve years, with suspected or diagnosed ADHD, were originally recruited as part of a genetic study. Child and Adolescent Psychiatrists and Paediatricians in the Greater Manchester, South Wales and Avon areas of the UK referred children to the study. The children underwent an extensive assessment, including research diagnostic interviews. Individuals were excluded if they had a full scale IQ below 70, Tourette's syndrome, Pervasive Developmental Disorder or any Neurological disorder including Epilepsy. The ethnicity of participants (as well as their parents and grandparents) was defined by the families themselves. As this is a genetic study, ethnicity was assessed to minimise genetic differences as the result of ethnic differences between participants.

The sample for this longitudinal study was drawn from an original cross-sectional study that included 375 children who met DSM-III-R/ DSM-IV criteria for ADHD or ICD-10 criteria for Hyperkinetic Disorder at baseline (mean age 9.2 years, SD = 2.1 years). If the child was taking stimulant medication, parents were interviewed regarding behaviour before medication was administered. To improve the accuracy of retrospective phenotypic measurement, participants who had been taking stimulant medication for more than a year were excluded. More detail on the original cross-sectional study and its findings can be found in Holmes et al. [18], Langley et al. [21] and Whittinger et al. [37]. The baseline genetic data have since been expanded due to additional genotyping.

This current paper focuses on a new longitudinal study of ADHD that included children from the original study who had reached adolescence. Five years later, those individuals aged 12 years or over were invited to participate in a follow up study. Of 198 individuals eligible, 190 were traced and 151 completed all components of reassessment (76% of those eligible). The mean age at follow up was 14.5 years, (SD = 1.7 years). Written informed consent from parents and assent from children was received at each wave of data collection. This study was reviewed and gained approval from the North West Multicentre Research Ethics Committee (UK).

■ Measures

At baseline, parents (typically the mother) were interviewed using the child and adolescent psychiatric

assessment (CAPA) [2]. The CAPA is a semi structured interview which enables the presence or absence of DSM-IV, DSM-III-R and ICD-10 symptoms and diagnosis of childhood psychiatric disorders to be determined. We used this measure to assess symptoms and diagnoses of ADHD, Conduct Disorder, Oppositional Defiant Disorder and Mood disorders. For ADHD, parents provided information regarding the presence of each symptom. Individuals had to demonstrate sufficient parent rated symptoms of the disorder to obtain a diagnosis.

The presence of ADHD symptoms or impairment in school, necessary for ICD-10 and DSM-IV diagnoses of the disorder was assessed using the child ADHD teacher telephone interview (ChATTI) [17]. Teacher ratings were used only to provide evidence of pervasiveness of symptoms across situations.

At follow up, parents and adolescents were interviewed using the CAPA-parent and child versions [1, 2] regardless of medication status. The teacher ChATTI was again completed to ascertain symptoms in a school setting. From this information, we generated a diagnostic subgroup of adolescents with "persistent" ADHD who continued to meet full DSM-IV diagnostic criteria for ADHD at follow up ($n = 93$, 62%).

All interviewers were trained in house to a high standard through intensive training by a child psychiatrist with extensive experience of the CAPA (AT) and by weekly supervision meetings by the same individual. High rates of inter-rater reliability between Time 1 and Time 2 were achieved with κ coefficients of 1.00 for diagnoses of ADHD.

■ Genotyping information

DNA was extracted by phenol chloroform extraction from venous blood or buccal mouthwash samples. Genotyping of each of these markers has been described in previous publications and was blind to phenotypic status with respect to the measures presented in this paper. Briefly, genotyping of the *DAT1* 480 bp VNTR was performed using primers and conditions described by Daly and colleagues [7] as detailed in Holmes and colleagues [19]. The *DRD5* CA(n) microsatellite marker was genotyped on an ABI 3100 capillary sequencer according to the primers and conditions described by Sherrington and colleagues [33]. For the *DRD4* 48 bp VNTR, primer sets and analyses described previously were used [8, 16, 36]. For some samples, adjacent SNPs known to be in strong linkage disequilibrium with the *DRD4* 7R VNTR [8, 36] were analyzed to confirm the genotype.

■ Control sample

Control data, previously utilised in studies of these gene variants were available from the UK Blood Transfusion Service and General Practice Registers. All individuals were of British Caucasian origin. No additional demographic or clinical information, was available. For *DRD4* [19] data from 442 controls were available, for *DRD5* data from 97 controls [38] and for *DAT1*, there were data for 295 controls [19].

■ Data analysis

For analysis of change in ADHD severity over time, linear regression analysis was performed with risk genotype as the independent variable and total number of DSM-IV ADHD symptoms at reassessment as the dependent variable, controlling for total number of DSM-IV ADHD symptoms at baseline. Where univariate analyses were found to be significant, analyses were repeated controlling for the significant covariates of age, sex, current DSM-IV conduct disorder symptoms and medication. All independent variables, including ADHD symptoms at baseline and follow up, as well as all linear covariates were normally distributed. Allele frequencies for those with baseline ADHD (all individuals) and "persistent" cases were compared to those for controls using analysis of 2×2 contingency tables. Individuals were classified as being "at risk" for a certain risk variant if they possessed; one or more *DRD4* 48 bp VNTR 7-repeat allele; one or more *DRD5* (CA)n microsatellite 148 bp marker; and two copies of the *DAT1* 480 bp VNTR 10-repeat allele.

Results

At follow up, 93 participants (62%) continued to meet full diagnostic criteria for DSM-IV ADHD. 69% ($n = 64$) of individuals with a diagnosis at Time 2 retained the same subtype diagnosis from Time 1 with the majority of those who changed subtype moving from Combined to either Inattentive or Hyperactive-Impulsive subtype. There were no significant differences for baseline measures of gender, number of ADHD, ODD or conduct disorder symptoms, between those individuals who participated in the follow up study ($n = 151$) and those who were eligible but did not participate ($n = 47$), although there was a trend for participants to be slightly younger ($t = 1.88$, $P = 0.06$). The distributions of all variants for both ADHD participants and control groups were in Hardy Weinberg equilibrium.

The mean number of DSM-IV ADHD symptoms at baseline was 14.7 (SD = 2.4) and 12.2 (SD = 4.8) at follow up. The mean ADHD symptom decline was -2.5 (SD = 4.6). This difference was statistically significant ($\beta = 0.35$, $t = 4.53$, $P \leq 0.001$). All data were normally distributed. At baseline, 23 individuals (15%) met diagnostic criteria for DSM-IV conduct disorder. At follow up 46 individuals (31%) met such criteria.

■ Change in ADHD severity over time

The *DRD4* 48 bp VNTR predicted the total number of DSM-IV ADHD symptoms at follow up controlling for total symptoms at baseline, even when the covariates of age, gender and current conduct disorder symptoms were taken into account (r^2 change = 0.04, $\beta = 0.20$, $t = 2.53$, $P = 0.01$). The mean reduction in ADHD symptoms also illustrated poorer prognosis for those with the *DRD4* 7 repeat variant; those carrying the 7 repeat allele showing a mean reduction of 1.4 symptoms (SD = 3.7), those without the 7 repeat allele showing a mean reduction of 3.3 symptoms (SD = 4.5). The magnitude of the association was not significantly different between baseline and follow up. The *DRD5* and *DAT1* gene variants did not predict ADHD symptom decline (see Table 1). Analysis of the inattentive and hyperactive-impulsive symptom dimensions separately indicated that this effect was not specific to either dimension.

■ Genetic variants predicting ADHD persistence into adolescence

Case-control analysis revealed significant association between the *DRD4* 48 bp VNTR 7-repeat allele and “persistent ADHD” ($\chi^2 = 15.41$, $df = 1$, $P \leq 0.0001$). The odds ratio (OR) was 1.86 (95% CI: 1.30, 2.65, $P = 0.001$) for diagnosis of the disorder at baseline and 2.12 (95% CI: 1.45, 3.11, $P < 0.0001$) at follow up.

Similarly, the 148 bp risk allele of the *DRD5* CA(n) microsatellite marker also significantly predicted baseline ($\chi^2 = 5.02$, $df = 1$, $P = 0.02$, OR = 1.62, 95% CI: 1.06, 2.47) persistent ADHD diagnosis ($\chi^2 = 5.78$, $df = 1$, $P = 0.02$, OR = 1.75, 95% CI: 1.11, 2.77). The *DAT1* variant was not associated with persistent ADHD ($\chi^2 = 0.38$, $df = 1$, $P = 0.54$) or baseline ADHD ($\chi^2 = 0.26$, $df = 1$, $P = 0.61$).

Discussion

The *DRD4* 48 bp VNTR significantly influenced decline in ADHD symptoms over time, with those carrying the 7 repeat allele showing less than half the decline in symptoms of those without the allele. Our case-control analyses revealed significant associations between “persistent” ADHD and the risk alleles in *DRD4* (VNTR 7 repeat) and *DRD5* (148 bp allele) but not with *DAT1*. For both associated variants, the odds ratios were greater in the persistent ADHD sample than in those with the baseline diagnosis but the differences in magnitude of odds ratios were not significant.

These findings suggest a role for the *DRD4* VNTR in the developmental course of ADHD as well as increasing susceptibility for childhood ADHD. The findings also support the hypothesis that some genes that influence ADHD will also affect its developmental course. To date, the focus of most psychiatric genetic studies has been to identify genes that increase susceptibility to specific disorders, including ADHD. Although this is an important goal, there is considerable variation in the course of psychiatric disorders such as ADHD over time. Identifying risk factors that influence the developmental course of ADHD is an additional and important aim. The risk factors and causal pathways that influence developmental course may be the same as those that increase susceptibility to onset but they could also differ [34]. Our findings support this hypothesis because the *DRD4* and *DRD5*

Table 1 Linear regression analysis of gene variants predicting change in ADHD severity over time

	R^2	Unstandardised coefficients		Standardised coefficients		
		β	Standard error	β	t	P -value
DRD4 48 bp VNTR						
Baseline ADHD severity	0.001	0.26	0.42	0.05	0.62	0.54
Change in ADHD severity at follow up	0.04	1.72	0.68	0.20	2.53	0.01
DRD5 CA(n) microsatellite						
Baseline ADHD severity	<0.0001	0.31	0.25	0.14	1.23	0.22
Change in ADHD severity at follow up	<0.0001	-0.13	0.79	-0.02	-0.17	0.87
DAT1 480 bp VNTR						
Baseline ADHD severity	0.009	-0.43	0.40	-0.09	-1.09	0.28
Change in ADHD severity at follow up	0.002	0.48	0.74	0.05	0.65	0.52

variants were both associated with the disorder, but only the *DRD4* 7-repeat allele predicted the developmental course.

Our case-control findings are in line with previous studies showing association between ADHD and the *DRD4* 48 bp VNTR and the *DRD5* CA(n) microsatellite marker. The magnitude of the Odds ratios for both variants was greater for the analysis of persistent ADHD, however, unfortunately, the number of non persistent individuals at follow up ($n = 58$) was insufficient to directly compare the differences between the persistent and non persistent groups.

Identifying genetic and other risk factors that influence the developmental course of ADHD is important for several reasons. First, it is important to identify the mechanisms that lead to poorer clinical outcomes. Second, clinical resources such as intensity of follow-up ideally need to be tailored according to need. Predictors, both clinical and etiological, could thus help target resources more effectively. The identification of non-genetic factors and how they may interact with genetic variants in influencing the developmental course of ADHD is also an important area for future research, although large longitudinal samples will be needed when testing for Gene x Environment interactions.

To date, to the best of our knowledge there have been four other longitudinal molecular genetic studies of ADHD. Our findings regarding *DRD4* are consistent with results from two of these. In the first community-based study [9] the authors also found that the influence of the *DRD4* 48 bp VNTR on diagnosis of ADHD in boys increased with age. This study, however, followed individuals only until the age of 11 years and so did not assess the impact of this variant during adolescence. It also had very small numbers of participants with an ADHD diagnosis. The second study showed association between the *DRD4* 7-repeat allele and worse adult psychosocial outcome [27]. The third study followed 122 ADHD participants and 67 controls across three time points during childhood, adolescence and young adulthood, did not however demonstrate an association between the *DRD4* 7 repeat allele and ADHD at any time point (although various associations with the *DAT1* 480 bp VNTR were reported) [4]. Finally, a case-control study of 67 individuals with ADHD found that possession of the 7-repeat allele was associated with better clinical outcome (retaining a diagnosis of combined type ADHD) [32]. However, this last study differed from ours in having a sample with a higher percentage of girls and higher IQ scores.

These results suggest that although the *DRD4* VNTR influences symptom decline, it is not possi-

ble to conclude that the *DRD4* and *DRD5* variants are more strongly associated with “persistent” ADHD; the group who continue to meet full diagnostic criteria at follow up. To date, there have been few molecular genetic studies of adult ADHD, but those that have been published suggest that the *DRD4* 7 repeat allele is also a risk allele in this age group. Thus far, there has been nothing to suggest that the effect sizes of risk gene variants are greater for adult or adolescent ADHD compared to childhood ADHD. However given our sample size we could not test for differences because of a lack of statistical power.

Although it would have been interesting to compare presence of the risk alleles between those with persistent and “non persistent” diagnoses at follow up, the number of individuals without a persistent diagnosis was too small. Moreover, although not meeting DSM-IV diagnostic criteria for ADHD at the adolescent follow up most individuals (89% of the sample) still had ADHD symptoms and impairment (which has important clinical implications) and therefore cannot truly be categorised as “non persistent”. That is, there is no clear-cut, clinically meaningful way of defining “non-persistence”.

As with any study, there are a number of limitations of this design. First, the sample size for analysis was modest. Nevertheless we still found evidence of association at both time points for the most strongly implicated susceptibility gene variant, the *DRD4* VNTR. This modest sample size illustrates the need for further replications of these findings in larger, diverse samples.

Second, our findings that the *DRD4* 7 repeat allele was associated with ADHD symptom severity at follow-up but not baseline may be considered surprising. However, as all ‘cases’ met diagnostic criteria for ADHD at baseline, they also all had high ADHD symptom counts in childhood (at baseline). Therefore, the range for the number of symptoms was restricted (8–18). By adolescence, the variation in symptom scores was much greater (range 0–18). Therefore, it remains possible that that our sample of clinical cases lacked power to detect childhood ADHD severity as a result of limited variation in symptom scores. Stimulant medication may have influenced symptom severity at follow up. However, controlling for medication in the analyses did not alter the results.

In conclusion, the findings of our longitudinal genetic study of ADHD indicate that the *DRD4* 7 repeat allele predicted a poorer developmental course with carriers of the 7 repeat allele showing less than half the ADHD symptom decline over a five year period of those without the allele.

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