

ADHD Attention Deficit and Hyperactivity Disorders

No genetic association between attention-deficit/hyperactivity disorder (ADHD) and Parkinson's disease in nine ADHD candidate SNPs

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Abstract:	Attention-Deficit/Hyperactivity Disorder (ADHD) and Parkinson's disease (PD) involve pathological changes in brain structures such as the basal ganglia, which are essential for the control of motor and cognitive behavior and impulsivity. The cause of ADHD and PD remains unknown, but there is increasing evidence that both seem to result from a complicated interplay of genetic and environmental factors affecting numerous cellular processes and brain regions. To explore the possibility of common genetic pathways within the respective pathophysiologies, nine ADHD candidate Single-Nucleotide Polymorphisms (SNPs) in seven genes were tested for association with PD in 5333 cases and 12019 healthy controls: one variant respectively in the genes coding for Synaptosomal-Associated Protein 25k (SNAP25), the dopamine (DA) transporter (SLC6A3; DAT1), DA receptor D4 (DRD4), serotonin receptor 1B (HTR1B), tryptophan hydroxylase 2 (TPH2), the norepinephrine transporter SLC6A2 and three SNPs in cadherin 13 (CDH13). Information was extracted from a recent meta-analysis of five Genome-Wide Association studies, in which 7,689,524 SNPs in European samples were successfully imputed. No significant association was observed after correction for multiple testing. Therefore, it is reasonable to conclude that candidate variants implicated in the pathogenesis of ADHD do not play a substantial role in PD.
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<p>Response to Reviewers:</p>	<p>We thank the reviewer für the very valuable suggestion to state more clearly the differences and similarities between PD and ADHD to make the rationale behind the study more readily understandable. We added a clear statement to that effect at the beginning of the discussion.</p>

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No genetic association between attention-deficit/hyperactivity disorder and Parkinson's disease

Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) and Parkinson's disease (PD) involve pathological changes in brain structures such as the basal ganglia, which are essential for the control of motor and cognitive behavior and impulsivity. The cause of ADHD and PD remains unknown, but there is increasing evidence that both seem to result from a complicated interplay of genetic and environmental factors affecting numerous cellular processes and brain regions. To explore the possibility of common genetic pathways within the respective pathophysiologies, nine ADHD candidate Single-Nucleotide Polymorphisms (SNPs) in seven genes were tested for association with PD in 5333 cases and 12019 healthy controls: one variant respectively in the genes coding for Synaptosomal-Associated Protein 25k (*SNAP25*), the dopamine (DA) transporter (*SLC6A3*; *DAT1*), DA receptor D4 (*DRD4*), serotonin receptor 1B (*HTR1B*), tryptophan hydroxylase 2 (*TPH2*), the norepinephrine transporter *SLC6A2* and three SNPs in cadherin 13 (*CDH13*). Information was extracted from a recent meta-analysis of five Genome-Wide Association studies, in which 7,689,524 SNPs in European samples were successfully imputed. No significant association was observed after correction for multiple testing. Therefore, it is reasonable to conclude that candidate variants implicated in the pathogenesis of ADHD do not play a substantial role in PD.

Keywords: ADHD, Parkinson's disease, GWAS, SNPs, CDH13, dopamine transporter

Introduction

1 Attention-Deficit/Hyperactivity Disorder (ADHD) is a clinically heterogeneous neurodevelopmental
2 syndrome with an onset in childhood, which persists at least partially into adulthood in up to 60% of
3 patients (Gerlach and Romanos, 2014). Patients with ADHD show characteristic symptoms of age-
4 inappropriate inattention, impulsiveness, and motor hyperactivity. Parkinson's disease (PD) is a
5 common and complex neurological disorder with age as a dominant risk factor. Prevalence and
6 incidence increase nearly exponentially with age and peak after the age of 80 (Kalia and Lang, 2015).
7 PD has long been characterized by the classical motor symptoms bradykinesia, rigidity and/or resting
8 tremor. However, PD is now recognized as a heterogeneous disease, with clinically significant non-
9 motor features including olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep
10 disorders, and impulse control disorders (Kalia and Lang, 2015).
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14 There is increasing evidence from imaging studies that disturbances in cortico-basal ganglia-thalamo-
15 cortical circuits may contribute to the development of motor, cognitive and impulsive symptoms
16 seen in both ADHD and PD (Geng et al., 2006; Mehler-Wex et al. 2006; Gerlach and Romanos, 2014;
17 Volkman et al. 2010). Cognitive and executive dysfunction is prevalent in both disorders (Craig et al.,
18 2016; Goldman et al., 2015). Impulse control disorders including compulsive gambling, shopping,
19 sexual behaviors, and eating occur relatively frequently in PD (Ramirez-Zamora et al. 2016) and are
20 often observed as an adverse reaction to PD treatment with dopaminergic drugs and deep brain
21 stimulation of the subthalamic nucleus (for review, see Volkman et al., 2010). Dopamine (DA) has
22 long been known to be a crucial modulator of striatal processing of cortical and thalamic signals,
23 mediated through glutamatergic synapses on the principal striatal neurons (medium spiny).
24 Regulation of these neurons by DA is important for a wide array of psychomotor functions ascribed
25 to the basal ganglia, including motor, cognitive and motivational functions. In PD, motor symptoms
26 are largely the consequence of a progressive degeneration of cells in the pars compacta of the
27 substantia nigra (SN), which constitute the nervous system's most important DA suppliers (Gibb &
28 Lees, 1991). Abnormalities of the SN have also been demonstrated with transcranial sonography,
29 with children with ADHD (Romanos et al., 2010) as well as PD patients (Berg et al., 2001) showing a
30 hyperechogenic SN. Available symptomatic therapies for ADHD and PD both target the dopaminergic
31 system (Gerlach and Romanos, 2014; Walitza et al., 2014; Kalia and Lang, 2015) by using drugs that
32 enhance intra-cerebral DA concentrations and/or stimulate DA receptors.
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38 The cause of ADHD and PD remains unknown, but there is increasing evidence that both seem to
39 result from a complicated interplay of genetic and environmental factors affecting numerous cellular
40 processes and brain regions (Kalia and Lang, 2015; Gerlach and Romanos, 2014). Based on the
41 common neurobiological pathways implicated in the development of motor, cognitive and impulsive
42 symptoms seen in ADHD and PD, the aim of this study was to examine whether there is a genetic
43 association between ADHD and PD. Interestingly, a recent study has shown that copy number
44 variations at the *PARK2* locus, contribute to the genetic susceptibility to ADHD (Jarick et al. 2014).
45 Mutations in the *PARK2* gene have been reported to cause autosomal recessive juvenile PD (Crosiers
46 et al. 2011). The *PARK2* gene encodes parkin, which has been suggested to increase DA uptake by
47 enhancing the ubiquitination and degradation of mis-folded DA transporter (Jiang et al. 2004).
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49 Nine variants in seven genes were tested for association with PD based on an extensive literature
50 review of genome-wide association studies (GWAS) and meta-analyses on ADHD involving single
51 nucleotide polymorphisms (SNPs): four variants in the genes coding for Synaptosomal-Associated
52 Protein, 25kDa1 (*SNAP25*), the DA transporter (*SLC6A3*; *DAT1*), DA receptor D4 (*DRD4*) and serotonin
53 receptor 1B (*HTR1B*) (Forero et al., 2009; Gizer et al., 2009), three SNPs in cadherin 13 (*CDH13*)
54 (Lasky-Su et al., 2008; Lesch et al., 2008; Neale et al., 2010), and single SNPs located within the genes
55 coding for tryptophan hydroxylase 2 (*TPH2*) and the noradrenaline transporter *SLC6A2* (Park et al.,
56 2013; Sengupta et al., 2012).
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Materials and Methods

We re-analyzed data from a recent meta-analysis of GWAS on PD (International Parkinson Disease Genomics Consortium, 2011) specifically for association of risk variants in ADHD candidate genes with PD. The International Parkinson Disease Genomics Consortium (IPDGC) is an international collaboration of genome-wide association studies in PD. The total cohort comprised 5,333 PD cases and 12,019 controls from European ancestry. This dataset included five GWA studies with patients and controls from the USA, the UK, France and Germany. All samples have been genotyped using Illumina platform and underwent extensive quality control criteria. Imputation has been performed using the Markov chain-based haplotyper (version 1.0.16) yielding a total of 7,689,524 SNPs. GWAS has been undertaken using logistic regression models. Details on the cohort and analyses are published elsewhere (Spencer et al., 2011). Nine ADHD risk variants described above were tested for association with PD. Reported p-values are not corrected for multiple testing.

Results

As shown in table 1, the SNP rs1843809 in *TPH2* was nominally associated with PD (uncorrected $p=0,037$). Here, the more frequent T allele showed a protective effect, while the G allele was identified as risk variant. However, after using Bonferroni correction for multiple testing, the association became non-significant. None of the other analyzed variants showed a significant p-value (Table 1). No substantial heterogeneity was detected in the analyzed cohort.

Discussion

Our hypothesis that risk variants in candidate genes for ADHD would also be significantly associated with PD could not be confirmed in this study.

Although ADHD is a developmental disorder with an onset in childhood while PD is a degenerative disease associated with older age, ADHD and PD share abnormalities in cortico-basal ganglia-thalamo-cortical circuits, which contribute to motor, cognitive and impulsive symptoms in both disorders. The SNPs analyzed in our study were selected because they were located within genes coding for proteins that are involved in the regulation of dopaminergic, noradrenergic and serotonergic neurotransmission, which in turn is implicated in the development of motor, cognitive and impulsive symptoms seen in ADHD and PD. DAT1 is a pre-synaptically located protein that plays a key role in regulating the DA concentrations in the synaptic cleft by removing DA from the synaptic cleft and returning it to the pre-synaptic neurons (Giros et al. 1996). Reduced DAT1 density and reduced binding of the remaining DAT1 has been reported in the striatum of PD patients (Galvin et al., 2006). In contrast, neuroimaging studies demonstrated an increased density of DAT1 in the striatum of ADHD patients (Fusar-Poli et al. 2012). SNAP25 constitutes part of the SNARE complex and is crucial for general neurotransmitter release (for a review, see Rizo & Südhof, 2002). A mutant mouse model of SNAP25 showed that the SNARE complex might be involved in the localization and accumulation of α -synuclein, a protein of unknown function that is located primarily in the presynaptic vesicles and modulates the DAT1 function (Sidhu et al. 2004). CDH13 propagates neuronal growth and brain plasticity. It is an interesting candidate for PD since it supports motility, growth and proliferation of neuronal cells (for a review, see Philippova et al., 2009) and is expressed in brain regions affected in PD (Takeuchi et al., 2000). Sequence variations in this gene may compromise the protein's function as a negative regulator of axonal growth during development and its protective properties against oxidative stress (Philippova et al., 2010), and ultimately play a role in the progressive cell loss in PD.

It is conceivable that despite an underlying common genetic basis, the proposed genetic structure of most psychiatric disorders prevents the detection of contributing variants by means of GWAS. In psychiatric conditions, state-of-the-art genetic theories assume an interaction of a multitude of genes (both common and rare variants) with small effect. Precisely for this kind of genetic architecture, GWAS are ill-suited to detect the contributing variants. Hence it is possible that genes

1 showing up in GWAS on ADHD might be reflective of very specific forms of ADHD, where those
2 variants are of high penetrance and immediate consequence and produce a distinct phenotype. The
3 SNPs analyzed in our study were selected because they are situated within genes which code for
4 products implicated in the etiopathogenesis of both disorders. Although no association survived
5 correction for multiple testing, the putative roles of those genes for PD shall briefly be expanded
6 upon. The negative finding regarding DAT1 is in line with a study on a Japanese sample, which could
7 not confirm an association of the 3' UTR VNTR polymorphism with PD, suggesting that the
8 investigated polymorphism (Higuchi et al., 1995) is of limited importance for the etiopathogenesis of
9 PD both in Asian and European populations. However, it has to be noted that there are some positive
10 reports as well. Morino et al. (2000) found a non-functional base exchange in exon 9 (1215A/G) to be
11 less common in PD, and there are reports of an association of other polymorphisms within this gene
12 with the disorder (Juyal et al, 2006; Le Couteur et al, 1997).
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15 However, putting our findings into perspective, there is doubt on common genetic bases in terms of
16 variants with large effects for both PD and ADHD. Several independent lines of evidence support that
17 conclusion. Firstly, a diagnosis of ADHD demands an early onset in childhood despite a high tendency
18 to persist into adulthood, whereas PD patients typically experience the first symptoms late in life –
19 the exception being rare recessive PD which typically has an early age of onset. It is conceivable that
20 for ADHD - a disorder which emerges at a time where particularly the prefrontal cortex as the seat of
21 cognitive control is still undergoing maturational processes (Shaw et al., 2006) and thus making it
22 particularly vulnerable for disturbances - a different set of genes or genetic variants might be acting
23 together to shape the developmental course of the brain. Furthermore, it is important to bear in
24 mind that the two forms of PD have extremely different heritabilities, since most published GWAS on
25 PD include only the sporadic and less strongly genetically triggered variant of the disorder, where a
26 putative common genetic background is more complex. While familial PD shows relatively consistent
27 associations with mutations in genes like *SNCA* encoding α -synuclein, *PARK2*, *PINK1*, *PARK7* and
28 *LRRK2* (Lesage & Brice, 2009), the predominant sporadic variant of the disorder seems more related
29 to combinations of common variants within several genes. So it stands to reason that sporadic PD
30 and the largely familial ADHD overall have divergent etiologies on a genetic level.
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34 **Conclusion**

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36 In a European sample, ADHD candidate SNPs within the genes coding for *CDH13*, *DRD4*, *HTR1B*,
37 *SLC6A2* (NET1), *SLC6A3* (DAT1), *SNAP25* and *TPH2* were not associated with PD after correction for
38 multiple testing. An overlap in the genetic architecture of both disorders cannot be ruled out,
39 although traditional candidate genes in ADHD do not show a major effect in PD.
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Ethical standards

All studies contributing data for this publication have been approved by the local ethics committees and were performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all participants prior to their inclusion in the study

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table 1: Results for Attention-Deficit/Hyperactivity Disorder candidate Single Nucleotide Polymorphisms in Parkinson's Disease Meta-Analysis

Gene	SNP	Effect allele / Other allele	Allele Frequency	P value	Effect	Het p
<i>CDH13</i>	rs6565113	T/G	0.53	0.20	0.032	0.76
<i>CDH13</i>	rs11646411	C/G	0.88	0.92	0.004	0.73
<i>CDH13</i>	rs7187223	A/G	0.96	0.65	-0.028	0.58
<i>DRD4</i>	rs1800955	T/C	0.65	0.70	-0.0115	0.63
<i>HTR1B</i>	rs6296	C/G	0.74	0.16	0.0405	0.45
<i>SLC6A2</i> (NET1)	rs3785143	T/C	0.091	0.958	0.0023	0.075
<i>SLC6A3</i> (DAT1)	rs27072	T/C	0.17	0.35	-0.031	0.33
<i>SNAP25</i>	rs3746544	T/G	0.65	0.97	9.00E-04	0.17
<i>TPH2</i>	rs1843809	T/G	0.85	0.037*	-0.071	0.77

*nominal significant; shown p values are not corrected for multiple testing; Het p = heterogeneity p value; data derived from the PD meta-analysis (Nalls et al., 2011)