J Neural Transm
DOI 10.1007/s00702-013-1065-2

Association between DPYSL2 gene polymorphisms and alcohol dependence in Caucasian samples

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Received: 16 October 2012 / Accepted: 2 July 2013

Abstract The DPYSL2 gene at 8p22-p21 is expressed widely in neuronal tissues and has been implicated in multiple psychiatric disorders such as Alzheimer's disease and schizophrenia. We therefore hypothesized that DPYSL2 gene polymorphisms may play a role in alcohol dependence (AD). We investigated the genetic associations of 57 single-nucleotide polymorphisms (SNPs) within the DPYSL2 gene with AD using two Caucasian samples—the Collaborative Study on the Genetics of Alcoholism (COGA) sample (660 AD cases and 400 controls), and the Study of Addiction: Genetics and Environment (SAGE) sample (623 cases and 1,016 controls). The SNP rs11995227 was most significantly associated with AD ($p = 0.000122$) in the COGA sample while one flanking SNP rs7832576 revealed the second most significant association with AD ($p = 0.00163$) in the COGA sample and association with AD ($p = 0.0195$) in the SAGE sample. Meta-analysis of two samples showed both rs119952227 and rs7832576 were associated with AD ($p = 0.000363$ and 0.000184, respectively). Furthermore, the C-A haplotype from rs11995227 and rs7832576 revealed significant association with AD ($p = 0.0000899$) in the COGA sample while the T-G haplotype revealed association with AD both in the COGA and SAGE samples ($p = 0.00098$ and 0.021, respectively). These findings suggest that genetic variants in DPYSL2 may play a role in susceptibility to AD.

Keywords Alcohol dependence · DPYSL2 · Single nucleotide polymorphism · Association · Meta-analysis · Haplotype

Introduction

Alcohol dependence (AD) is a common and highly familial disorder that is a top cause of morbidity and premature death in the United States and the world (Campbell et al. 1995). Family, twin and adoption studies support that AD has a genetic component (Heath et al. 1997; Kendler et al. 1992; Prescott and Kendler 1999). The DRD2 gene is the first candidate gene that has shown promise of an association with AD (Gordis et al. 1990). Recently, candidate gene and genome-wide association studies have identified several regions and candidate genes such as GABRA2, ADH, ALDH, CHRM2, OPRM1 and NPY, and SLC10A2 for AD and related phenotypes (e.g., Ducci and Goldman 2008; Mayfield et al. 2008; Gelernter and Kranzler 2009; Bierut et al. 2010; Edenberg et al. 2010; Lind et al. 2010; Wang et al. 2011).

Dihydropyrimidinase-like 2 (DPYSL2), also known as DRP2; N2A3; CRMP2 or ULIP2 is located at 8p22-p21. This gene encodes a member of the collapsin response mediator protein family. Collapsin response mediator proteins form homo- and hetero-tetramers and facilitate neuron guidance, growth and polarity. The encoded protein promotes microtubule assembly and is required for Sema3A-mediated growth cone collapse, and also plays a role in synaptic signaling through interactions with calcium channels. Hamajima et al. (1996) isolated a human

Electronic supplementary material The online version of this article (doi:10.1007/s00702-013-1065-2) contains supplementary material, which is available to authorized users.

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Published online: 12 July 2013

cDNA encoding DPYSL2, whose transcript was measured in all tissues except liver. Fukata et al. (2002) found that this gene regulates axonal growth and branching as a partner of the tubulin heterodimer in a manner that differs from other microtubule-associated proteins. Vincent et al. (2005) proposed that DPYSL2 might have a role in pathogenesis of neuroinflammatory disease. In animal models, it has been found that CRMP2 is expressed in the major neural clusters of the embryonic brain during the primary stages of neurogenesis (Christie et al. 2006). The DPYSL2 gene encodes a cytosolic phosphoprotein that can act as a mediator of growth cone collapse as well as modify axon number, length, and neuronal polarity (Brittain et al. 2011). CRMP2 is a cytosolic phosphoprotein that mediates axon/dendrite specification and axonal growth, and CRMP2 is expressed widely in neuronal tissues, such as the brain, retinal ganglia, spinal cord and dorsal root ganglion (Goshima et al. 1995; Khanna et al. 2012). Recently, the protein of DPYSL2 has already been suggested to be the biomarkers of psychiatric disorders at protein or genome level (Kékesi et al. 2012). Previous studies have shown that polymorphisms within DPYSL2 gene are associated with several psychiatric disorders. For example, polymorphisms in the 3′-end of DPYSL2 have been found to be associated with schizophrenia in a Japanese population (Nakata et al. 2003). Fallin et al. (2011) reported linkage and association to a schizophrenia susceptibility region on chromosome 8p21 within the largest schizophrenia linkage sample to date. This gene has been implicated in multiple neurological disorders, and hyperphosphorylation of the encoded protein may play a key role in the development of Alzheimer's disease (Williamson et al. 2011). Incorporating biologically relevant information, we hypothesized that DPYSL2 might be a novel target candidate gene region associated with AD. In the present study, we reported the first genetic association study of 57 single nucleotide polymorphisms (SNPs) in DPYSL2 gene with AD using two datasets—1,639 people (623 cases and 1,016 controls) from Study of Addiction:Genetics and Environment (SAGE) sample and 1,060 people (660 cases and 400 controls) from the Collaborative Study on the Genetics of Alcoholism (COGA) sample.

Materials and methods

Study samples

The COGA sample, the Collaborative Study on the Genetics of Alcoholism case control study, is a case–control genome-wide association (GWA) study of alcoholism in which the subjects have been drawn from the COGA (Edenberg et al. 2010). The SAGE sample, the Study of Addiction:Genetics and Environment, is a comprehensive GWA study using approximately 4,000 unrelated subjects of European and African-American descent. Cases with AD include 1,944 subjects with the primary phenotype being DSM-IV AD (Bierut et al. 2010). Phenotypes include AD as a binary trait according to DSM-IV diagnosis. Based on the previous genome-wide association meta-analysis study (Wang et al. 2011), 660 cases and 400 controls (572 males and 488 females) were available in the COGA sample while 623 cases and 1,016 controls (635 males and 1,004 females) remained in the SAGE sample (Table 1). In the present study, we chose the DPYSL2 gene a priori based on biologically relevant information without prior knowledge from GWA association studies using these samples. There are 57 SNPs within DPYSL2 gene available in both samples.

Statistical analysis

Hardy–Weinberg equilibrium was tested in the controls using Haploview software (Barrett et al. 2005). Then, minor allele frequency (MAF) was determined for each SNP and the linkage disequilibrium (LD) structure was constructed. Logistic regression analysis of AD as a binary trait, adjusted for age and sex, was performed for the COGA and SAGE samples using PLINK v1.07 (Purcell et al. 2007). The asymptotic p values for this test were observed, while the odds ratio (OR) and standard error of

Table 1 Descriptive characteristics of cases and controls

	Cases		Controls	
	SAGE	COGA	SAGE	COGA
Number	623	660	1,016	400
Sex, *N* (%)				
Males	329 (53 %)	465 (70 %)	306 (30 %)	107 (27 %)
Females	294 (47 %)	195 (30 %)	710 (70 %)	293 (73 %)
Age, years				
Mean ± SD	35.1 ± 7.7	38.6 ± 10.7	36.2 ± 7.6	44.3 ± 11.6
Range	18–61	18–72	18–65	18–73

OR were estimated. For logistic regression, the additive model was applied. Empirical p values were generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK. In this procedure, two sets of empirical significance values were calculated: pointwise estimates of an individual SNP's significance (empirical pointwise p-values) and corrected values for multiple testing (corrected empirical p-values). The COGA and SAGE samples used the same genotyping platform: Illumina Human BeadChips. Results from the two GWA analyses were directly meta-analysed by combining the separate results of the COGA and SAGE samples (OR and standard error of OR) into one meta-analysis of overall effects. For meta-analysis of two datasets, the basic meta-analysis function in PLINK was applied. Fixed-effect meta-analysis p value and fixed-effect OR were estimated. The between-study heterogeneity was tested by the χ^2-based Cochrane's Q statistic. Haplotype analysis was performed for the COGA and SAGE samples separately using UNPHASED version 3.1.0 (Dudbridge 2008).

Results

All 57 SNPs were in Hardy–Weinberg equilibrium in the controls. Table 2 shows 12 SNPs with p-value <0.05 either in single SNP analysis or meta-analysis. A more comprehensive list of SNPs (total 57 SNPs) is presented in Supplementary Table S1. Five SNPs (rs2585458, rs11774146, rs11995227, rs7832576 and rs930470) showed associations with AD in the COGA sample while one of them (rs7832576) showed association in the SAGE sample ($p < 0.05$). For the five SNPs mentioned above, the empirical p-values yielded significant p values ($p < 0.05$). Applying a permutation procedure for multiple test correction also yielded a significant p value (corrected empirical p-value) for SNP rs11995227 ($p = 0.0279$) in the COGA sample (Table 2). Single marker analysis showed that the SNP rs11995227 was most significantly associated with AD ($p = 0.000122$) and one flanking SNP rs7832576 revealed the second most significant association with AD ($p = 0.00163$) in the COGA sample. The SNP rs7832576 demonstrated the most significant association with AD ($p = 0.0195$) in the SAGE sample while the rs11995227 showed the borderline association with AD ($p = 0.107$) in the SAGE sample.

Meta-analysis showed both rs119952227 and rs7832576 were associated with AD ($p = 0.000363$ and 0.000184, respectively). All p-values based on Q statistic were larger than 0.05, which indicated that there was no heterogeneity for these 12 SNPs between COGA and SAGE samples (Table 2).

Using Haploview, we identified haplotype blocks of SNPs around the most significantly associated SNP rs11995227. Figure 1 shows the LD (showed D') structure of 15 flanking SNPs (including rs11995227). SNPs rs11995227 and rs7832576 were within one haplotype block ($D' = 1.00$). Two-SNP haplotype analyses based on UNPHASED (Table 3) revealed that the C-A haplotype from rs11995227 and rs7832576 was significantly associated with AD ($p = 0.0000899$) in the COGA sample while the T-G haplotype from rs11995227 and rs7832576 was associated with AD both in the COGA and SAGE samples ($p = 0.00098$ and 0.021, respectively).

Discussion

Using two samples, we found statistically significant associations between several SNPs of DPYSL2 gene and AD (p values are smaller than 0.000877 using the Bonferroni correction of 57 SNPs). Haplotype analyses further supported the single marker analysis results. To our knowledge, this is the first study to investigate association between the DPYSL2 gene and AD.

The DPYSL2 gene has been implicated in multiple psychiatric disorders such as schizophrenia (e.g., Nakata et al. 2003; Koide et al. 2010; Fallin et al. 2011) and Alzheimer's disease (Williamson et al. 2011). The DPYSL2 gene is one of the most likely candidate gene to be involved in neuronal development in the autistic phenotype and may contribute to neuropsychiatric disorders (schizophrenia, autism, bipolar disorder and depression), neurodegenerative disorders (Parkinson's and Alzheimer's disease) and cancer (see the review by Tabarés-Seisdedos and Rubenstein 2009). Recently, Koide et al. (2010) reported that DPYSL2 does not have a major function in schizophrenia of Japanese subjects; however, one SNP was found to be weakly associated with schizophrenia (rs2585458 with $p = 0.046$). In the present study, we found an association of the same SNP rs2585458 with AD in the COGA sample ($p = 0.00326$), which supported previous reports that the DPYSL2 gene might implicate in multiple psychiatric disorders.

Previous linkage studies have found linkage region on 8p22-p21 for Alzheimer (Baron et al. 2012), bipolar disorder (Park et al. 2004), cancer (Maier et al. 2005), major depression (Zubenko et al. 2004), schizophrenia (Kendler et al. 2000; Fallin et al. 2011), and personality traits (Cloninger et al. 1998; Zohar et al. 2003). AD coexists frequently with other psychiatric diseases, including both internalizing disorders (e.g. depression and anxiety) as well as externalizing disorders (e.g. antisocial personality disorder, conduct disorder, and attention deficit hyperactivity disorder) (Grant et al. 2004a, b). Alcohol consumption is

Table 2 Association between 12 polymorphisms of DYSL2 gene and risk of alcohol dependence

SNP	Position	Allele[a]	P_meta[b]	Q[c]	MAF[d]	HWE[e]	OR[f]	P_COGA[g]	EMP1[h]	EMP2[i]	MAF[j]	OR[k]	P_SAGE[l]	EMP1[m]	EMP2[n]
rs327232	26511632	T	0.149	0.25	0.22	0.91	0.82	0.0764	0.085	1	0.24	0.96	0.637	0.65	1
rs7835006	26517027	T	0.0386	0.96	0.21	0.92	1.15	0.214	0.21	1	0.19	1.15	0.0984	0.10	1
rs11775497	26517618	T	0.0437	0.81	0.22	0.98	1.13	0.291	0.28	1	0.19	1.17	0.083	0.079	1
rs2585458	26523749	A	0.0268	0.05	0.05	0.99	0.51	0.00326	0.00099	0.522	0.03	0.94	0.749	0.69	1
rs11774146	26536278	C	0.134	0.05	0.07	0.22	1.51	0.014	0.0089	0.942	0.08	0.99	0.985	0.99	1
rs1561818	26538746	A	0.0476	0.66	0.44	0.98	1.16	0.119	0.13	1	0.42	1.09	0.195	0.20	1
rs4872457	26539981	T	0.0457	0.65	0.45	0.86	1.16	0.113	0.12	1	0.42	1.1	0.196	0.21	1
rs11995227	26542172	T	0.000363	0.05	0.12	0.98	1.66	0.000122	0.00099	0.0279	0.15	1.17	0.107	0.11	1
rs7832576	26542659	G	0.000184	0.24	0.06	0.56	1.79	0.00163	0.0019	0.325	0.07	1.37	0.0195	0.016	0.98
rs930470	26548805	G	0.0211	0.23	0.26	0.99	1.28	0.0186	0.015	0.978	0.26	1.09	0.273	0.27	1
rs13277175	26553930	G	0.0572	0.39	0.42	0.43	1.19	0.0653	0.071	1	0.40	1.07	0.326	0.33	1
rs17666	26571375	C	0.0773	0.43	0.30	0.57	1.18	0.0866	0.089	1	0.30	1.07	0.367	0.38	1

[a] Minor allele

[b] *p*-value for the meta-analysis

[c] *p*-value for Cochrane's Q statistic

[d] Minor allele frequency in the COGA sample

[e] Hardy–Weinberg equilibrium test

[f] Odds ratio for the COGA sample

[g] *p*-value for the COGA sample based on logistic regression

[h] Empirical *p*-value for the COGA sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

[i] Corrected empirical *p*-value for the COGA sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

[j] Minor allele frequency in the SAGE sample

[k] Odds ratio for the SAGE sample

[l] *p*-value for the SAGE sample based on logistic regression

[m] Empirical *p*-value for the SAGE sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

[n] Corrected empirical *p*-value for the SAGE sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

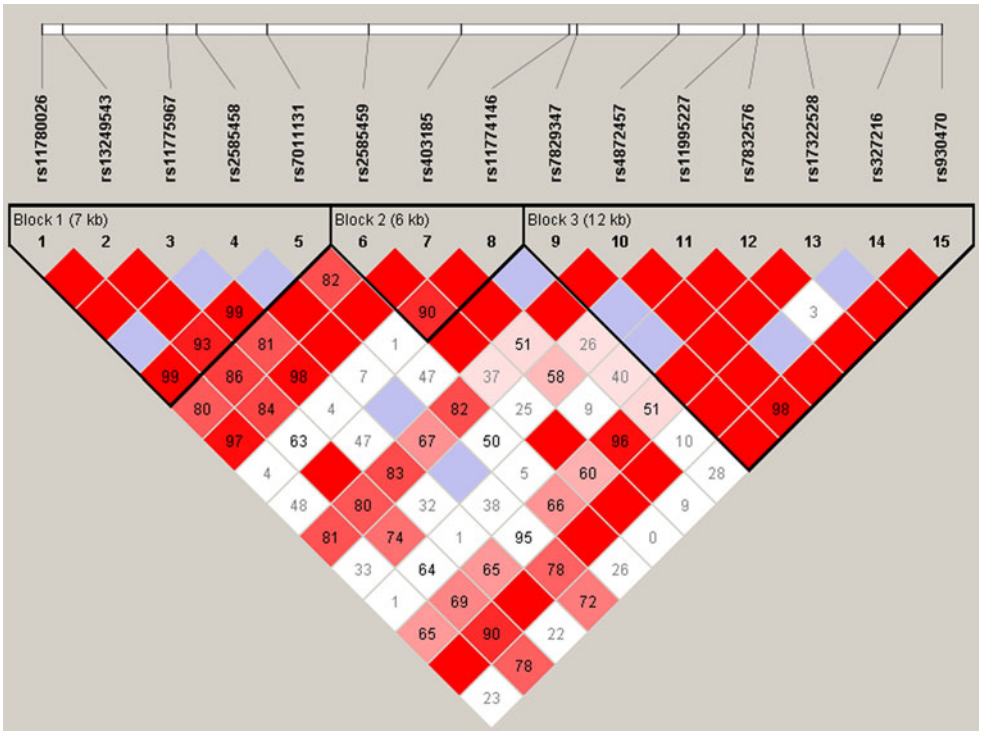

Fig. 1 Linkage disequilibrium structure of 15 SNPs within DPYSL2. The numbers indicate the D' values between the corresponding two SNPs

Table 3 Haplotype analysis of DPYSl2 gene in the COGA and SAGE samples

Haplotype		COGA			SAGE		
rs11995227	rs7832576	Case[a]	Csontrol[b]	p[c]	Case	Control	p
C	A	1,054 (0.82)	694 (0.88)	0.0000899	1,028 (0.83)	1,706 (0.85)	0.13
T	A	115 (0.09)	51 (0.06)	0.0434	107 (0.09)	177 (0.09)	0.86
T	G	121 (0.09)	43 (0.05)	0.00098	111 (0.09)	135 (0.07)	0.021

[a] Haplotype number and frequency in cases

[b] Haplotype number and frequency in controls

[c] p-value based on standard case–control haploype analysis

increasing in many countries and is an important cause of cancer worldwide (Longnecker 1995; Boffetta and Hashibe 2006; Druesne-Pecollo et al. 2009). Our single marker analysis, meta-analysis and haplotype analysis revealed that several genetic variants in DPYSL2 were associated with AD. Considering previous studies in other psychiatric disorders such as Alzheimer disease and schizophrenia, we could assume that the DPYSL2 gene might have effect on multiple psychiatric disorders.

In conclusion, we report the first genetic association study of DPYSL2 in AD. We found several SNPs associated with AD while meta-analysis and haplotype analyses further support the associations using single marker analysis. These findings may serve as a resource for replication in other populations to elucidate the potential role of these genetic variants in AD. Further study to identify additional variants and the disease-causing polymorphisms in the loci and to examine the functions of these polymorphisms would help us better understand the pathogenesis of AD.

Acknowledgments Funding support for the (CIDR-COGA Study) was provided through the [the Center for Inherited Disease Research (CIDR) and the Collaborative Study on the Genetics of Alcoholism (COGA)]. The CIDR-COGA Study is a genome-wide association studies funded as part of the Collaborative Study on the Genetics of Alcoholism (COGA). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the COGA. Assistance with data cleaning was provided by the National Center for Biotechnology Information. Support for collection of datasets and samples was provided by the Collaborative Study on the Genetics of Alcoholism (COGA; U10 AA008401). Funding support for genotyping, which was performed at the Johns Hopkins University Center for Inherited Disease Research, was provided by the NIH GEI (U01HG004438), the National Institute on Alcohol Abuse and Alcoholism, and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease" (HHSN268200782096C). The datasets used for the

analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gap through dbGaP accession number: phs000125.v1.p1. Funding support for the SAGE was provided through the National Institutes of Health (NIH) Genes, Environment and Health Initiative (GEI) Grant U01 HG004422. SAGE is one of the GWAS funded as part of the GENEVA under GEI. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (Grant U01 HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Support for collection of datasets and samples was provided by COGA (Grant U10 AA008401), COGEND (Grant P01 CA089392), and FSCD (Grant R01 DA013423). Funding support for genotyping, which was performed at the Johns Hopkins University Center for Inherited Disease Research, was provided by NIH GEI Grant U01HG004438, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease" (HHSN268200782096C). The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/projects/gap/cgibin/study.cgistudy_id=phs000092.v1.p1 through dbGaP accession number phs000092.v1.p.1. This study was approved by Internal Review Board (IRB), East Tennessee State University.

Conflict of interest All authors have reported no financial interests or potential conflict of interest.

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