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Associations between *LSAMP* gene polymorphisms and major depressive disorder and panic disorder

K Koido[1,2], T Traks[1,2], R Balõtšev[3], T Eller[3], A Must[1,2], S Koks[1,2], E Maron[3,4], I Tõru[3], J Shlik[5], V Vasar[3] and E Vasar[1,2]

The purpose of this case–control genetic association study was to explore potential relationships between polymorphisms in the limbic system-associated membrane protein (*LSAMP*) gene and mood and anxiety disorders. A total of 21 single-nucleotide polymorphisms (SNPs) from the *LSAMP* gene were analyzed in 591 unrelated patients with the diagnoses of major depressive disorder (MDD) or panic disorder (PD) and in 384 healthy control subjects. The results showed a strong association between *LSAMP* SNPs and MDD, and a suggestive association between *LSAMP* SNPs and PD. This is the first evidence of a possible role of *LSAMP* gene in mood and anxiety disorders in humans.
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Introduction

Major depressive disorder (MDD) and panic disorder (PD) are prevalent and serious psychiatric disorders commonly manifesting in young adult age and affecting females more often than males.[1,2] The data from twin and family studies suggest a substantial involvement of genetic factors in the familial transmission of MDD and PD, with heritability estimates for MDD in the range of 31 – 42%,[3] or as high as 70%,[4] and for PD near 40%.[5] It has been established that MDD and PD are highly comorbid and that shared genetic risk factors largely account for their comorbidity.[6] However, the specific genes or their variants responsible for heritability or expression of these disorders remain undetermined.

The limbic system-associated membrane protein (LSAMP) is a 64- to 68-kDa glycoprotein that is found on the somata and dendrites of neurons of cortical and subcortical regions comprising the adult mammalian limbic system, which is involved in the mediation of emotional behavior, learning, memory and central autonomic regulation.[7,8] LSAMP is a member of immunoglobulin superfamily, with three immunoglobulin domains and a glycosyl–phosphatidylinositol anchor.[9] It has been suggested that LSAMP acts as a necessary molecular component for the formation of proper connections between the limbic system regions.[7] In humans, the *LSAMP* gene is located in the 3q13.2-q21 chromosomal region, which consists 7 exons and shows 94% identity at the nucleotide level, and 99% sequence identity at the encoded 338-amino-acid polypeptides level with rat *LSAMP* cDNA.[10] Human studies have shown that *LSAMP* may have a role in the neurobiology of suicidal behavior.[11] Proteomic assessment has strongly implicated LSAMP in schizophrenia and bipolar disorder,[12] demonstrating its increased level in the dorsolateral prefrontal cortex. Furthermore, stronger or weaker linkages have been shown in the long arm of chromosome 3 with recurrent early-onset MDD or anxiety,[13] agoraphobia,[14] schizophrenia,[15–18] bipolar disorder[19,20] and autism-spectrum disorders.[21] A number of genome-wide association studies of depression have mainly given results that did not meet a genome-wide threshold for significance, but there were associations between depression and *LSAMP* or adjacent gene loci in top findings of all publications.[22–29]

In animal studies, it has been shown that the anxious rats display 1.6-fold higher expression of *Lsamp* gene compared to the non-anxious rats in the periaqueductal gray.[30] Similar results have been reported for the amygdala, demonstrating that the anxious rats display 2.4-fold higher expression of the *Lsamp* gene compared with the non-anxious rats.[31] Upregulated *Lsamp* expression was also detected in the raphe, the hippocampus and the frontal cortex of the highly anxious rats.[32] The studies in *Lsamp*-deficient mice demonstrated the reduced anxiety and increased sensitivity to anxiolytic action of diazepam in these animals.[33] The findings above suggest the importance of LSAMP in emotional regulation and make the *LSAMP* gene a good candidate for genetic research on mood and anxiety disorders. The purpose of the present study was to detect associations of genetic polymorphisms in the *LSAMP* gene with MDD and PD.

Materials and methods

Subjects and psychiatric assessment. Unrelated patients with the diagnoses of MDD or PD ($n = 591$) were enrolled in the study along with healthy control individuals ($n = 384$). The patients were recruited from consecutive outpatients and inpatients at the Clinic of Psychiatry of the Tartu University

[1]Department of Physiology, University of Tartu, Tartu, Estonia; [2]Centre of Excellence for Translational Medicine, University of Tartu, Tartu, Estonia; [3]Department of Psychiatry, University of Tartu, Tartu, Estonia; [4]Department of Neuropsychopharmacology and Molecular Imaging, Imperial College London, London, UK and [5]Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada
Correspondence: Dr K Koido, Department of Physiology, University of Tartu, 19 Ravila Street, Tartu 50411, Estonia.
E-mail: kati.koido@ut.ee
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Hospital, and healthy subjects were recruited by newspaper advertisement in Tartu, Estonia. The diagnostic status of the patients was substantiated by a psychiatric interview and verified by the Mini International Neuropsychiatric Interview (MINI 5.0.0) based on DSM-IV criteria.[34] Controls were evaluated by the MINI and family history interview, to exclude those with psychiatric morbidity and a history of major psychiatric disorders in first-degree relatives. All subjects were of white European ancestry and living in Estonia. The patients were divided into MDD ($n=395$) and PD ($n=196$) subgroups according to the primary diagnosis. MDD or PD was considered primary if it was the principal diagnosis at the time of the investigation and/or had an earlier onset in the course of illness. Patients in MDD group were either pure MDD or MDD comorbid with anxiety disorders. Patients in PD group were either pure PD, or comorbid with mood or other anxiety disorders. The control group was the same for MDD and PD, with an exception of reducing the number of male subjects in control group for PD to reflect the respective male/female ratio in the PD group. There were no significant differences in age or sex between the patients and healthy controls (χ^2 and *P*-value for gender of MDD and PD groups are 2.74 and $P=0.098$, and 3.35 and $P=0.067$, respectively). Demographic characteristics of the study subjects are presented in Table 1. The study protocol was approved by the Ethics Review Committee on Human Research of the University of Tartu. Each subject provided a written informed consent before participation.

SNP selection, DNA preparation and genotyping. Tag single-nucleotide polymorphisms (SNPs) were selected from the *LSAMP* gene and flanking regions (150 kb fragment from 116931222–117081732; and 242 kb fragment from 117428563–117670401) using the Tagger algorithm ($r^2=0.8$, minor allele frequency >0.05) implemented in Haploview 3.32.[11] Standard high-salt extraction method was used to isolate genomic DNA from 9 ml venous blood samples. SNP detection was performed by SNPlex Genotyping System (Applied Biosystems, Foster City, CA, USA). This system is based on the oligonucleotide ligation/PCR assay with a universal ZipChute (Applied Biosystems) probe detection for high throughput SNP genotyping. Fluorescent-labeled ZipChute probes are hybridized to complementary ZipCode (Applied Biosystems) sequences that are part of genotype-specific amplicons. These ZipChute probes are eluted and detected by electrophoretic separation on Applied Biosystems 3730 DNA Analyzers. The system analysis software collects and manages raw data and provides automated allele calling and quality metrics.[35]

Table 1 Demographic characteristics of the subjects

Characteristic	*MDD patients*	*MDD controls*	*PD patients*	*PD controls*
N	395	384	196	364
Sex (male/female)	114/281	132/252	46/150	112/252
Age (years), mean ± s.d.	37.0 ± 13.8	37.6 ± 13.6	38.1 ± 12.7	37.8 ± 13.6
Range (years)	17–73	16–71	18–73	16–71

Abbreviations: MDD, major depressive disorder; PD, panic disorder.

Statistical analysis. Genotypes were determined by GeneMapper 3.7 (Applied Biosystems). Allelic association, linkage disequilibrium and haplotype analyses between groups of patients and controls, and Hardy–Weinberg equilibrium calculations in the control group were performed using Haploview Version 4.0 software.[36] The significance level for all statistical tests was 0.05. The algorithm for defining haplotype blocks was an internally developed method Solid Spine of linkage disequilibrium ($D'>0.75$). Ten thousand permutations were used to correct *P*-values for multiple testing. Closer analysis of haplotype block nr 5 was performed with Statistica software (Information Technology Office, University of Tartu, Tartu, Estonia).

Results

We genotyped a total of 22 SNPs from the *LSAMP* gene in 591 unrelated psychiatric patients and 384 healthy controls. One SNP (rs4831129) was excluded from the further analysis because of a bias from Hardy–Weinberg equilibrium in the control group (*P*-value cut-off 0.01).

Allelic association analysis. The results of allelic association analysis of 21 SNPs are presented in Table 2. Four SNPs showed significant associations in MDD group—rs16824691, rs1461131, rs4831089 and rs9874470 (*P*-values 0.004, <0.001, <0.001 and <0.001, respectively). For the last three of these SNPs, the *P*-values remained statistically significant after 10 000 permutations (odds ratios, 95% confidence intervals and permutation *P*-values 1.43, 1.17–1.76 and 0.0228; 1.53, 1.24–1.89 and 0.0015; and 0.63, 0.5–0.78 and 0.0005, respectively). Two SNPs showed significant associations in PD group—rs1461131 and rs4831089 (*P*-values 0.033 and 0.018, respectively). These *P*-values did not remain statistically significant after correction for multiple testing.

A separate analysis of allelic association by gender revealed significant associations with the same four SNPs as whole-group analysis. The SNPs rs1461131, rs4831089 and rs9874470 (*P*-values 0.005, 0.005 and 0.007, respectively) differed significantly between females of the MDD group and their respective controls. No significant association was detected in the female PD group. The SNPs rs1682469, rs4831089 and rs9874470 (*P*-values 0.01, 0.004 and <0.001, respectively) differed significantly between males of the MDD group and their controls. The SNPs rs1461131, rs4831089 and rs9874470 (*P*-values 0.003, 0.005 and 0.03, respectively) differed significantly between males of PD group and their controls. These *P*-values did not remain statistically significant after correction for multiple testing, except rs9874470 in the male MDD group (odds ratio (95% confidence intervals) = 0.49 (0.33–0.73); permutation $P=0.01$).

Haplotype analysis. Haplotype analysis revealed seven haplotype blocks in both patient groups (see Figure 1 for haplotype blocks in MDD group). Haplotypes of block nr 5 (rs9874470, rs4831089, rs16824691 and rs1461131) in MDD and PD groups differed statistically significantly between patient groups and healthy control groups (Tables 3 and 4). Haplotype TATA was a risk haplotype in MDD group ($P<0.001$) and in PD group ($P=0.020$). *P*-value remained

Table 2 Results of allelic association analysis

#	Name	Area	Major/minor alleles	Min allele frequency of MDD cases	Min allele frequency of MDD controls	MDD P-value	Min allele frequency of PD cases	Min allele frequency of PD controls	PD P-value
1	rs16824996	5′-Flanking region	T/C	0.14	0.15	0.380	0.14	0.15	0.585
2	rs6787168	5′-Flanking region	T/C	0.33	0.37	0.081	0.36	0.37	0.623
3	rs4831140	5′-Flanking region	A/T	0.21	0.25	0.123	0.24	0.25	0.552
4	rs988803	Intron 1	T/A	0.24	0.24	0.887	0.23	0.25	0.586
5	rs7634137	Intron 1	T/C	0.16	0.18	0.167	0.15	0.18	0.277
6	rs1920191	Intron 1	G/A	0.28	0.29	0.618	0.28	0.30	0.595
7	rs1461131	Intron 1	G/A	0.44	0.36	**<0.001***	0.43	0.37	**0.033**
8	rs16824691	Intron 1	T/A	0.19	0.26	**0.004**	0.23	0.26	0.210
9	rs4831089	Intron 1	G/A	0.43	0.33	**<0.001***	0.41	0.34	**0.018**
10	rs9874470	Intron 1	T/C	0.26	0.36	**<0.001***	0.31	0.36	0.059
11	rs2944425	Intron 3	C/T	0.41	0.41	0.794	0.41	0.41	0.796
12	rs9830559	Intron 3	T/C	0.41	0.40	0.765	0.41	0.40	0.798
13	rs10511350	Intron 3	G/C	0.10	0.11	0.541	0.13	0.11	0.310
14	rs6763835	Intron 4	C/T	0.40	0.39	0.803	0.39	0.39	0.921
15	rs4416377	Intron 4	T/C	0.21	0.21	0.866	0.21	0.21	0.974
16	rs2918213	Intron 6	C/T	0.32	0.33	0.629	0.33	0.33	0.981
17	rs2918215	Intron 6	G/A	0.09	0.11	0.362	0.10	0.11	0.570
18	rs2918217	Intron 6	G/A	0.14	0.13	0.385	0.14	0.13	0.727
19	rs9822311	Intron 6	G/C	0.29	0.27	0.428	0.29	0.27	0.559
20	rs9821809	3′-Flanking region	G/A	0.21	0.22	0.694	0.19	0.22	0.244
21	rs2918239	3′-Flanking region	T/G	0.16	0.16	0.861	0.15	0.15	0.774

Abbreviations: MDD, major depressive disorder; Min allele, minor allele; PD, panic disorder.
P-value $\leqslant 0.05$ bolded.
**P*-value $\leqslant 0.05$ after 10 000 permutations.

statistically significant after 10 000 permutations in MDD group (odds ratio (95% confidence intervals) = 1.55 (1.26–1.91); permutation $P = 0.0008$), but did not survive the correction in the PD group. Two haplotypes were protective in the MDD group—CGAG and CGTG, with respective $P = 0.003$ and $P = 0.020$. These *P*-values did not remain statistically significant after correction for multiple testing. ATT-risk haplotype from block nr 7 (rs4831140, rs6787168 and rs16824996) differed statistically significantly in the MDD group ($P = 0.042$), but this *P*-value also did not survive the correction. Other haplotypes did not significantly differ between the patient and control groups (data not shown). On a closer analysis of frequencies of minor alleles of haplotype block nr 5, the risk haplotype TATA appeared more frequently than protective haplotype CGAG in the MDD group (41 vs 17%) as compared with their respective control group (31 vs 23%; χ^2-test $P < 0.001$). The same trend was observed in PD group-risk haplotype TATA was more frequent than protective haplotype CGAG (38 vs 20%) as compared with their respective control group (31 vs 24%; χ^2-test $P = 0.003$).

Discussion

Our findings indicate that the *LSAMP* gene is possibly related to MDD and PD. We detected statistically significant allelic associations between four *LSAMP* SNPs and MDD. Two SNPs out of these four contributed to the increased risk (rs1461131 and rs4831089) and two were protective (rs16824691 and rs9874470). Only two risk SNPs above were related to PD. Haplotype block nr 5 was formed from the forenamed SNPs giving three statistically significant haplotypes in the MDD group: TATA being risk haplotype and CGAG and CGTG being a protective haplotype. Risk haplotype TATA was also statistically significant in the PD group. Closer analysis of minor alleles of haploblock 5 indicated that the proportion of risk SNPs was higher in patient groups as compared with control groups. Sub-analysis by gender suggested that *LSAMP* gene polymorphisms are evidently more related to males than to females, as no statistically significant association was detected in the female PD group. Plausibly, *LSAMP* gene polymorphisms contribute to shared genetic factors of MDD and PD, as associations were detected across both groups.

The *LSAMP* gene and protein show high similarity between the humans and rodents, suggesting strong phylogenetic conservation of the protein structure and associated functional properties.[10] The *LSAMP* gene has two alternative first exons (1a and 1b) separated by a 1.5-Mb-long intron, which give rise to two different mRNA transcripts.[37] A preliminary *in situ* RNA hybridization analysis has demonstrated substantially different expression patterns of Lsamp 1a and 1b transcripts in mouse brain, with the 1b predominantly expressed in sensory nuclei of the brainstem, in the thalamus and in sensory areas of the cortex (Philips *et al.*, unpublished). It has been suggested that large 5′-introns contain regulatory elements involved in silencing and spatial and temporal patterns of gene expression.[37] Interestingly, all associated SNPs in our study reside in the first intron (1b) and may affect regulation of gene expression. Two different *Lsamp* gene knockout mouse lines have been created.[33,38] Overlapping between the phenotype of these lines is remarkable; both knockout mice are vital and fertile with no gross abnormalities.[33] The first line, in which the second exon of *Lsamp* is deleted, exhibits hyperactivity in novel situations, altered synaptic transmission and impaired plasticity in the hippocampus, inducing deficits in spatial memory acquisition and retention.[38,39] The other line, in which the 1b exon of *Lsamp* is deleted, exhibits slower swim velocity, hyperactivity in novel situations, reduced anxiety, reduced aggressiveness and decrease of barbering behavior in male mice; however, their

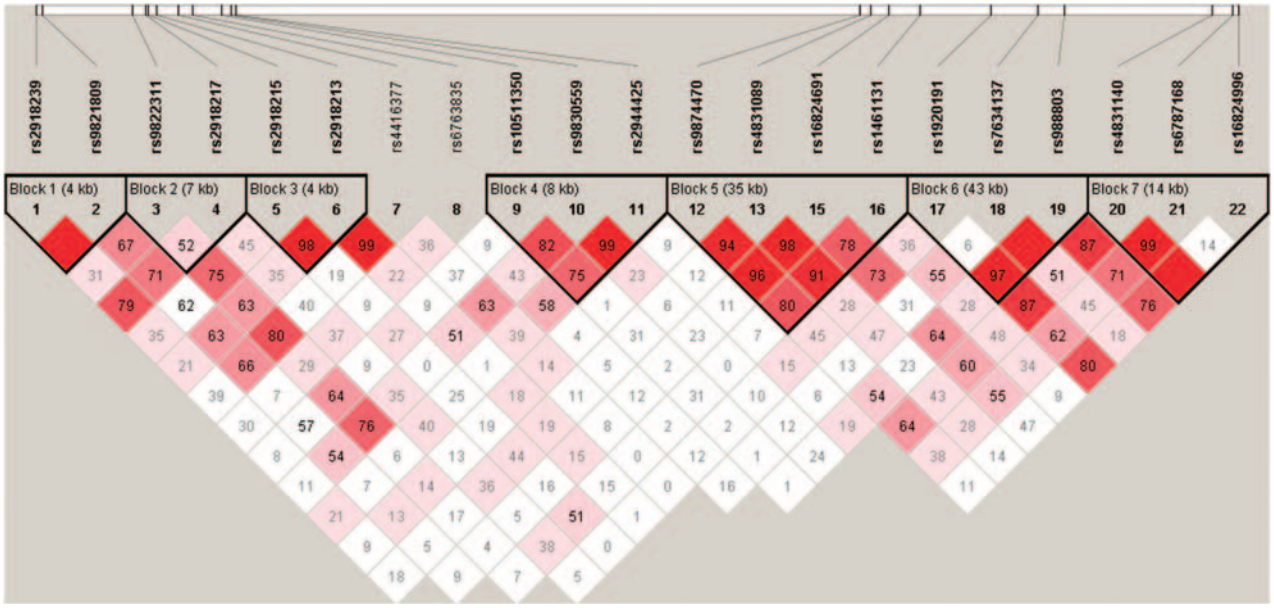

Figure 1 Haplotype blocks of the limbic system-associated membrane protein (*LSAMP*) gene in major depressive disorder (MDD) group.

Table 3 Haplotypes of block 5 in MDD group

rs9874470 T/C	*rs4831089 G/A*	*rs16824691 T/A*	*rs1461131 G/A*	*Haplotype frequencies*	*Case frequencies*	*Control frequencies*	P-*value*
T	A	T	A	0.36	0.41	0.31	<**0.001***
T	G	T	G	0.29	0.29	0.29	0.932
C	G	A	G	0.20	0.17	0.23	**0.003**
C	G	T	G	0.09	0.07	0.10	**0.020**
T	G	T	A	0.02	0.02	0.02	0.403
T	A	T	G	0.02	0.02	0.02	0.961
C	G	A	A	0.02	0.01	0.02	0.423

Abbreviation: MDD, major depressive disorder
P-value ⩽0.05 bolded.
**P*-value ⩽0.05 after 10 000 permutations.

Table 4 Haplotypes of block 5 in PD group

rs9874470 T/C	*rs4831089 G/A*	*rs16824691 T/A*	*rs1461131 G/A*	*Haplotype frequencies*	*Case frequencies*	*Control frequencies*	P-*value*
T	A	T	A	0.34	0.38	0.31	**0.020**
T	G	T	G	0.28	0.27	0.28	0.757
C	G	A	G	0.22	0.20	0.24	0.124
C	G	T	G	0.09	0.08	0.10	0.330
T	G	T	A	0.02	0.01	0.02	0.248
T	A	T	G	0.02	0.02	0.02	0.858
C	G	A	A	0.02	0.02	0.02	0.845

Abbreviation: PD, panic disorder.
P-value ⩽0.05 bolded.

spatial memory and learning curve were similar to that of wild-type mice.[33,40] Altogether, these results suggest that altered expression of LSAMP leads to differences in neuronal connectivity, causing only subtle disturbance in signaling but measurable changes in functional output.[38] Furthermore, the lack of LSAMP protein seems to result in an inability to adapt or react to novel environments or stressful environmental manipulations.[40] Thus, a properly regulated level of LSAMP expression appears to be required for normal neuronal functioning. A former study has demonstrated that intraventricular administration of anti-LSAMP to postnatal rats resulted in aberrant growth of the mossy fiber projection in the hippocampus.[9] However, more recent study showed no major alterations in the brain organization and gross connectivity in the *Lsamp*-deficient mouse.[38] To our knowledge, the direct impact of LSAMP overexpression on neuronal

circuitry has not yet been investigated, but the animal studies indicate a relationship between heightened expression of LSAMP and anxiety. Our speculation is that risk SNPs in 1b intron may cause an increased expression of the *LSAMP* gene, which results in elevated anxiety and a negative effect.

Several limitations of our study should be recognized. The sample sizes were rather small, especially the PD male group. The patients in both MDD and PD groups had comorbid diagnoses. Not all associations survived correction for multiple testing, and we cannot exclude false-positive results. Also, our study lacks functional analysis of the associated SNPs. Therefore, replication association studies in independent samples and imaging genetic studies are needed to confirm and extend our findings. Further functional research is required to determine the relevance of LSAMP function to the molecular mechanisms of psychiatric disorders.

Conflict of Interest

The authors declare no conflict of interest.

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