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Geissler, J.M.; Romanos, M.; Gerlach, M.; Berg, D.; Schulte, C.; Int Parkinson Dis Genomics

HHS Public Access

Author manuscript

Atten Defic Hyperact Disord. Author manuscript; available in PMC 2018 November 13.

Published in final edited form as:

Atten Defic Hyperact Disord. 2017 June ; 9(2): 121–127. doi:10.1007/s12402-017-0219-8.

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 12,019 healthy controls: one variant, respectively, in the genes coding for synaptosomal-associated protein 25 k (*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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Compliance with ethical standards

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

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.

Keywords

ADHD; Parkinson's disease; GWAS; SNPs; CDH13; Dopamine transporter

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a clinically heterogeneous neurodevelopmental syndrome with an onset in childhood, which persists at least partially into adulthood in up to 60% of patients (Gerlach and Romanos 2014). Patients with ADHD show characteristic symptoms of age-inappropriate inattention, impulsiveness and motor hyperactivity. Parkinson's disease (PD) is a common and complex neurological disorder with age as a dominant risk factor. Prevalence and incidence increase nearly exponentially with age and peak after the age of 80 (Kalia and Lang 2015). PD has long been characterized by the classical motor symptoms such as bradykinesia, rigidity and/or resting tremor. However, PD is now recognized as a heterogeneous disease, with clinically significant non-motor features including olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders and impulse control disorders (Kalia and Lang 2015).

There is increasing evidence from imaging studies that disturbances in cortico-basal ganglia-thalamo-cortical circuits may contribute to the development of motor, cognitive and impulsive symptoms seen in both ADHD and PD (Geng et al. 2006; Mehler-Wex et al. 2006: Gerlach and Romanos 2014; Volkmann et al. 2010). Cognitive and executive dysfunction is prevalent in both disorders (Craig et al. 2016; Goldman et al. 2015). Impulse control disorders including compulsive gambling, shopping, sexual behaviors and eating occur relatively frequently in PD (Ramirez-Zamora et al. 2016) and are often observed as an adverse reaction to PD treatment with dopaminergic drugs and deep brain stimulation of the subthalamic nucleus (for review, see Volkmann et al. 2010). Dopamine (DA) has long been known to be a crucial modulator of striatal processing of cortical and thalamic signals, mediated through glutamatergic synapses on the principal striatal neurons (medium spiny). Regulation of these neurons by DA is important for a wide array of psychomotor functions ascribed to the basal ganglia, including motor, cognitive and motivational functions. In PD, motor symptoms are largely the consequence of a progressive degeneration of cells in the pars compacta of the substantia nigra (SN), which constitute the nervous system's most important DA suppliers (Gibb & Lees 1991). Abnormalities of the SN have also been demonstrated with transcranial sonography, with children with ADHD (Romanos et al. 2010) as well as PD patients (Berg et al. 2001) showing a hyperechogenic SN. Available symptomatic therapies for ADHD and PD both target the dopaminergic system (Gerlach and Romanos 2014; Walitza et al. 2014; Kalia and Lang 2015) by using drugs that enhance intracerebral DA concentrations and/or stimulate DA receptors.

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 (Kalia and Lang 2015; Gerlach and Romanos 2014). Based on the common neurobiological pathways implicated in the development of motor, cognitive and impulsive symptoms seen in ADHD and PD, the aim of this study was

to examine whether there is a genetic association between ADHD and PD. Interestingly, a recent study has shown that copy number variations at the *PARK2* locus contribute to the genetic susceptibility to ADHD (Jarick et al. 2014). Mutations in the PARK2 gene have been reported to cause autosomal recessive juvenile PD (Crosiers et al. 2011). The *PARK2* gene encodes parkin, which has been suggested to increase DA uptake by enhancing the ubiquitination and degradation of mis-folded DA transporter (Jiang et al. 2004).

Nine variants in seven genes were tested for association with PD based on an extensive literature review of genome-wide association studies (GWAS) and meta-analyses on ADHD involving single nucleotide polymorphisms (SNPs): four variants in the genes coding for synaptosomal-associated protein, 25kDa1 (*SNAP25*), the DA transporter (*SLC6A3*; DAT1), DA receptor D4 (*DRD4*) and serotonin receptor 1B (*HTR1B*) (Forero et al. 2009; Gizer et al. 2009), three SNPs in cadherin 13 (*CDH13*) (Lasky-Su et al. 2008; Lesch et al. 2008; Neale et al. 2010), and single SNPs located within the genes coding for tryptophan hydroxylase 2 (*TPH2*) and the noradrenaline transporter *SLC6A2* (Park et al. 2013; Sengupta et al. 2012).

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 5333 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 have 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 listed 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 nonsignificant. 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.

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 presynaptically 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 presynaptic neurons (Giros et al. 1996). Reduced DAT1 density and reduced binding of the remaining DAT1 have been reported in the striatum of PD patients (Galvin 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 neuro-transmitter release (for a review, see Rizo and 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. 2009) 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 showing up in GWAS on ADHD might be reflective of very specific forms of ADHD, where those variants are of high penetrance and immediate consequence and produce a distinct phenotype. The SNPs analyzed in our study were selected because they are situated within genes which code for products implicated in the etiopathogenesis of both disorders. Although no association survived correction for multiple testing, the putative roles of those genes for PD shall briefly be expanded upon. The negative finding regarding DAT1 is in line with a study on a Japanese sample, which could not confirm an association of the 3′ UTR VNTR polymorphism with PD, suggesting that the investigated polymorphism (Higuchi et al. 1995) is of limited importance for the etiopathogenesis of PD both in Asian and European populations. However, it has to be noted that there are some positive reports as well. Morino et al. (2000) found a nonfunctional base exchange in exon 9 (1215A/G) to be less common in PD, and there are reports of an association of other polymorphisms within this gene with the disorder (Juyal et al. 2006; Le Couteur et al. 1997).

However, putting our findings into perspective, there is doubt on common genetic bases in terms of variants with large effects for both PD and ADHD. Several independent lines of evidence support that conclusion. Firstly, a diagnosis of ADHD demands an early onset in childhood despite a high tendency to persist into adulthood, whereas PD patients typically experience the first symptoms late in life—the exception being rare recessive PD which typically has an early age of onset. It is conceivable that for ADHD—a disorder which emerges at a time where particularly the prefrontal cortex as the seat of cognitive control is still undergoing maturational processes (Shaw et al. 2006) and thus making it particularly vulnerable for disturbances—a different set of genes or genetic variants might be acting together to shape the developmental course of the brain. Furthermore, it is important to bear in mind that the two forms of PD have extremely different heritabilities, since most published GWAS on PD include only the sporadic and less strongly genetically triggered variant of the disorder, where a putative common genetic background is more complex. While familial PD shows relatively consistent associations with mutations in genes like *SNCA* encoding α-synuclein, *PARK2, PINK1, PARK7* and *LRRK2* (Lesage and Brice 2009), the predominant sporadic variant of the disorder seems more related to combinations of common variants within several genes. So it stands to reason that sporadic PD and the largely familial ADHD overall have divergent etiologies on a genetic level.

Conclusion

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

Acknowledgements

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Université Pierre et Marie Curie-Paris; CNRS; and AP-HP, Pitié-Salpêtrière Hospital), Sarah Edkins (Wellcome Trust Sanger Institute), Jonathan R Evans (Cambridge Centre for Brain Repair, Cambridge, UK), Thomas Foltynie (UCL Institute of Neurology), Jianjun Gao (Epidemiology Branch, National Institute of Environmental Health Sciences), Michelle Gardner (Department of Molecular Neuroscience, UCL Institute of Neurology), J Raphael Gibbs (Laboratory of Neurogenetics, National Institute on Aging; and Department of Molecular Neuroscience, UCL Institute of Neurology), Alison Goate (Department of Psychiatry, Department of Neurology, Washington University School of Medicine, MI, USA), Emma Gray (Wellcome Trust Sanger Institute), Rita Guerreiro (Department of Molecular Neuroscience, UCL Institute of Neurology), Omar Gustafsson (deCODE genetics and Department of Psychiatry, Oslo University Hospital, N-0407 Oslo, Norway), Clare Harris (University of Aberdeen), Jacobus J van Hilten (Department of Neurology, Leiden University Medical Center, Leiden, Netherlands), Albert Hofman (Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands), Albert Hollenbeck (AARP, Washington DC, USA), Janice Holton (Queen Square Brain Bank for Neurological Disorders, UCL Institute of Neurology), Michele Hu (Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK), Xuemei Huang (Departments of Neurology, Radiology, Neurosurgery, Pharmacology, Kinesiology, and Bioengineering, Pennsylvania State University–Milton S Hershey Medical Center, Hershey, PA, USA), Heiko Huber (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research), Gavin Hudson (Neurology M4104, The Medical School, Newcastle upon Tyne, UK), Sarah E Hunt (Wellcome Trust Sanger Institute), Johanna Huttenlocher (deCODE genetics), Thomas Illig (Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany), Pálmi V Jónsson (Department of Geriatrics, Landspítali University Hospital, Reykjavík, Iceland), Jean-Charles Lambert (INSERM U744, Lille, France; and Institut Pasteur de Lille, Université de Lille Nord, Lille, France), Cordelia Langford (Cambridge Centre for Brain Repair), Andrew Lees (Queen Square Brain Bank for Neurological Disorders), Peter Lichtner (Institute of Human Genetics, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany), Patricia Limousin (Institute of Neurology, Sobell Department, Unit of Functional Neurosurgery, London, UK), Grisel Lopez (Section on Molecular Neurogenetics, Medical Genetics Branch, NHGRI, National Institutes of Health), Delia Lorenz (Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein), Alisdair McNeill (Department of Clinical Neurosciences, UCL Institute of Neurology), Catriona Moorby (School of Clinical and Experimental Medicine, University of Birmingham), Matthew Moore (Laboratory of Neurogenetics, National Institute on Aging), Huw R Morris (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK), Karen E Morrison (School of Clinical and Experimental Medicine, University of Birmingham; 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References

Berg D, Siefker C, Becker G (2001) Echogenicity of the substantia nigra in Parkinson's disease: its relation to clinical findings. J Neurol 248(8):684–689. doi:10.1007/s004150170114 [PubMed: 11569897]

Craig F, Margari F, Legrottaglie AR, Palumbi R, de Giambattista C, Margari L (2016) A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat 12:1191–1202 [PubMed: 27274255]

Crosiers D, Theuns J, Cras P, Van Broeckhoven C (2011) Parkinson disease: insights in clinical, genetic and pathological features of monogenic disease subtypes. J Chem Neuroanat 42(2):131–141 [PubMed: 21810464]

Forero DA, Arboleda GH, Vasquez R, Arboleda H (2009) Candidate genes involved in neural plasticity and the risk for attention-deficit hyperactivity disorder: a meta-analysis of 8 common variants. J Psychiatry Neurosci 34:361–366 [PubMed: 19721846]

Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U (2012) Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J Psychiatry 169:264–272 [PubMed: 22294258]

Galvin JE (2006) Interaction of alpha-synuclein and dopamine metabolites in the pathogenesis of Parkinson's disease: a case for the selective vulnerability of the substantia nigra. Acta Neuropathol 112:115–126. doi:10.1007/s00401-006-0096-2 [PubMed: 16791599]

Geng DY, Li YX, Zee CS (2006) Magnetic resonance imaging-based volumetric analysis of basal ganglia nuclei and substantia nigra in patients with Parkinson's disease. Neurosurgery 58:256–261. doi:10.1227/01.NEU.0000194845.19462.7B [PubMed: 16462479]

Gerlach M, Romanos M (2014) Attention-deficit/hyperactivity disorder. In: Wolters E, Baumann C (eds) Parkinson disease and other movement disorders. Motor behavioural disorders and behavioural motor disorders. International Association of Parkinsonism and Related Disorders, VU University Press, Amsterdam, pp 705–727

Gibb WR, Lees AJ (1991) Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 54:388–396. doi:10.1136/jnnp.54.5.388 [PubMed: 1865199]

Giros B, Jaber M, Jones SR, Wightman RM, Caron MG (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature 379:606–661 [PubMed: 8628395]

Gizer I, Ficks C, Waldman I (2009) Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 126:51–90. doi:10.1007/s00439-009-0694-x [PubMed: 19506906]

Goldman JG, Aggarwal NT, Schroeder CD (2015) Mild cognitive impairment: an update in Parkinson's disease and lessons learned from Alzheimer's disease. Neurodegener Dis Manag 5(5): 425–443 [PubMed: 26517759]

Higuchi S, Muramatsu T, Arai H, Hayashida M, Sasaki H, Trojanowski JQ (1995) Polymorphisms of dopamine receptor and transporter genes and Parkinson's disease. J Neural Transm 10:107–113

International Parkinson Disease Genomics C, Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM et al. (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 377(9766):641–649 [PubMed: 21292315]

Jarick I, Volckmar AL, Putter C, Pechlivanis S, Nguyen TT, Dauvermann MR et al. (2014) Genome-wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/hyperactivity disorder. Mol Psychiatry 19(1):115–121 [PubMed: 23164820]

Jiang H, Jiang Q, Feng J (2004) Parkin increases dopamine uptake by enhancing the cell surface expression of dopamine transporter. J Biol Chem 279(52):54380–54386 [PubMed: 15492001]

Juyal RC, Das M, Punia S, Behari M, Nainwal G, Singh S, Swaminath PV, Govindappa ST, Jayaram S, Muthane UB, Thelma BK (2006) Genetic susceptibility to Parkinson's disease among South and North Indians: I. Role of polymorphisms in dopamine receptor and transporter genes and association of DRD4 120-bp duplication marker. Neurogenetics 7:223–229. doi:10.1007/s10048-006-0048-yl [PubMed: 16816977]

Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386(9996):896–912 [PubMed: 25904081]

Lasky-Su J, Neale BM, Franke B, Anney RL, Zhou K, Maller JB, Vasquez AA, Chen W, Asherson P, Buitelaar J, Banaschewski T, Ebstein R, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Daly M, Laird M, Lange Faraone SV (2008) Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. Am J Med Genet B Neuropsychiatr Genet 147B:1345–1354. doi:10.1002/ajmg.b.30867 [PubMed: 18821565]

Le Couteur DG, Leighton PW, McCann SJ, Pond SM (1997) Association of a polymorphism in the dopamine-transporter gene with Parkinson's disease. Mov Disord 12:760–763. doi:10.1002/mds.870120523 [PubMed: 9380062]

Lesage S, Brice A (2009) Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet doi:10.1093/hmg/ddp012

Lesch K-P, Timmesfeld N, Renner TJ, Halperin R, Röser C, Nguyen TT, Craig DW, Romanos J, Heine M, Meyer J, Freitag C, Warnke A, Romanos M, Schäfer H, Walitza S, Reif A, Stephan D, Jacob C (2008) Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. J Neural Transm 115:1573–1585. doi:10.1007/s00702-008-0119-3 [PubMed: 18839057]

Mehler-Wex C, Riederer P, Gerlach M (2006) Dopaminergic dysbalance in distinct basal ganglia neurocircuits: implications for the pathophysiology of Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder. Neurotox Res 10:167–179. doi:10.1007/BF03033354 [PubMed: 17197367]

Morino H, Kawarai T, Izumi Y, Kazuta T, Oda M, Komure O, Udaka F, Kameyama M, Nakamura S, Kawakami H (2000) A single nucleotide polymorphism of dopamine transporter gene is associated with Parkinson's disease. Ann Neurol 47:528–531 [PubMed: 10762168]

Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin U-M, Saad M, Simón-Sánchez J, Schulte C, Lesage S, Sveinbjörnsdóttir S, Stefánsson Ki, Martinez M, Hardy J, Heutink P, Brice A, Gasser T,

Singleton AB, Wood NW (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 377:641–649. doi:10.1016/S0140-6736(10)62345-8 [PubMed: 21292315]

Neale BM, Medland S, Ripke S, Anney RJL, Asherson P, Buitelaar J, Franke B, Gill M, Kent L, Holmans Middleton F, Thapar A, Lesch K-P, Faraone SV, Daly M, Nguyen TT, Schäfer H, Steinhausen H-C, Reif A, Renner TJ, Romanos M, Romanos J, Warnke A, Walitza S, Freitag C, Meyer J, Palmason H, Rothenberger A, Hawi Z, Sergeant J, Roeyers H, Mick E, Biederman J (2010) Case-control genome-wide association study of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 49:906–920. doi:10.1016/j.jaac.2010.06.007 [PubMed: 20732627]

Park TW, Park YH, Kwon HJ, Lim MH (2013) Association between TPH2 gene polymorphisms and attention deficit hyperactivity disorder in Korean children. Genet Test Mol Biomarkers 17:301–306. doi:10.1089/gtmb.2012.0376 [PubMed: 23461725]

Philippova M, Joshi MB, Kyriakakis E, Pfaff D, Erne P, Resink TJ (2009) A guide and guard: the many faces of T-cadherin. Cell Signal 21:1035–1044. doi:10.1016/j.cellsig.2009.01.035 [PubMed: 19399994]

Ramirez-Zamora A, Gee L, Boyd J, Biller J (2016) Treatment of impulse control disorders in Parkinson's disease: practical considerations and future directions. Expert Rev Neurother 16(4): 389–399 [PubMed: 26923084]

Rizo J, Südhof TC (2002) Snares and Munc18 in synaptic vesicle fusion. Nat Rev Neurosci 3:641–653. doi:10.1038/nrn898 [PubMed: 12154365]

Romanos M, Renner TJ, Schecklmann M, Hummel B, Roos M, von Mering C, Pauli P, Reichmann H, Warnke A, Gerlach M (2010) Structural abnormality of the substantia nigra in children with attention-deficit hyperactivity disorder. J Psychiatry Neurosci 35:55–58. doi:10.1503/jpn.090044 [PubMed: 20040247]

Sengupta SM, Grizenko N, Thakur GA, Bellingham J, Deguzman R, Robinson S, Terstepanian M, Poloskia A, Shaheen SM, Fortier ME, Choudhry Z, Joober R (2012) Differential association between the norepinephrine transporter gene and ADHD: role of sex and subtype. J Psychiatry Neurosci 37:129–137. doi:10.1503/jpn.110073 [PubMed: 22297068]

Shaw P, Lerch JP, Greenstein D, Sharp W, Clasen LS, Evans AC, Giedd JN, Castellanos FX, Rapoport JL (2006) Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 63:540–549. doi: 10.1001/archpsyc.63.5.540 [PubMed: 16651511]

Sidhu A, Wersinger C, Vernier P (2004) α-Synuclein regulation of the dopaminergic transporter: a possible role in the pathogenesis of Parkinson's disease. FEBS Lett 565:1–5 [PubMed: 15135042]

Spencer CA, Plagnol V, Strange A, Gardner M, Paisan-Ruiz C, Band G, Barker RA, Bellenguez C, Bhatia Blackburn H, Blackwell JM, Bramon E, Brown MA, Brown MA, Burn D, Casas JP, Chinnery PF, Clarke CE, Corvin A, Craddock N, Deloukas P, Edkins S, Evans J, Freeman C, Gray E, Hardy J, Hudson G, Hunt S, Jankowski J, Langford C, Lees AJ, Markus HS, Mathew CG, McCarthy MI, Morrison KE, Palmer CNA, Pearson JP, Peltonen L, Pirinen M, Plomin R, Potter S, Rautanen A, Sawcer SJ, Su Z, Trembath RC, Viswanathan AC, Williams NW, Morris HR, Donnelly P, Wood NW (2011) Dissection of the genetics of Parkinson's disease identifies an additional association 5′ of SNCA and multiple associated haplotypes at 17q21. Hum Mol Genet 20:345–353. doi:10.1093/hmg/ddq469 [PubMed: 21044948]

Takeuchi T, Misaki A, Liang SB, Tachibana A, Hayashi N, Sonobe H, Ohtsuki Y (2000) Expression of T-cadherin (CDH13, H-Cadherin) in human brain and its characteristics as a negative growth regulator of epidermal growth factor in neuroblastoma cells. J Neurochem 74:1489–1497 [PubMed: 10737605]

Volkmann J, Daniels C, Witt K (2010) Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease. Nat Rev Neurol 6:487–498. doi:10.1038/nrneurol.2010.111 [PubMed: 20680036]

Walitza S, Romanos M, Warnke A, Greenhill L, Gerlach M (2014) Psychostimulants and other drugs used in the treatment of attention-deficit/hyperactivity disorder (ADHD). In: Gerlach M, Warnke A, Greenhill L (eds) Psychiatric drugs in children and adolescents. Basic pharmacology and practical applications Springer, Wien, pp 293–333

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

* Nominal significant; the 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)