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Psychiatry Res. Author manuscript; available in PMC 2013 August 26.

Published in final edited form as:
Psychiatry Res. 2009 December 30; 170(0): 199–203. doi:10.1016/j.psychres.2008.12.016.

The effect of ADHD candidate gene polymorphisms on the course of ADHD

Joseph Biederman[a], **Carter R. Petty**[a], **Kristina Ten Haagen**[a], **Jacqueline Small**[a], **Alysa E. Doyle**[a], **Thomas Spencer**[a], **Eric Mick**[a], **Michael C. Monuteaux**[a], **Jordan W. Smoller**[b], and **Stephen V. Faraone**[c]

[a]Pediatric Psychopharmacology Department, Massachusetts General Hospital, Boston, Massachusetts

[b]Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts

[c]Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY

Abstract

Objective—The main aim of this study was to examine the association between ADHD-associated genes and the course of ADHD.

Methods—Subjects were derived from identically designed case-control family studies of boys and girls with ADHD and a genetic linkage study of families with children with ADHD. Caucasian probands and family members with ADHD and with available genetic data were included in this analysis (N=563). The course of ADHD was compared in subjects with and without putative risk alleles (*DRD4* 7-repeat allele, *DAT1* 10-repeat allele, and *5HTTLPR* long

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Address correspondence to Joseph Biederman, MD, Clinical and Research Program in Pediatric, Psychopharmacology, Yawkey Center, Suite 6A, Massachusetts General Hospital, Boston, MA 02114. jbiederman@partners.org.

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FINANCIAL DISCLOSURE

Dr. Joseph Biederman receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following Pharmaceutical Companies: Alza, AstraZeneca, Bristol Myers Squibb, Eli Lilly and Co., Janssen Pharmaceuticals Inc., McNeil, Merck, Organon, Otsuka, Shire, Novartis, UCB Pharma Inc., Abbott, Celltech, Cephalon, Esai, Forest, Glaxo, Gliatech, NARSAD, New River, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, The Stanley Foundation, Wyeth, National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD) and National Institute on Drug Abuse (NIDA).

Dr. Alysa E. Doyle is a member of the McNeil speaker’s Bureau and has served on the Eli Lilly Cognition advisory board.

Dr. Thomas Spencer receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following sources: Shire Laboratories, Inc, Eli Lilly & Company, Glaxo-Smith Kline, Pfizer Pharmaceutical, McNeil Pharmaceutical, Wyeth Ayerst, Pfizer Pharmaceutical, Novartis Pharmaceutical, and NIMH

Dr. Eric Mick receives/d grant support from the following pharmaceutical companies: McNeil Pediatrics and Janssen Pharmaceuticals.

Dr. Jordan W. Smoller has served as a consultant for Eli Lilly and Company; has received honoraria from Hoffmann-La Roche, Inc, Enterprise Analysis Corp, and MPM Capital; and has served on an advisory board for Roche Diagnostics Corporation.

Dr. Stephen Faraone receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following companies: Eli Lilly & Company, McNeil Consumer & Specialty Pharmaceuticals, Shire US Inc., Noven Pharmaceuticals, Cephalon, National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHHD), and National Institute of Neurological Disorders and Stroke (NINDS).

Mr. Carter R. Petty, Ms. Kristina Ten Haagen, Ms. Jacqueline Small, and Dr. Michael C. Monuteaux do not have any financial interests to disclose.

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allele). The persistence of ADHD (full or subthreshold diagnosis in the last month) was plotted using Kaplan-Meier survival functions and tested with Cox proportional hazard models.

Results—Survival analyses revealed that by 25 years of age 76% of subjects with a *DRD4* 7-repeat allele were estimated to have persistent ADHD compared to 66% of subjects without the risk allele (hazard ratio=1.66, z=2.05, p=0.04). In contrast, there were no significant associations between the course of ADHD and the *DAT1* 10-repeat allele (p=0.94) and *5HTTLPR* long allele (p=0.65).

Conclusions—Our findings suggest that the *DRD4* 7-repeat allele is associated with a more persistent course of ADHD.

Keywords

ADHD; genetics; dopamine; serotonin

1. INTRODUCTION

Behavioral and molecular genetic studies indicate that ADHD is a complex phenotype influenced by multiple genes of small effect. Multiple candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder (Faraone et al., 2005; Li et al., 2006; Purper-Ouakil et al., 2005; Yang et al., 2007). For the eight genes for which the same variant has been studied in three or more case–control or family-based studies, seven have shown statistically significant evidence of association with ADHD on the basis of the pooled odds ratio across studies (*DRD4*, *DRD5*, *DAT1 [SLC6A3]*, *DBH*, *HTT [SLC6A4]*, *HTR1B*, and *SNAP25)* (Faraone et al., 2005; Mick and Faraone, 2008). Maher and colleagues' (2002) meta-analysis of dopamine system genes showed positive associations of ADHD with *DRD4* and *DRD5*, while *DAT1* did not reach significance (p=0.06). However, the functional implications of these genes remain unclear.

One possibility of the putative functional effect of ADHD-associated genes could be on their impact on the course of ADHD. Prior work suggests that persistent ADHD may have a higher familial loading than remitting forms of the disorder (Biederman et al., 1995; Manshadi et al., 1983): the risk of ADHD among children of ADHD adults was much higher than the risk for ADHD among relatives of children with ADHD (Biederman et al., 1995). This high familial loading in persistent cases of ADHD suggests that genes may play a role in persistent ADHD.

Two studies have examined the effects of genes on functional outcomes into adulthood and have produced inconsistent results. Mill and colleagues (2006) showed longitudinal evidence that risk variants in *DRD4* (7-repeat allele in exon 3 VNTR) and *DAT1* 3'-untranslated region 40 base-pair VNTR (10/10 genotype) predicted poor adult outcomes such as a criminal conviction, evidence of aggression, or long-term unemployment. Barkley, Smith, Fischer, and Navia (2006b) found that the *DAT1* 9/10 genotype was associated with greater symptoms of ADHD, externalizing scores, and family, educational, and occupational deficits into adulthood. Additionally, the two studies that have examined the effects of genes on the persistence of an ADHD diagnosis have also produced inconsistent results. Shaw and colleagues (2007) found that subjects with at least one copy of the *DRD4* 7-repeat allele were significantly less likely to retain the diagnosis of combined-type ADHD after six years. Langley and colleagues (2008) found that the *DRD4* 7-repeat allele was associated with persistent ADHD. Most recently, Franke et al. (2008) found that a 9-6 *DAT1* haplotype was associated with adult ADHD, and Johansson et al. (2007) showed an association between adult ADHD and *DRD5* but not *DAT1* or *DRD4*. The inconsistencies among these findings call for additional studies on the molecular genetics of persistence of ADHD.

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The main aim of this study was to examine the association between ADHD-associated genes and the course of the disorder. To this end we examined data from large samples of well-characterized youth with ADHD and their affected first-degree relatives who had been genotyped at three loci in three genes implicated in the risk for ADHD: *DRD4*, *DAT1*, and *HTT*. Based on the evidence from longitudinal twin studies that show a strong genetic influence on the stability of ADHD symptoms (Kuntsi et al., 2005; Larsson et al., 2004; Price et al., 2005), we hypothesized that variants in these genes would predict a more persistent course of ADHD.

2. METHODS

2.1 Subjects

Subjects were derived from identically designed case-control family studies of boys (Biederman et al., 2006b) and girls (Biederman et al., 2006a) diagnosed with ADHD as well as a genetic linkage study of families with children with ADHD (Faraone et al., 2007). Boys from the family study were reassessed at 4-year and 10-year follow-ups and girls from the family study were reassessed at a 5-year follow-up, while subjects from the genetic linkage study and parents from the family studies were assessed only once. All subjects were Caucasian. Subjects who met full criteria for ADHD at their first (or only) assessment, had a current diagnosis of ADHD at their last (or only) assessment, and who had genetic data were included in this analysis (N=563 total; N=74 from boys study, N=128 from girls study, and N=361 from linkage study). Of the 563 subjects, 59% (N=332) were male. The mean age of the sample was 19.5 years (standard deviation=14.4) at subjects' last assessment. Offspring of families made up 77% of the sample (N=432), while 23% (N=131) were parents. Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study.

2.2 Assessment Procedures

All subjects were assessed with the same assessment battery. Detailed study methodologies for each study had been previously reported (Biederman et al., 2006b; Faraone et al., 2007). Briefly, in all studies, psychiatric assessments relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic (K-SADS-E)(Orvaschel and Puig-Antich, 1987) for subjects younger than 18 years of age and the Structured Clinical Interview for DSM-IV (SCID)(First et al., 1997) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects 18 years of age and older. Diagnoses were based on independent interviews with the mothers and direct interviews with subjects, except that children younger than twelve years of age were not directly interviewed. We considered a diagnostic criterion positive if it was endorsed in either interview.

The interviewers were blind to the subject's ascertainment source and any prior assessments. The interviewers had undergraduate degrees in psychology and were extensively trained. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria and coding algorithms. Then, they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least three study interviews while being observed by senior interviewers. Trainees were not permitted to conduct interviews independently until they executed at least three interviews that achieved perfect diagnostic agreement with an observing senior interviewer. We computed kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists

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diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, the kappa coefficient for ADHD was 0.88.

We considered a diagnosis of ADHD present if DSM diagnostic criteria were unequivocally met (DSM-III-R for boys study baseline and 4-year follow-up and girls study baseline; DSM-IV for boys study 10-year follow-up, girls study 5-year follow-up, and the genetic linkage study). A committee of board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source, and all other data resolved diagnostic uncertainties. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For ADHD, the reliability between individual clinicians and the review committee was a kappa of 1.0.

2.3 Genotyping

Genotyping of the *HTT* polymorphism and *DRD4* VNTRs was performed using the following protocol. Genomic DNA (5 ng) was amplified in a 7 µl reaction using KlenTaq DNA Polymerase (0.2 U; DNA Polymerase Technology, Inc., St. Louis, Missouri, USA), the proprietary KlenTaq Buffer (1X), dNTPs (200 µM each), glycerol (5% for *HTT* and 10% for DRD4), Betaine (1 M) and the marker specific primers (0.2 µM). The *DRD4* VNTR primers were as follows: DRD4-EX03B-F VICGACCGCGACTACGTGGTCTACTC, DRD4-EX03B-R CTCAGGACAGGAACCCACCGAC. The DRD4-EX03B-R primer also contains a proprietary tail that helps stabilize the amplified product. The *HTT* promoter VNTR primers were as follows: SLC6A4_PRO-F 6FAMATGCCAGCACCTAACCCCTAATGT, SLC6A4_PRO-R GGACCGCAAGGTGGGCGGGA. Amplification was performed with the following protocol: thirteen cycles of denaturation for 30 seconds at 93°C, annealing for 30 seconds beginning at 61.5ºC for the *HTT* marker and 69.5°C for the *DRD4* marker and dropped 0.5° C every cycle and primer extension at 72°C for 30 second; 37 cycles of denaturation for 30 seconds at 93°C, annealing for 30 seconds at 55° C for the *HTT* marker and 63°C for the *DRD4* marker and primer extension at 72°C for 30; 72°C for 1 hour.

Genotyping of *DAT1* VNTRs used the following protocol. Genomic DNA (5 ng) was amplified in a of 7 µl reaction using HotStarTaq DNA Polymerase (0.2 U; Qiagen, Valencia, California, USA), the proprietary HotStarTaq Buffer (1X), dNTPs (200 µM each), and the marker specific primers (0.2 µM). Primers were as follows: DAT1-F 6FAM-TGTGGTGTAGGGAACGGCCTGAG, DAT1-R CCTCCTGGAGGTCACGGCTCAAGG. The DAT1-R primers also contain the proprietary tail. Amplification for *DAT1* was performed as follows. Samples were heated at 92° C for 9 minutes to activate the HotStarTaq Polymerase. This is followed by twelve cycles of denaturation for 30 seconds at 93°C, annealing for 30 seconds beginning at 64.5°C and dropped 0.5° C every cycle and primer extension at 72°C for 30 second; 37 cycles of denaturation for 30 seconds at 93°C, annealing for 30 seconds at 58° C and primer extension at 72°C for 30; 72°C for 1 hour.

Amplified products were pooled and combined with size standard (LIZ-500, Applied Biosystems, Foster City, California, USA) before being analyzed on an ABI-3730 (Applied Biosystems). GeneMapper v3.5 (Applied Biosystems) was used to analyze the raw results from the ABI3730, however, a genotype was not considered final until two laboratory personnel had independently checked (and corrected) the GeneMapper results and both individuals were in agreement.

Additional quality control parameters were considered. Rates of missing alleles fell within the acceptable range (less than 3% for all genes). Hardy-Weinberg equilibrium was also acceptable (all $p>0.10$), and allele frequencies were consistent with the literature.

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2.4 Statistical Analysis

The course of ADHD was compared in subjects with and without putative risk alleles (*DRD4* 7-repeat allele, *DAT1* 10-repeat allele, and *HTT* long allele). In keeping with previous studies (Barkley et al., 2006b; Langley et al., 2008; Mick and Faraone, 2008; Mill et al., 2006; Shaw et al., 2007), the risk genotypes were defined as at least one copy of the *DRD4* 7-repeat allele, at least one copy of the *HTT* long allele, and two copies of the *DAT1* 10-repeat allele. Persistence of ADHD was defined as subjects meeting full or subthreshold (more than half of the symptoms required for a full diagnosis) DSM criteria for ADHD in the month prior to the subject’s assessment (most recent assessment if more than one). That is, while subjects with only one assessment met criteria for a lifetime diagnosis of ADHD, they were considered to be in remission if they did not meet full or subthreshold DSM criteria during the month prior to their assessment. Our definition of remission is more accurately described as “symptomatic remission” (Biederman et al., 2000; Keck et al., 1998) and is consistent with numerous prospective follow-up studies of ADHD (Faraone et al., 2006). Analyses were truncated at age 25 years because of the very few failures (i.e., ADHD remission) that occurred after that age. That is, subjects who had an offset of ADHD after age 25 were considered persistent. A DSM-IV ADHD diagnosis was available to define persistence for the large majority of subjects at their last assessment (N=523); otherwise, DSM-III-R criteria were used (N=40). Biederman and colleagues (1997) showed that 93% of children with a DSM-III-R diagnosis also received a DSM-IV diagnosis.

The persistence of ADHD was plotted using Kaplan-Meier survival functions and tested with Cox proportional hazard models. On the plots, vertical drops indicate the proportion of the sample whose ADHD had remitted at a particular age. This survival analysis censors subjects based on their age at last interview, which is essential given the large range of ages of this sample. The failure event of the survival functions was remission of ADHD (i.e., non-persistence) and the analysis-time variable was the age of offset of ADHD (the oldest age reported if the subject had multiple assessments). We controlled for study of ascertainment in the Cox regression models. To account for the non-independence of family members, we used the Huber (Huber, 1967) correction to produce robust variances. All tests were two-tailed with alpha set at 0.05. Statistical analyses were conducted using STATA (Stata Corporation, 2005).

3. RESULTS

Table 1 shows demographic characteristics and comorbid disorders of the sample. Of the 563 subjects, 13 were missing *DRD4* data, 11 were missing *DAT1* data, and 7 were missing *HTT* data. Rates of risk genotypes are presented here as a comparison to other studies of subjects with ADHD or population studies. Table 2 shows the distribution of genotypes for *DRD4*, *DAT1*, and *HTT*. Thirty-one percent (171/550) of subjects had at least one copy of the *DRD4* 7-repeat allele, 55% (301/552) had two copies of the *DAT1* 10-repeat allele, and 79% (442/556) at least one copy of the *HTT* long allele. Neither age at interview nor sex was associated with any of the risk alleles (all $p>0.05$). Genotypes were in Hardy-Weinberg equilibrium (all $p>0.10$).

Of the three polymorphisms examined, only the *DRD4* 7-repeat allele was significantly associated with a more persistent course of ADHD (Figure 1). Survival analyses revealed that by 25 years of age 76% of subjects with a *DRD4* 7-repeat allele were estimated to have persistent ADHD compared to 66% of subjects without the risk allele (hazard ratio=1.66, z=2.05, p=0.04, Figure 1A). In contrast, there were no significant associations between the course of ADHD and the *DAT1* 10-repeat allele (p=0.94, Figure 1B), and the *HTT* long allele (p=0.65, Figure 1C).

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To further evaluate whether these findings were due to pharmacotherapy for ADHD, we reanalyzed the data attending to lifetime and current pharmacotherapy for ADHD. There were no main effects of current (last month) or lifetime pharmacotherapy for ADHD on the persistent course of ADHD (p=0.24 and p=0.89, respectively). There were also no interaction effects of risk alleles and current or lifetime pharmacotherapy (all p>0.05) on the persistent course of ADHD.

4. DISCUSSION

In a large sample of children and adults with ADHD, a polymorphism in a *DRD4* gene was found to have an effect on the course of ADHD. Specifically, a survival function indicated that subjects with at least one copy of the *DRD4* 7-repeat allele had a significantly more persistent course of ADHD compared to subjects with ADHD without this risk allele. These results suggest that the *DRD4* 7-repeat allele genotype is associated with a more persistent course of ADHD.

Our results are consistent with recent findings by Langley and colleagues (2008) showing that the *DRD4* 7-repeat allele was associated with a more persistent course of ADHD. However, Johansson et al. (2007) did not find an association between *DRD4* and adult ADHD. Our *DRD4* finding also stands in contrast to those of Shaw and colleagues (2007) who found that subjects with the *DRD4* 7-repeat allele were less likely to have persistent course of ADHD. Although the reasons for these discrepant findings are unclear, they could be due to Shaw et al.'s requirement that subjects meet full diagnostic criteria for ADHD combined-type to be considered persistent. In fact, if Shaw and colleagues had used any DSM-IV ADHD subtype to define persistence there would have been no effect of the *DRD4* 7-repeat allele.

Although more work is needed to clarify this issue, this discrepancy raises the possibility that *DRD4* may have a differential effect on inattentive and hyperactive symptoms. For example, Rowe et al. (1998), McCracken et al. (2000), and Lasky-Su et al. (2007; 2008) found the *DRD4* 7-repeat allele had a significant association with inattentive symptoms but not hyperactive-impulsive symptoms. On the other hand, a link between the *DRD4* 7-repeat allele and hyperactivity was implicated by a knockout mouse study. When that study disabled *DRD4* in a knockout mouse model, dopamine synthesis increased in the dorsal striatum and the mice showed locomotor supersensitivity to ethanol, cocaine, and methamphetamine (Rubinstein et al., 1997). *DRD4* knockout mice also showed reduced novelty-related exploration (Dulawa et al., 1999), which is consistent with human data suggesting a role for *DRD4* in novelty seeking behaviors. However, a recent study of knockout mice by Helms et al. (2008) suggests that the absence of dopamine receptors is not sufficient to cause psychopathologies associated with heightened impulsivity and novelty seeking.

Our finding that subjects with the *DAT1* 10/10 genotype were not at higher risk for a persistent course of ADHD are inconsistent with those of Mill et al. (2006) who found that the *DAT1* 10/10 genotype was associated with a worse adult prognosis. It is important to note that Mill et al. (2006) relied on a range of negative outcomes in subjects with ADHD including criminal conviction, substance dependence, and unemployment, as adulthood outcome measures while we relied on the persistence of the clinical diagnosis of ADHD, which may account for the difference in findings. Our findings are also inconsistent with findings reported by Barkley and colleagues (2006a) who found that the *DAT1* 9/10 polymorphism was associated with poorer adult outcomes compared to the 10/10 homozygous condition. Our findings suggest that *DAT1* is not associated with a persistent or remittent course of ADHD, and are consistent with recent findings by Johansson et al.

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(2007) showing no association between *DAT1* and adult ADHD. More work is needed to help reconcile these discrepant findings.

Although meta-analyses suggest that *DRD4* represents a small risk factor for the development of ADHD (Faraone et al., 2001; Faraone et al., 2005; Li et al., 2006; Maher et al., 2002), the present findings indicate that this gene may also play a role in the persistence of the condition. Additionally, if a persistent course of ADHD is associated with genetic variants, then persistent ADHD may be a more powerful phenotype for identifying susceptibility genes. Our group has previously put forth such a hypothesis (Faraone et al., 2000) based on the fact that persistent ADHD cases have a higher relative risk for the disorder in parents and siblings (19.7 and 17.2) than non-persistent cases (5.4 and 4.0).

The findings reported here should be viewed in light of some methodological limitations. Our borderline significant finding for *DRD4* would not have survived any correction for multiple comparisons. However, our sound *a priori* hypothesis and the testing of only three polymorphisms alleviate this concern somewhat. The majority of our subjects did not have follow-up assessments and ages of offset of ADHD for remittent cases were made retrospectively. Because many persistent cases of ADHD were young children, it is unclear how long the ADHD would persist. However, the use of survival analysis assured that the estimated rates of persistence accounted for the wide range of subjects' ages. We truncated our survival analyses at age 25 years due to the few remitting cases beyond this age. Future adult studies of ADHD should examine the effect of *DRD4* after age 25. Because all of the subjects were Caucasian, the present results may not generalize to other populations. While not all subjects were referred, they were all derived from families of a referred child, so results may not generalize to non-referred samples. We did not investigate the persistence of ADHD subtypes, mainly because a third of the sample was first assessed with DSM-III-R. Future studies should investigate the role of these genes on the persistence of inattentive versus hyperactive/impulsive symptoms. Although we did not find any effect of psychotropic medications on the course of ADHD, our measures of medication assessment may have been too crude to find significant relationships. Future studies should investigate the relationships between medication, genotype, and course of ADHD. Despite these limitations, our findings suggest that the *DRD4* 7-repeat allele is associated with a more persistent course of ADHD.

Acknowledgments

This work was supported by NIH grants R01HD037694, R01HD037999, and R01MH066877 to Dr. Faraone and R01MH050657 and R01HD036317 to Dr. Biederman.

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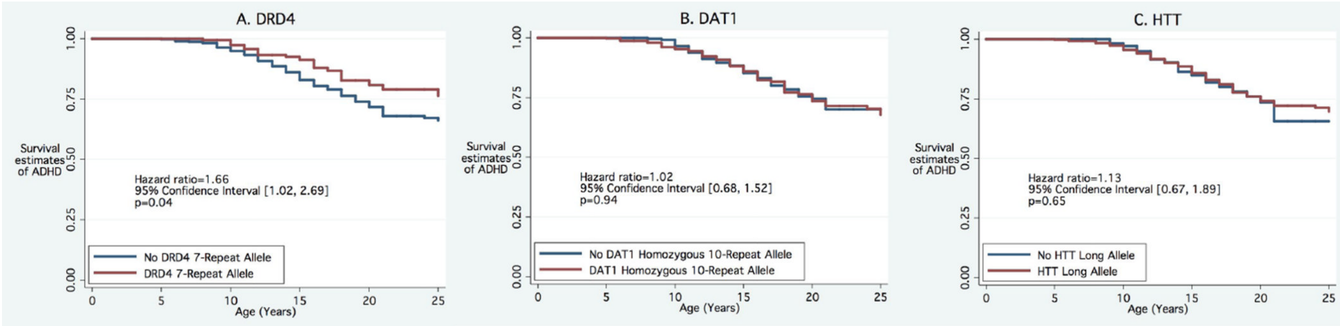

Figure 1.
Course of ADHD by genotype

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Table 1

Demographic and clinical characteristics of ADHD sample (N=563)

	Mean ± SD or N (%)
Age (years)	19.5 ± 14.4
Sex (male)	332 (59)
Study	
ADHD boys study	74 (13)
ADHD girls study	128 (23)
ADHD linkage study	361 (64)
Parents	131 (23)
Children	432 (77)
Lifetime ADHD pharmacotherapy	419 (74)
Current (last month) ADHD pharmacotherapy	296 (53)
Lifetime Psychopathology	
Conduct disorder/antisocial personality disorder	126 (22)
Multiple (≥2) anxiety disorders	220 (39)
Mood disorder	177 (31)

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Table 2

Distribution of genotypes

Genotype	Number (percent)
DRD4	
2-2	4 (0.7)
2–3	5 (0.9)
2–4	78 (14.2)
2–5	1 (0.2)
2–7	15 (2.7)
3-3	1 (0.2)
3–4	33 (6.0)
3–7	8 (1.4)
4-4	246 (44.7)
4–5	7 (1.3)
4–6	1 (0.2)
4–7	131 (23.8)
4–8	2 (0.4)
5–7	1 (0.2)
5–8	1 (0.2)
6–7	1 (0.2)
7-7	13 (2.4)
7–8	2 (0.4)
DAT1	
8–9	3 (0.5)
8–10	3 (0.5)
9-9	45 (8.2)
9–10	189 (34.2)
9–11	4 (0.7)
10-10	301 (54.5)
10–11	7 (1.3)
HTT	
Short-short	114 (20.5)
Short-long	277 (49.8)
Long-long	165 (29.7)