



Published in final edited form as:

Mol Psychiatry. 2011 June ; 16(6): 584–585. doi:10.1038/mp.2011.1.

A non-synonymous polymorphism in galactose mutarotase (*GALM*) is associated with serotonin transporter binding potential in the human thalamus: Results of a genome-wide association study

Xinmin Liu¹, Dara M. Cannon^{2,3}, Nirmala Akula¹, Pablo R. Moya⁴, Gitte M. Knudsen⁵, Tine E. Arentzen⁵, Jo Steele¹, Gonzalo Laje¹, Wayne C. Drevets^{2,6,*}, and Francis J. McMahon^{1,*}

¹Genetics of Mood and Anxiety Disorders Section, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA ²Section on Neuroimaging in Mood and Anxiety Disorders, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA ³Department of Psychiatry, Clinical Neuroimaging Laboratory, National University of Ireland Galway, Galway, Ireland ⁴Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA ⁵Center for Integrated Molecular Brain Imaging, Rigshospitalet, and University of Copenhagen, 9201, Blegdamsvej 9, DK-2100 Copenhagen, Denmark ⁶Laureate Institute for Brain Research, and Department of Psychiatry, University of Oklahoma College of Medicine, Tulsa, OK, USA

Keywords

[¹¹C]DASB; mood disorder; bipolar; GALM; PET

Positron emission tomography (PET) imaging using the tracer [¹¹C]DASB is a sensitive and noninvasive technique for measuring brain serotonin transporter (5-HTT) levels in vivo¹. Previously, Cannon et al. found that 5-HTT levels were increased in thalamus, striatum, insular and cingulate cortices in unmedicated, depressed subjects with major depressive disorder² or bipolar disorder³. To explore this potential biomarker for mood disorders, we undertook a proof-of-principle genome-wide association study.

5-HTT levels, measured as [¹¹C]DASB binding potential (BP_{ND}), were assessed in six brain regions-of-interest (ROIs). Healthy (n=22) and unmedicated participants diagnosed with bipolar disorder (n=16) or major depressive disorder (n=17), aged 18 to 48 years (Mean ± SD, 34 ± 9 yr) underwent PET scanning with [¹¹C]DASB. Subject ascertainment, PET scanning, and analysis were described previously²⁻³. DNA was extracted from peripheral blood and genotyped on the Illumina Human-1 SNP array. Genotypes were called with

Users may view, print, copy, download and text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

Correspondence: Xinmin Liu, Ph.D., The Taub Institute, Columbia University Medical Center, 630 West 168 Street, Black Building 12-1206, New York, NY 10032; Tel: 212-304-5481; x12269@columbia.edu.

*These senior authors contributed equally to the manuscript.

The authors report no conflicts of interest.

BeadStudio v3.0. Data were filtered for minor allele frequencies < 1%, missing genotype rates > 8%, Hardy-Weinberg Equilibrium p-values < 0.05, gender mismatch, and hidden relatedness. A total of 93,427 SNPs passed all quality control filters for all of the ROIs tested. Association analysis was performed by linear regression in PLINK⁴ (v1.02), with 3 covariates to control for ancestry. Genomic Control lambda values were all < 1.05, indicating good control of confounding factors

Overall, 5 SNPs representing 5 different genes met our FDR<0.1 criterion for being declared of interest: rs6741892 in *GALM*, rs390704 near *FRY*, rs7161217 near *TTL5*, rs583241 near *CPLX4*, and rs7095106 near *CASC2*. The strongest association was between thalamic [¹¹C]DASB-BP_{ND} and a coding SNP in the gene *GALM* (rs6741892, $p=4.67\times 10^{-8}$; FDR=0.004). This result meets the threshold of genome-wide significance under typical frequentist assumptions, but not if corrected for 6 ROIs. rs6741892 accounted for about 50% of the variance in [¹¹C]DASB-BP_{ND} in thalamus. Carriers of the “TT” genotype showed the highest [¹¹C]DASB-BP_{ND}.

Since the T-allele frequency differed by self-reported ancestry (10/13 in African-Americans, 3/13 in whites, and 0/7 in Hispanics), we also performed the analysis within each ancestry group, then combined the p-values by meta-analysis (META 5.3, http://userpage.fuberlin.de/~health/meta_e.htm), with similar results. We further confirmed this finding in a voxel-based analysis (Fig 1).

Nominally-significant associations were also observed between rs6741892 and [¹¹C]DASB-BP_{ND} in dorsal cingulate cortex (DCC; $p=4.03\times 10^{-2}$) and insula ($p=1.14\times 10^{-3}$). No SNPs near the gene encoding the 5-HTT (SLC6A4) showed significant association in this sample, consistent with one prior study⁵, but we may have missed a true association due to lack of power. Rs6741892 was also individually genotyped using a modification of the 5' nuclease (Taqman) assay, with similar results.

Consistent with our prior findings²⁻³, we found a significant main effect of diagnosis on [¹¹C]DASB-BP_{ND} measured in thalamus ($F(2, 52)=7.07$, $p<0.002$) due to significantly higher thalamic [¹¹C]DASB-BP_{ND} in participants with mood disorders. However, the overall association results were not dependent on diagnosis: rs6741892 was also associated with [¹¹C]DASB-BP_{ND} in healthy participants.

Supportive evidence of association with rs6741892 was obtained from an independent replication sample of 51 European-ancestry subjects (16 females aged 43±20 yr, 35 males aged 34±18 yr) ascertained in Denmark, using TaqMan. Imaging and analysis were as described⁶. Significant associations were observed between rs6741892 and [¹¹C]DASB-BP_{ND} in DCC ($p=3.5\times 10^{-3}$) and insula ($p=4.9\times 10^{-3}$), but not in thalamus, although [¹¹C]DASB-BP_{ND} is highly correlated across subcortical structures⁷. Combined analysis with META 5.3 supported association between rs6741892 and [¹¹C]DASB-BP_{ND} in all 3 regions of interest (DCC, $p=9.18\times 10^{-4}$; insula, $p=3.25\times 10^{-5}$; and thalamus, $p=4.6\times 10^{-6}$).

GALM encodes galactose mutarotase, which catalyzes the conversion of beta-D-galactose to alpha-D-galactose⁸, important in carbohydrate metabolism and the production of complex oligosaccharides. Galactose mutarotase might affect regional neurophysiology, leading to

local increases in serotonin release and in membrane trafficking of 5-HTT⁹, thereby increasing [¹¹C]DASB-BP_{ND}. Galactose mutarotase may also play a role in N-glycosylation, which is important for surface expression of 5-HTT¹⁰.

To our knowledge, this is the first genome-wide association study of brain 5-HTT. These preliminary results suggest that neuroimaging phenotypes could represent informative targets for a GWAS, even in relatively small samples. Further studies are needed to confirm these findings and determine the underlying biological mechanisms.

Acknowledgments

Funded by the NIMH Intramural Research Program.

References

1. Ichimiya T, Suhara T, Sudo Y, Okubo Y, Nakayama K, Nankai M, et al. *Biological Psychiatry*. 2002; 51(9):715–722. [PubMed: 11983185]
2. Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, et al. *Biol Psychiatry*. 2007; 15(62):870–877. [PubMed: 17678634]
3. Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, et al. *Biol Psychiatry*. 2006; 60(3):207–217. [PubMed: 16875929]
4. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. *American journal of human genetics*. 2007; 81(3):559–575. [PubMed: 17701901]
5. Shioe K, Ichimiya T, Suhara T, Takano A, Sudo Y, Yasuno F, et al. *Synapse*. 2003; 48(4):184–188. [PubMed: 12687637]
6. Kalbitzer J, Frokjaer VG, Erritzoe D, Svarer C, Cumming P, Nielsen FA, et al. *Neuroimage*. 2009; 45(2):280–285. [PubMed: 19135154]
7. Erritzoe D, Holst K, Frokjaer VG, Licht CL, Kalbitzer J, Nielsen FA, et al. *J Neurosci*. 2010; 30(9):3391–3397. [PubMed: 20203198]
8. Frey PA. *Faseb J*. 1996; 10(4):461–470. [PubMed: 8647345]
9. Blakely RD, Ramamoorthy S, Schroeter S, Qian Y, Apparsundaram S, Galli A, et al. *Biol Psychiatry*. 1998; 44(3):169–178. [PubMed: 9693389]
10. Blakely RD, De Felice LJ, Hartzell HC. *J Exp Biol*. 1994; 196:263–281. [PubMed: 7823027]

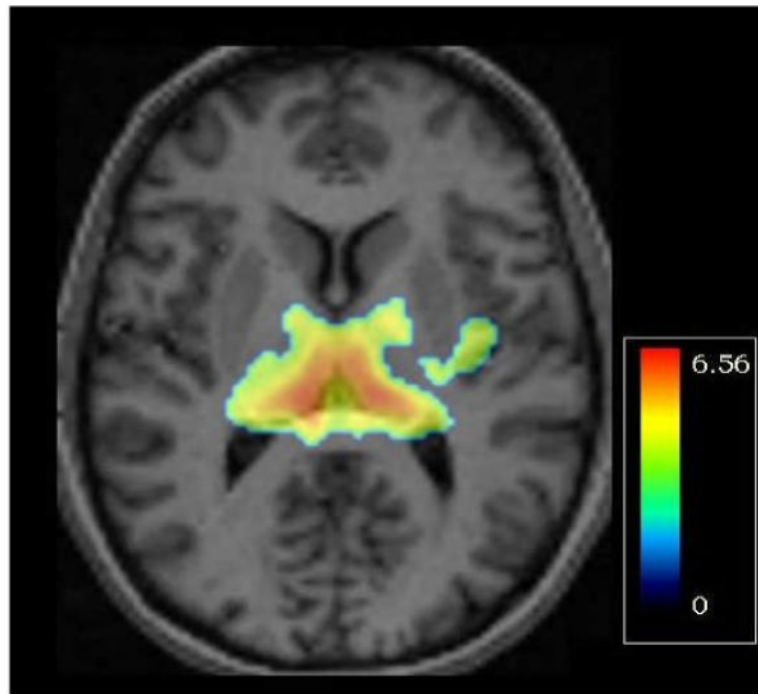


Figure 1.

Map of t-values from voxel-wise analysis of rs6741892, overlaid on a sample axial MRI slice at the level of the medial thalamus ($z=6$ mm). Bilaterally, T-allele carriers ($n=13$) have greater serotonin-transporter binding potential than AA homozygotes ($n=42$). The color bar indicates the range of t-values displayed (max $t = 6.56$, $df=53$, $p=2.3 \times 10^{-8}$).