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ORIGINAL ARTICLE

No evidence for association between a functional promoter variant of the Norepinephrine Transporter gene *SLC6A2* and ADHD in a family-based sample

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Abstract Noradrenergic neurotransmission influences executive functions, attentional performance, and general alertness, involving neuronal networks affected in attention deficit/hyperactivity disorder (ADHD). The norepinephrine transporter facilitates the reuptake of norepinephrine and dopamine in the prefrontal cortex and represents the main target of atomoxetine, an effective drug in the treatment of ADHD. Due to its influence on catecholaminergic signaling, variants of the coding gene (*SLC6A2*) have been widely investigated in ADHD. Several previous studies report an association between single nucleotide polymorphisms located in *SLC6A2* and ADHD; however, the findings are inconsistent. The variant A-3081T (rs28386840) has been shown to have major influence on the expression levels of *SLC6A2* due to sequence alteration at a repressor binding site, with the T-allele being associated with ADHD. We tested this potential association of A-3081T in a German family-based ADHD sample of 235 children from 162 families, which has a power >99% based on the previously reported odds ratios. There was no evidence for an over-transmission of the risk allele T (transmission rate: 48.5%, $P = 0.55$). We conclude that A-3081T is not a major risk variant in our ADHD sample, though *SLC6A2* remains an interesting candidate gene in ADHD, especially for the inattentive subtype.

Keywords SLC6A2 · Gene · ADHD · Association · A-3081T · rs28386840 · Functional · NET

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is estimated to affect about 3–6% of children in school age, and its core symptoms are reported to persist in adulthood in a considerable percentage (Polanczyk and Rohde 2007). High heritability of up to 0.8 suggests a genetical predisposition and has been the incentive for comprehensive research on the molecular genetic basis of this sociologically relevant disorder (Faraone et al. 2005). Based on pathophysiologic considerations, numerous studies investigating candidate genes encoding effectors of monoaminergic neurotransmission have been conducted (Brookes et al. 2006; Schimmelmann et al. 2006; Albayrak et al. 2008).

One promising candidate in ADHD is the norepinephrine transporter (NET) gene, also known as *solute carrier family 6, member 2* (*SLC6A2*). Norepinephrine is suggested to play a crucial role in the neurotransmitter disequilibrium

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underlying ADHD pathophysiology. Interference with noradrenergic signal transduction in prefrontal brain areas was correlated with ADHD-like symptoms in rodents as well as in primates (Arnsten 2006; Kostrzewa et al. 2008; Sontag et al. 2010). Dysbalance between dopamine and norepinephrine activity with a relative hypernoradrenergic state is also found in *SNAP-25* knock-out mice as well as in spontaneously hypertensive rats (SHR), animal models previously characterized to display ADHD-like behavior (Bruno et al. 2007; Russell 2007). This is in line with knowledge on noradrenaline's capacity to influence attention, executive functions, and general alertness.

The synaptic neurotransmitter homeostasis of dopamine and norepinephrine in prefrontal areas is modulated by reuptake into the presynaptic neuron via NET. While norepinephrine is the main substrate of NET, it is also capable of mediating the reuptake of dopamine in prefrontal areas, underlining the importance of this effector in prefrontal brain activity. Moreover, atomoxetine, a drug alleviating ADHD symptoms, is suggested to bind predominantly to NET, blocking its transporter function (Seneca et al. 2006). Based on this knowledge, *SLC6A2*, located on chromosome 16q12.2, is an interesting candidate gene for molecular genetic studies in ADHD.

Several studies investigated the association between genetic variants of *SLC6A2* and ADHD with divergent results (Brookes et al. 2006; Retz et al. 2008; Xu et al. 2005; Bobb et al. 2005; Kim et al. 2008; Kim et al. 2010; Joung et al. 2010), while an a priori gene analysis of genome-wide association data pointed to *SLC6A2* as one of the most promising candidates (Lasky-Su et al. 2008). However, most of the studies have been focussing on polymorphisms whose capacity to influence the functionality of *SLC6A2* is not clarified yet. Generally, genetic variants proven to be functional either by altering amino acid sequence or due to being located in regions with potential influence on gene expression are valuable targets for association studies. Previously, Kim and colleagues reported a T/A single nucleotide polymorphism (SNP) rs28386840, located 3081 base pairs upstream the transcription start site, and confirmed a markable loss of expression caused by the T-variant (Kim et al. 2006). In an elaborated set of assays, they showed that the E2-box motif formed by the T-allele enables the binding of the repressing transcription factors Slug and Scratch, reducing the expression of *SCL6A2* ($p < 0.0005$). Moreover, in a small case–control sample including 90 ADHD patients, they identified the minor T-allele as a risk allele in ADHD with an odds ratio of 1.8 and 4.3 for the AT-genotype and the TT-genotype, respectively, compared with the AA-genotype.

However, this intriguing finding, linking a functional genetic variant causing down regulation of *SLC6A2* with ADHD, the association between T-3081A and ADHD, has to be confirmed in a larger sample. Though Kim et al. (2008) further underlined the importance of *SLC6A2* in ADHD by an extended association study, the T-3081A variant was not included in the set of investigated variants. In a recent combined case–control and family-based study on Korean children affected by ADHD, Cho et al. (2008) were not able to confirm the association for the T-3081A SNP, while Joung et al. reported association in a further Korean sample with relatively high odds ratios (Cho et al. 2008; Joung et al. 2010).

In this study, we focussed on this functionally relevant SNP in the promoter of *SLC6A2* and aimed to replicate the results of Kim et al. (2006) and Joung et al. (2010) in a family-based ADHD sample with 162 families of German descent. To detect the odds ratio reported by Kim and colleagues, our sample provides a power of more than 99%.

Materials and methods

Sample

Two hundred and thirty-five children (178 boys) with ADHD from 162 families were recruited and phenotypically characterized by a team of experienced child and adolescent psychiatrists in the outpatient unit of the Department of Child and Adolescent Psychiatry and Psychotherapy, University of Würzburg, according to DSM-IV criteria American Psychiatric Association (2009). All patients agreed to participate in the study, and written informed consent was obtained from all participants. The study was approved by the appropriate local Ethics Committee of the University of Würzburg.

Families were included if they had one or more children affected with ADHD to perform family-based association and genome-wide linkage studies. The index patient was required to be older than 8 years and to fulfill DSM-IV criteria for the combined subtype, and further affected siblings had to be at least 6 years of age. The lower limit was chosen in order to ensure relative persistence of ADHD symptoms and to exclude children who may show phenocopies of the disorder during preschool age, but do not fulfill diagnostic criteria for ADHD during subsequent developmental stages (Shelton et al. 2000). The mean age of the affected children was 11.03 years (SD: 3.12 years). In 107 families one child, in 40 families two, in 12 families three and in 3 families four affected children were recruited.

Exclusion criteria were as follows: (a) general IQ $\leq$ 85, (b) potentially confounding psychiatric diagnoses such as schizophrenia, any pervasive developmental disorder,

Tourette's disorder, and primary mood or anxiety disorder, (c) neurological disorders such as epilepsy, (d) history of any acquired brain damage or evidence of the fetal alcohol syndrome, (e) premature deliveries, and/or (f) maternal reports of severe prenatal, perinatal, or postnatal complications. Psychiatric classification was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL). Mothers received the unstructured Introductory Interview and the Diagnostic Screening Interview including diagnostic supplements when applicable. The child was interviewed with the screening interview of the K-SADS in case of positive screening with the respective supplements of the K-SADS-PL. Additionally, we employed the Child Behavior Checklist and a German Teachers' Report on ADHD symptoms according to DSM-IV. We consider our index patients as representative of ADHD patients of child and adolescent psychiatric units in Germany. See Table 1 for clinical characteristics.

Genotyping

DNA was extracted out of whole-blood samples according to standard protocols. To genotype the variant A-3081T (rs28386840), polymerase chain reaction was performed as described by Kim et al. (2006). PCR products underwent enzymatic digestion by BsrI at 65°C over 3 h, and genotypes were identified by subsequent gel electrophoresis using a 3% agarose gel (Table 2).

Table 1 Clinical characteristics of the ADHD sample

	N	%
ADHD subtype[a]		
Combined	203	86.38
Predominantly inattentive	30	12.77
Predominantly hyperactive	2	0.85
Comorbidities[a, b]		
Conduct disorder	28	14.91
Oppositional defiant disorder	94	40
Mood disorder[c]	3	1.28
Anxiety disorder[d]	27	11.49
Tic disorder	23	9.79

[a] Current DSM-IV diagnosis according to K-SADS

[b] Multiple scoring possible

[c] Diagnoses: major depression and dysthymic disorders

[d] Diagnoses: separation anxiety disorder, social phobia, specific phobia

Statistical analysis

Genotypes were checked for Mendelian inconsistencies using PedCheck (O'Connell and Weeks 1998). Here, we found an inconsistency in a trio and set the genotypes of all family members on missing. Hardy–Weinberg equilibrium was checked for on parental genotypes by chi-square tests. The two-sided pedigree disequilibrium test weighting on family size (PDT-sum) was performed to assess the transmission rates and to test for association (Martin et al. 2000). A nominal p-value lower than 0.05 was considered statistically significant.

Given the number and the structure of our ADHD families, we used the program TDT Power Calculator (Version 1.2.1) (Chen and Deng 2001) to calculate power at the alpha level of 0.05 for an observation of the effect magnitudes reported by Kim et al. (2006). Therefore, ADHD prevalence of 5% and, according to Kim and colleagues, a T-allele frequency of 22.5% and a genotypic relative risk of 1.8 and 4.3 for the AT-genotype and the TT-genotype, respectively, were assumed. This results in a power of >99% with our sample size.

Results

To confirm the association between the functional SNP rs28386840 located in the promoter region of *SLC6A2* and ADHD, a family-based association study including 162 families including 235 affected children was conducted. The parent genotype distribution (AA: 159, AT: 136, TT: 27) and the offspring genotype distribution (AA: 125, AT: 88, TT: 21) did not show significant difference from Hardy–Weinberg equilibrium ($P = 0.78$ and 0.34, respectively). There was no evidence for an overtransmission of the risk T-allele (transmission rate: 48.5%, $P = 0.55$; Table 3).

Discussion

In this study, we aimed to replicate the reported association of a functional genetic variant rs28386840 located in the

Table 2 Oligo sequences and restriction enzyme used for genotyping

Marker	Position	Primers	Enzyme
rs28386840	−3081	Forward: CTCTAGTTTTCTTGCCCCTCAAG Reverse: GAGACAGCAAAGGGAAGGAAACCA	BsrI

Table 3 Family-based association analysis of *SLC6A3* marker rs28386840 (numbers of transmissions from all parents)

Allele	Transmitted	Non-transmitted	Transmission rate	*P* value (PDT-sum)
T	130	138	48.51%	0.5532
A	338	330	50.60%	

promoter region of *SLC6A2* in a family-based German ADHD sample. This SNP was shown to downregulate the expression of *SLC6A2* significantly, representing a very interesting candidate for molecular genetic studies in ADHD. In contrast to the results reported by Kim et al. (2006) and Joung et al. (2010) and in line with the findings of Cho et al. (2008), we did not detect significant transmission disequilibrium for the T-allele in our sample (Kim et al. 2006; Joung et al. 2010; Cho et al. 2008). Our study is based on family data and provides robust results against stratification admixture in contrast to case–control studies. In addition, since the study size allowed considerable power (>99%) to detect genotype effects of the magnitude reported by Kim et al. (2006), we assume that the functional variant rs2838680 plays no major role in our German ADHD sample.

Since norepinephrine is considered to be regulating attentive and executive functions (Brennan and Arnsten 2008), *SLC6A2* is suggested to impact specific clinical ADHD features. In the present study, the investigated sample consists of children predominantly affected by combined type ADHD, as was the sample investigated by Cho et al. (2008). Considering that the sample in the study of Kim et al. (2006) reporting positive association between two SNPs of *SLC6A2* and ADHD comprised 30% inattentive subtype, the negative finding in this study may indicate that *SLC6A2* could be of higher importance in the predominantly inattentive subtype.

For most of the investigated variants in candidate gene studies, functional impact is unknown, as it is the case with two SNPs of *SLC6A2* for which Kim et al. (2008) reported nominal association (Kim et al. 2008). Therefore, frequently in case of positive association results linkage disequilibrium with a variant harboring, the actual functionality is assumed for the respective SNPs. In this study, we focussed on a genetic variant that to our knowledge is the only one in *SLC6A2* whose capacity to influence gene expression directly has been shown in biochemical assays, confirming the formation of a new transcription factor binding site. Genetic variants of candidate genes recently have been reported to influence the efficacy of pharmacological therapy in ADHD (Kooij et al. 2008; Tharoor et al. 2008). Recent studies investigating the association of *SLC6A2* polymorphisms with response to stimulant medication reported differing results (Kim et al. 2010; Song et al. 2011; Lee et al. 2011). However, for SNP rs2838680, a potential modulating role was indicated in a Korean sample (Kim et al. 2010). In our opinion, the promoter SNP qualifies as a preferable polymorphism in studies especially on atomoxetine, since it is considered to interact mainly with *SLC6A2*. Thus, a change in genetic expression could be linked with altered general response to pharmacological therapy. However, the only study on the pharmacogenomics of *SLC6A2* and atomoxetine response did not include the functional SNP rs2838680 (Ramoz et al. 2009). Further molecular genetic studies with a special emphasis on ADHD subtypes are recommended to clarify the pathophysiologic role of *SLC6A2* and its regulation in ADHD.

In conclusion, the present study showed no association of a functional variant, capable to downregulate the expression of *SLC6A2,* in a German family-based ADHD sample. Since the study design provided sufficient power to detect the reported odds ratios, we conclude that it has no major impact in this sample, consisting mostly of combined type ADHD patients. Due to its impact on monoaminergic neurotransmission including norepinephrine as well as dopamine, *SLC6A2* remains an interesting candidate gene in ADHD. Further studies on genetic variants of *SLC6A2* will focus on its role in specific subtypes of ADHD with deficiencies in attentional networks and their response to pharmacotherapy.

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Conflict of interest None.

References

Albayrak O, Friedel S, Schimmelmann BG, Hinney A, Hebebrand J (2008) Genetic aspects in attention-deficit/hyperactivity disorder. J Neural Transm 115:305–315

American Psychiatric Association (2009) Diagnostic and statistical manual of mental disorders, 4th ed., text rev., 13. print. American Psychiatric Association, Arlington

Arnsten AF (2006) Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J Clin Psychiatry 67(8):7–12

Bobb AJ, Addington Am, Sidransky E, Gornick MC, Lerch JP, Greenstein DK, Clasen LS, Sharp WS, Inoff-Germain G, Wavrant-De VF, Arcos-Burgos M, Straub RE, Hardy JA, Castellanos FX, Rapoport JL (2005) Support for association

between ADHD and two candidate genes: NET1 and DRD1. Am J Med Genet B Neuropsychiatr Genet 134B:67–72

Brennan AR, Arnsten AFT (2008) Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann NY Acad Sci 1129:236–245

Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, Anney R, Aneey R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, Campbell D, Knight J, Andreou P, Altink M, Arnold R, Boer F, Buschgens C, Butler L, Christiansen H, Feldman L, Fleischman K, Fliers E, Howe-Forbes R, Goldfarb A, Heise A, Gabriëls I, Korn-Lubetzki I, Johansson L, Marco R, Medad S, Minderaa R, Mulas F, Müller U, Mulligan A, Rabin K, Rommelse N, Sethna V, Sorohan J, Uebel H, Psychogiou L, Weeks A, Barrett R, Craig I, Banaschewski T, Sonuga-Barke E, Eisenberg J, Kuntsi J, Manor I, McGuffin P, Miranda A, Oades RD, Plomin R, Roeyers H, Rothenberger A, Sergeant J, Steinhausen H, Taylor E, Thompson M, Faraone SV, Asherson P (2006) The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry 11:934–953

Bruno KJ, Freet CS, Twining RC, Egami K, Grigson PS, Hess EJ (2007) Abnormal latent inhibition and impulsivity in coloboma mice, a model of ADHD. Neurobiol Dis 25:206–216

Chen WM, Deng HW (2001) A general and accurate approach for computing the statistical power of the transmission disequilibrium test for complex disease genes. Genet Epidemiol 21:53–67

Cho S, Kim J, Kim B, Hwang J, Park M, Kim SA, Cho D, Yoo H, Chung U, Son J, Park T (2008) No evidence of an association between norepinephrine transporter gene polymorphisms and attention deficit hyperactivity disorder: a family-based and case-control association study in a Korean sample. Neuropsychobiology 57:131–138

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1313–1323

Joung Y, Kim CH, Moon J, Jang WS, Yang J, Shin D, Lee S, Kim KS (2010) Association studies of -3081(A/T) polymorphism of norepinephrine transporter gene with attention deficit/hyperactivity disorder in Korean population. Am J Med Genet B Neuropsychiatr Genet 153B:691–694

Kim C, Hahn MK, Joung Y, Anderson SL, Steele AH, Mazei-Robinson MS, Gizer I, Teicher MH, Cohen BM, Robertson D, Waldman ID, Blakely RD, Kim K (2006) A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder. Proc Natl Acad Sci USA 103:19164–19169

Kim JW, Biederman J, McGrath CL, Doyle AE, Mick E, Fagerness J, Purcell S, Smoller JW, Sklar P, Faraone SV (2008) Further evidence of association between two NET single-nucleotide polymorphisms with ADHD. Mol Psychiatry 13:624–630

Kim BN, Kim JW, Hong SB, Cho SC, Shin MS, Yoo HJ (2010) Possible association of norepinephrine transporter-3081(A/T) polymorphism with methylphenidate response in attention deficit hyperactivity disorder. Behav Brain Funct 6:57

Kooij JS, Boonstra Am, Vermeulen SH, Heister AG, Burger H, Buitelaar JK, Franke B (2008) Response to methylphenidate in adults with ADHD is associated with a polymorphism in SLC6A3 (DAT1). Am J Med Genet B Neuropsychiatr Genet 147B:201–208

Kostrzewa RM, Kostrzewa JP, Kostrzewa RA, Nowak P, Brus R (2008) Pharmacological models of ADHD. J Neural Transm 115:287–298

Lasky-Su J, Neale BM, Franke B, Anney RJ, 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 N, Lange C, 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

Lee SH, Kim SW, Lee MG, Yook KH, Greenhill LL, Frandin KN, Hong HJ (2011) Lack of association between response of OROS-methylphenidate and norepinephrine transporter (SLC6A2) polymorphism in Korean ADHD. Psychiatry Res 186:338–344

Martin ER, Monks SA, Warren LL, Kaplan NL (2000) A test for linkage and association in general pedigrees: the pedigree disequilibrium test. Am J Hum Genet 67:146–154

O'Connell JR, Weeks DE (1998) PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 63:259–266

Polanczyk G, Rohde LA (2007) Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 20:386–392

Ramoz N, Boni C, Downing Am, Close SL, Peters SL, Prokop Am, Allen AJ, Hamon M, Purper-Ouakil D, Gorwood P (2009) A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology 34:2135–2142

Retz W, Rösler M, Kissling C, Wiemann S, Hünnerkopf R, Coogan A, Thome J, Freitag C (2008) Norepinephrine transporter and catecholamine-O-methyltransferase gene variants and attention-deficit/hyperactivity disorder symptoms in adults. J Neural Transm 115:323–329

Russell VA (2007) Reprint of "Neurobiology of animal models of attention-deficit hyperactivity disorder". J Neurosci Methods 166:1–14

Schimmelmann BG, Friedel S, Christiansen H, Dempfle A, Hinney A, Hebebrand J (2006) Genetische Befunde bei der Aufmerksamkeitsdefizit- und Hyperaktivitatsstorung (ADHS). Z Kinder Jugendpsychiatr Psychother 34:425–433

Seneca N, Gulyás B, Varrone A, Schou M, Airaksinen A, Tauscher J, Vandenhende F, Kielbasa W, Farde L, Innis RB, Halldin C (2006) Atomoxetine occupies the norepinephrine transporter in a dose-dependent fashion: a PET study in nonhuman primate brain using (S, S)-[18F]FMeNER-D2. Psychopharmacology (Berl) 188:119–127

Shelton TL, Barkley RA, Crosswait C, Moorehouse M, Fletcher K, Barrett S, Jenkins L, Metevia L (2000) Multimethod psychoeducational intervention for preschool children with disruptive behavior: two-year post-treatment follow-up. J Abnorm Child Psychol 28:253–266

Song J, Song DH, Jhung K, Cheon KA (2011) Norepinephrine transporter gene (SLC6A2) is involved with methylphenidate response in Korean children with attention deficit hyperactivity disorder. Int Clin Psychopharmacol 26:107–113

Sontag TA, Tucha O, Walitza S, Lange KW (2010) Animal models of attention deficit/hyperactivity disorder (ADHD): a critical review. Atten Defic Hyperact Disord 2:1–20

Tharoor H, Lobos EA, Todd RD, Reiersen AM (2008) Association of dopamine, serotonin, and nicotinic gene polymorphisms with methylphenidate response in ADHD. Am J Med Genet B Neuropsychiatr Genet 147B:527–530

Xu X, Knight J, Brookes K, Mill J, Sham P, Craig I, Taylor E, Asherson P (2005) DNA pooling analysis of 21 norepinephrine transporter gene SNPs with attention deficit hyperactivity disorder: no evidence for association. Am J Med Genet B Neuropsychiatr Genet 134B:115–118