Sex-specific influence of DRD2 on ADHD-type temperament in a large population-based birth cohort

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Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder with a significant public-health impact. Previously, we described a candidate gene study in a population-based birth cohort that demonstrated an association with ADHD-affected males and the dopamine receptor 2 (DRD2). The current study evaluates potential associations of dopamine receptor genes and Cloninger temperament traits within this same sample. Participants with stringent lifetime ADHD diagnoses were ascertained systematically from the genetically isolated Northern Finland 1986 Birth Cohort (n=9432), resulting in 178 cases and 157 controls. Markers in all known dopamine receptor genes were genotyped. We report an association of DRD2 with low Persistence in females (rs1079727 $P$=0.02, rs1124491 $P$=0.03). The associated DRD2 minor allele haplotype (CAA, $P$=0.03) is the same haplotype we previously associated with ADHD in males in this birth cohort. The current study further supports previous results on the role of DRD2 in individuals with ADHD. Investigations suggest that DRD2 may have an impact on both males and females, but the particular outcome appears sex-specific, manifesting as ADHD in males and low Persistence in females. Furthermore, these findings suggest that the putative role of low Persistence as an endophenotype for ADHD deserves further investigation. Psychiatric Genetics 2011, 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: attention-deficit/hyperactivity disorder, birth cohort, DRD2, sex-specific, temperament

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood and often persists into adulthood. Although ADHD is among the most heritable psychiatric disorders with heritability estimated at 76\% (Faraone \textit{et al.}, 2005), the search for specific genetic risk variants remains inconclusive (Mick and Faraone, 2008). Some have argued that endophenotypes that serve to decrease phenotypic heterogeneity might provide clues to the genetic underpinnings of psychiatric disorders (Gottesman and Gould, 2003). Given the relationship between ADHD risk and temperament, heritable temperament traits such as those based on Cloninger’s psychobiological model could serve as useful endophenotypes for investigations of genetic risk for ADHD (Lynn \textit{et al.}, 2005). Heritabilities of Temperament and Character Inventory (TCI) temperament traits including Persistence have been estimated at 50–65\% (Cloninger \textit{et al.}, 1993), and there is also prior evidence of correlation of personality traits (Nigg \textit{et al.}, 2004) such as low Persistence (Rettew \textit{et al.}, 2004; Lynn \textit{et al.}, 2005; Yoo \textit{et al.}, 2006) with ADHD.

In previous work, we studied potential associations of dopaminergic, noradrenergic, and serotonergic candidate genes with ADHD in the isolated, population-based Northern Finland 1986 Birth Cohort (NFBC 1986) and demonstrated an association of dopamine receptor D2 (DRD2) among males (Nyman \textit{et al.}, 2007). In the current study, we examine the potential impact of dopamine receptor gene variants within the same ADHD sample on temperament traits as defined by Cloninger.

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Methods
Participants
NFBC 1986 (N = 9432 live births) is a 1-year population-based birth cohort, with data collected prospectively from the prenatal period onwards (Järvelin et al., 1993). This unique cohort from the two northernmost provinces of Finland is an isolated founder population maximizing linkage disequilibrium (LD), limiting genetic heterogeneity, and thus simplifying disease allele detection (Variloh and Peltonen, 2004). As previously described, participants were ascertained systematically with stringent inclusion criteria for lifetime diagnoses of ADHD defined by Diagnostic and Statistical Manual of Mental Disorders, fourth edition (Smalley et al., 2007). Briefly, after initial screening based on parent ratings, potential individuals at ages 16–18 underwent clinical evaluations that included the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version, a semistructured child psychiatric interview for the assessment of psychiatric disorders in 6–18-year-old adolescents (Kaufman et al., 1997). This resulted in the study sample of 335 individuals with genotypes available (genotypes unavailable from 10 cases included in Smalley et al., 2007). This sample is exactly the same as the one used in our previous study (Nyman et al., 2007). There were 178 definitive or probable (falling one symptom short) ADHD cases (53 females) and 157 symptom-free controls (64 females). The symptom-free controls were individuals defined as ‘Unaffected with ADHD’ by a Best Estimate procedure (using Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria and all information gathered), and classified as controls at age 15 based on parentally filled Strengths and Weaknesses of ADHD-symptoms and Normal-behavior rating scale. Participants also filled out a validated Finnish translation of Cloninger’s TCI-125, quantifying temperament traits of Novelty seeking, Harm avoidance, Reward dependence, and Persistence, which we focused on in our study, as well as character traits Self-directedness, Cooperativeness, and Self-transcendence (Cloninger et al., 1993). The shorter TCI-125 version has similar psychometric properties to the original longer TCI. The distribution of temperament traits was normal and similar in the complete study sample (and in cases and controls separately) to the whole general population sample, the NFBC 1986 cohort. Before initiation of any study procedures, all participants and their respective parent/guardian provided written informed consent under procedures approved by the University of Oulu and UCLA Institutional Review Boards.

Genotyping methods
Altogether, we genotyped 23 single-nucleotide polymorphisms (SNPs) in DRD1, DRD2, DRD3, DRD4, and DRD5 from the dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and Celera (http://www.celera.com/) databases, as well as the DRD4 variable number of tandem repeats (VNTR) (Table 1). Selected SNPs included HapMap tag SNPs (http://www.hapmap.org/index.html.en), and were relatively evenly spaced (distance ≈ 4 kb) to cover genes and flanking regions. DNA was extracted from blood according to standard protocols, and all genotyping was performed blind to case–control status. Sequenom’s MassARRAY technology (Sequenom, San Diego, California, USA) was used for SNP genotyping with primers designed using Sequenom SpectroDESIGNER 2.0 software, and genotyping was performed in 384-well plates in three to six-plex reactions using standard protocols and quality controls. The VNTR polymorphism was amplified as previously suggested with modifications (Loukola et al., 2008). All genotyping was performed at the Institute for Molecular Medicine Finland FIMM, University of Helsinki, and National Institute for Health and Welfare facilities, and at the Finnish Genome Center. The average genotyping success rate was 94%. All the markers were in Hardy–Weinberg equilibrium (P > 0.05). A pilot sample of 62 anonymous father–mother–child trios from the general Finnish population was used for genotyping quality control. No Mendelian inconsistencies were found using Pedcheck (O’Connell and Weeks, 1998) for any of the genotyped markers in the pilot data. DRD4 VNTR allele frequencies in the study sample were similar to those in the pilot sample and those reported in the literature (Table 1, Supplementary Fig. 1, Supplementary digital content 1, http://links.lww.com/PG/A32).

Data analysis
Haplblocks were determined using Haplovie (Barrett et al., 2005) and haplotype combinations were constructed using PHASE 2.1.1. (Stephens et al., 2001; Stephens and Donnelly, 2003; Adkins, 2004). Linear regression between genotypes/haplotype combinations and temperament traits was performed using the general linear model procedure of the SAS Software Package Version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA). Modeling was carried out in the complete sex-adjusted study sample (ADHD cases and controls combined) and for males and females separately. When there were fewer than 10 observations in a given homozygote class, the minor homozygotes were merged with the heterozygote class for decisive analyses. The DRD4 VNTR was analyzed based on the presence or absence of at least seven repeat alleles, as previously suggested (Kluger et al., 2002; Schinka et al., 2002; Munafò et al., 2003). Haplotype analyses were performed only when adjacent single SNP findings within the LD block were significant. Results were not conventionally corrected because of the limitations of sample size and expected magnitude of gene effects in complex traits, and we therefore report uncorrected P-values.

Results
Linear regression provided evidence of association with temperament for markers in DRD2. Association with Persistence in females was evident for three intronic
DRD2 SNPs (rs1079727, rs1079595, and rs1124491) and an SNP in the 3' untranslated region (rs1800497), that is, the DRD2 Taq1A restriction fragment length polymorphism (Table 2; see Table 1 for allele frequencies). These SNPs are located within a single haplblock in the 3'-end of DRD2. Females carrying any copies of the minor alleles (C, C, A, and A, respectively) had lower Persistence scores than major allele homozygotes (P = 0.02, 0.04, 0.02, and 0.03, respectively). The addition of copies of each minor allele appeared to have an additive effect, with minor allele homozygotes scoring lowest in Persistence compared with the heterozygotes, whose scores were intermediate. There were no significant associations of the associating DRD2 markers with temperament traits other than Persistence, or of markers in the other dopamine receptor genes with any of the temperament traits.

We constructed allelic haplotypes using the three associated DRD2 SNPs. We discarded one of the SNPs (rs1079595) because of full LD (D' = 1, r^2 = 1) with another associating SNP (rs1124491). The three-SNP haplotype thus obtained (minor allelic haplotype frequency 0.178) gave similar evidence of association with Persistence in females to the single SNPs. Females carrying any copies of the minor allelic haplotype (CAA) had lower Persistence scores than homozygotes for the major allelic haplotype (P = 0.03). Again, additional copies of the minor allelic haplotype appeared to have an additive effect. No evidence of association of single SNPs or haplotypes was observed for males or in the complete sex-adjusted study sample.

**Discussion**

The current study within an isolated Northern Finnish founder population provides evidence of association of DRD2 with low Persistence among females from an ADHD case-control study, but not males. Evidence arose of minor alleles of four DRD2 SNPs (rs1079727, rs1079595, rs1124491, and rs1800497), that is, the DRD2 Taq1A restriction fragment length polymorphism. These SNPs are located within a single haplblock in the 3'-end of DRD2. Females carrying any copies of the minor alleles (C, C, A, and A, respectively) had lower Persistence scores than major allele homozygotes (P = 0.02, 0.04, 0.02, and 0.03, respectively). The addition of copies of each minor allele appeared to have an additive effect, with minor allele homozygotes scoring lowest in Persistence compared with the heterozygotes, whose scores were intermediate. There were no significant associations of the associating DRD2 markers with temperament traits other than Persistence, or of markers in the other dopamine receptor genes with any of the temperament traits.

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**Table 1** Genotyped markers, genotyping quality control data, and allele frequencies in the study sample and in the pilot data from the general Finnish population

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marker</th>
<th>Position</th>
<th>Success (%)</th>
<th>H-W</th>
<th>MAF</th>
<th>Success (%)</th>
<th>H-W</th>
<th>MAF</th>
</tr>
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<td>DRD1</td>
<td>rs267418 (G/C)</td>
<td>174861588</td>
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<td>rs265981 (G/A)</td>
<td>174851825</td>
<td>95</td>
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<td>98</td>
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<td>0.348</td>
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<td>99</td>
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<td>76</td>
<td>0.111</td>
<td>0.328</td>
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<td>1.000</td>
<td>0.497</td>
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<td>0.838</td>
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<td>rs4245149 (G/A)</td>
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<td>rs1079727 (T/C)</td>
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<td>0.177</td>
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<td>0.499</td>
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<td>rs6279 (G/C)</td>
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<td>0.353</td>
<td>87</td>
<td>0.437</td>
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<td>rs2234689 (G/C)</td>
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<td>0.155</td>
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<td>rs1800497 (G/C)</td>
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<td>96</td>
<td>0.461</td>
<td>0.181</td>
<td>86</td>
<td>0.845</td>
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<tr>
<td>DRD3</td>
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<td>0.055</td>
<td>99</td>
<td>0.595</td>
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<td>1.000</td>
<td>0.187</td>
<td>99</td>
<td>0.556</td>
<td>0.179</td>
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<td>DRD4</td>
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<td>0.331</td>
<td>86</td>
<td>0.527</td>
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<td>allele 3</td>
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<td>0.070</td>
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<td>0.012</td>
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<td>DRD5</td>
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<td>635564</td>
<td>96</td>
<td>0.481</td>
<td>0.030</td>
<td>98</td>
<td>0.777</td>
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<td>rs2076907 (C/G)</td>
<td>9534311</td>
<td>100</td>
<td>1.000</td>
<td>0.031</td>
<td>100</td>
<td>0.779</td>
<td>0.024</td>
</tr>
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</table>

DRD, dopamine receptor; H–W, Hardy–Weinberg equilibrium; MAF, minor allele frequency. 

1Markers are listed in 5'–3' order per gene, with major/minor alleles indicated in parentheses. 

2Allele 2, two repeats; allele 3, three repeats, etc. 

3On the basis of NCBI34 build (SNPs) or UCSC in-silico PCR (VNTR). 

4P-value from Hardy–Weinberg equilibrium test. 

5Minor allele frequency. 

6On the basis of 62 anonymous trios (n = 184 including one incomplete trio), Hardy–Weinberg tests and minor allele frequencies calculated using founders only ( trio parents, n = 123).
rs1079595, rs1124491, and rs1800497) and their three-SNP haplotype (rs1079727–rs1124491–rs1800497). For SNP rs1079595, the major allele associating with high Persistence is ancestral, whereas in the case of the Taq1A restriction fragment length polymorphism (rs1800497) the minor allele associating with low Persistence is ancestral, implying that negative selection may have decreased its frequency. Taq1A minor allele carriers have higher DRD2 expression in lymphoblast cell lines (Cheung et al., 2005), and the polymorphism correlates with DRD2 brain density (Pohjalainen et al., 1998), further implying its functional significance, although the results are equivocal.

The associating DRD2 minor allelic haplotype (CAA) is the same haplotype previously associated with ADHD in males, but not females, in this sample (Nyman et al., 2007). These results suggest that DRD2 may affect ADHD-type temperament in both sexes, but the particular outcome appears sex-specific, manifesting as ADHD in males and low Persistence in females. However, it is known and must be noted here that Persistence has fewer subitems and is weaker than the other TCI temperament traits. ADHD itself is clinically heterogeneous with sex specificities evident. Notably, the predominately inattentive subtype is more common among females (Biederman et al., 2002), and it is possible that low Persistence shares common features with this subtype. Females may also be less likely to exhibit psychiatric comorbidities or cognitive and functional impairment (Biederman et al., 2002), and their disorder may therefore remain undiagnosed, although this does not always hold in other studies or in the NFBC 1986 cohort, where the comorbidities in males and females seem to differ mostly in the spectrum of disorders observed (Smalley et al., 2007). Nevertheless, sex-specific effects of risk variants in the dopamine receptor genes such as those observed here could be expected. Furthermore, there is prior evidence of sex-specific estrogen-dependent dopaminergic function and sex divergence in DRD2 density during development (Andersen and Teicher, 2000; Sawada and Shimohama, 2000).

Our findings suggest that the putative role of low Persistence as an endophenotype for ADHD should be further investigated. ADHD individuals’ inattention and impulsivity could be accounted for by low Persistence in sustaining a task. Some prior correlations between ADHD and low Persistence have been reported (Rettew et al., 2004; Nyman et al., 2009), and there is evidence of genetic heritability of Persistence (Cloninger et al., 1993). Both the TCI Persistence items and the ADHD diagnostic criteria measure the degree of sustained attention, even though the Persistence items measure attention sustained in the longer term. Moreover, this difference may in part be explained by the ADHD diagnostic criteria having been constructed for school-age children, whereas the TCI items were designed for adults.

Previous reports suggest a role for DRD2 in both temperament and ADHD, although results are inconsistent. The DRD2 minor allelic haplotype (CAA) that was found to associate with low Persistence in the current study, was also previously found to associate with low Persistence as described [i.e. ‘in an analogous, but earlier collected NFBC 1966 cohort, especially among females (P = 0.002), but also in the whole sample (P = 0.02, n = 1434’)] (Nyman et al., 2009). One previous study reported an association between three DRD2 polymorphisms (Taq1A, Taq1B, and intron 6) and Persistence (Noble et al., 1998). Studies on ADHD have suggested both positive and negative associations (Mick and Faraone, 2008).

This study has several limitations. As with all investigations of complex traits, difficulties arise from limited sample size, genetic heterogeneity, environmental effects, and phenotypic ambiguity. Moreover, because of...
the sample size and the expected magnitudes of putative gene effects, we did not correct for multiple testing, as correction methods in use are too conservative. As such, our findings must be considered exploratory, and require confirmation in independent samples. Nonetheless, an a-priori hypothesis concerning the involvement of DRD2 based on the previous results discussed above (Noble et al., 1998; Mick and Faraone, 2008; Nyman et al., 2009) provides further support for our conclusions. Findings from the present and previous (Nyman et al., 2007) work in the NFBC 1986 constitute evidence of sex-specific involvement of the 3′-end of DRD2 (including Taq1A), a region potentially involved in transcript level regulation, in ADHD-type temperament, with low Persistence serving as a possible endophenotype for susceptibility.

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Conflicts of interest

There are no conflicts of interest.

References


