Published in final edited form as:

Psychiatr Genet. 2016 April ; 26(2): 81–86. doi:10.1097/YPG.0000000000000111.

Lack of Association of SNPs from the *FADS1-FADS2* Gene Cluster with Major Depression or Suicidal Behavior

M. Elizabeth Sublette, M.D., Ph.D.^{1,2,*}, Concepcion Vaquero, Ph.D.³, Enrique Baca-Garcia, M.D., Ph.D.^{1,3,4,5}, Gabriela Pachano, M.D.¹, Yung-yu Huang, M.S.², Maria A. Oquendo, M.D.^{1,2}, and J. John Mann, M.D.^{1,2,6}

¹Department of Psychiatry, Columbia University, NY, NY, USA

²Department of Molecular Imaging & Neuropathology, New York State Psychiatric Institute, NY, NY, USA

³Psychiatry Department, IIS Fundación Jiménez-Díaz Madrid, Spain

⁴CIBERSAM

⁵Universidad Autonoma de Madrid, Spain

⁶Department of Radiology, Columbia University, NY, NY, USA

Abstract

Fatty acid desaturase genes (*FADS1-FADS2*) encode for desaturases participating in biosynthesis of long-chain polyunsaturated fatty acids (LC-PUFAs). Since LC-PUFAs are implicated in major depressive disorder (MDD) and suicide risk, and both are partly heritable, we studied the association of *FADS1-FADS2* polymorphisms with MDD (635 cases, 480 controls), and suicide attempt status (291 attempters, 338 non-attempters). Eighteen *FADS*-related single-nucleotide polymorphisms (SNPs) were genotyped from Caucasians enrolled in Madrid ($n=791$) or New York City ($n=324$), and entered as predictors into logistic regression analyses with diagnostic group or suicide attempt history as outcomes, and covariates location and sex. No associations were observed between any SNPs and diagnosis or attempt status. As statistical power was adequate, we conclude that *FADS1-FADS2* genetic variants may not be a common determinant of MDD.

Keywords

fatty acid desaturase; major depression; suicidal behavior; polyunsaturated fatty acids

*To whom correspondence should be addressed: New York State Psychiatric Institute, 1051 Riverside Drive, Unit 42, NY, NY 10032, Tel: (646) 774 – 7514, Fax: (646) 774 – 7589, es2316@columbia.edu.

Financial Disclosure

Dr. Baca-Garcia is the Lilly Suicide Scholar at Columbia University. Dr. Mann received past unrelated grants from Novartis and GSK, and receives royalties for the Columbia Suicide Severity Rating Scale (C-SSRS) from the Research Foundation for Mental Health. Dr. Oquendo received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire as well as financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year of the salary for a Lilly Suicide Scholar. In addition, her family owns stock in Bristol Myers Squibb. Dr. Sublette received a grant of nutritional supplements from Unicity International for an unrelated study. All other authors have no conflicts of interest to report.

Introduction

The fatty acid desaturase (*FADS1-FADS2*) gene cluster (H. P. Cho, M. Nakamura, & S. D. Clarke, 1999; H. P. Cho, M. T. Nakamura, & S. D. Clarke, 1999), located in a head-to-head orientation on chromosome 11 (11q12 – 13.1), encodes for the 5- and 6-desaturases. These desaturases are key enzymes in the biosynthesis of long-chain polyunsaturated fatty acids (LC-PUFAs) such as docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) from shorter-chain precursor α -linolenic acid (ALA, 18:3n-3) and arachidonic acid (AA, 20:4n-6) from precursor linoleic acid (LA, 18:2n-6) (Sprecher, 1981). The *FADS3* gene shares a high sequence similarity (Marquardt, Stohr, White, & Weber, 2000) but its function is less clear (Blanchard, Boulter-Monthean, Legrand, & Pedrono, 2014; Reardon et al., 2013). Genotyping studies report that genetic variants of *FADS1-FADS2*, together with diet, affect levels of n-3 and n-6 LC-PUFAs in serum phospholipids (Koletzko, Demmelmair, Schaeffer, Illig, & Heinrich, 2008; Malerba et al., 2008; Schaeffer et al., 2006), plasma (Gillingham et al., 2013; Solakivi et al., 2013), erythrocytes (Harslof et al., 2013), and brain (Rizzi et al., 2013). Genetic polymorphisms of *FADS1-FADS2* also are associated with oxidative stress markers (Hong, Kwak, Paik, Chae, & Lee, 2013), peroxidation susceptibility (Solakivi et al., 2013) and risk of coronary artery disease (Li et al., 2013; Molto-Puigmarti et al., 2013), and may act as a moderator for breastfeeding effects on infant intelligence quotient (IQ) (Caspi et al., 2007).

In addition to effects on cardiovascular health and inflammation (Martinelli et al., 2008), LC-PUFAs are critical for normal brain function and impact risk for psychiatric illness. For instance, a meta-analysis finds lower levels of n-3 PUFAs in depressed compared with healthy individuals (Lin, Huang, & Su, 2010). Lower n-3 PUFAs also are seen in suicide attempters, compared with other trauma visitors to the emergency room (Huan et al., 2004), and in suicides among military personnel, compared with other causes of death (Lewis et al., 2011; McNamara et al., 2013). We also have shown, in a small prospective study of patients with major depression, that low levels of DHA predict subsequent suicide attempts (Sublette, Hibbeln, Galfalvy, Oquendo, & Mann, 2006). Furthermore, in comparison with healthy volunteers, patients with bipolar disorder exhibit lower levels of LC-PUFAs DHA and AA (Chiu, 2003) and patients with schizophrenia exhibit lower DHA, AA and docosapentaenoic acid (DPA) (van der Kemp, Klomp, Kahn, Luijten, & Hulshoff Pol, 2012).

LC-PUFA status is regulated through dietary content (Simopoulos, 2011), LC-PUFA breakdown (Evans et al., 2003; Horrobin, Glen, & Vaddadi, 1994; Peet, Laugharne, Rangarajan, Horrobin, & Reynolds, 1995; Ross, Maxwell, & Glen, 2010), and synthesis of LC-PUFAs from LA and ALA. The physiologic importance of the latter pathway is unclear, however, given the low estimated rates of conversion: the proportion of ALA converted to EPA is less than 10% (Emken et al. 1994; Burdge et al. 2002), and to DHA is only about 0.05% (Burdge, Finnegan, Minihane, Williams, & Wootton, 2003; Emken, Adlof, & Gulley, 1994). However, studies in rats under conditions of dietary DHA deficiency find that liver conversion coefficients of ALA to DHA, a measure of increased activity of 5- and 6-desaturases and elongases 2 and 5, can increase as much as 7-fold (S. Rapoport, Rao, & Igarashi, 2007), with liver DHA synthesis that is 30 times in excess of the daily brain DHA

consumption rate, if there is enough ALA from the diet (S. I. Rapoport, Ramadan, & Basselin, 2011). Thus the effects of *FADS1-FADS2* genetic variants on 5- and 6-desaturase activity and phospholipid LC-PUFA levels could have important implications for mental health and disease. Elevated 6-desaturase expression has been demonstrated, *postmortem*, in schizophrenia (Liu, Jandacek, Rider, Tso, & McNamara, 2009), and antipsychotic medications appear to upregulate genes involved in lipid biosynthesis (Ferno et al., 2005; Raeder, Ferno, Vik-Mo, & Steen, 2006) including increased *FADS1-FADS2* mRNA expression in human cell lines (Polymeropoulos et al., 2009).

The expression of *FADS1* is lower in MDD suicides compared with nonpsychiatric controls *postmortem* (Lalovic, Klempan, Sequeira, Luheshi, & Turecki, 2010). Both suicide and major depression are partly heritable (Mann, 2003; Statham et al., 1998) but the specific genes involved remain to be identified. However, genetic variants of *FADS1-FADS2* have not been directly examined in context of depression. Therefore we sought to test whether genetic polymorphisms in *FADS1-FADS2* are associated with major depression and/or suicide attempts.

Method

Sample

Participants were Caucasian adults, aged 18–99 yrs, who provided written informed consent to participate in mood disorders studies at the New York State Psychiatric Institute in New York City ($n=324$) or the Fundacion Jimenez-Diaz in Madrid ($n=791$). The study was approved by the appropriate ethics committees (New York State Psychiatric Institute Institutional Review Board [IRB], Fundacion Jimenez Diaz IRB) and performed in accordance with the Declaration of Helsinki. All participants had a lifetime diagnosis of Major Depressive Disorder (MDD) ($n=635$) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), or were healthy volunteers ($n=480$) with no history of any Axis I or Axis II psychiatric disorders with the exception of simple phobia. MDD diagnosis was established by consensus using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) (First, 2002b) in cases and the SCID non-patient edition (NP) (First, 2002a) for healthy volunteers. MDD participants did not have any other current Axis I disorders except comorbid anxiety disorders, and Axis II disorders were permitted. Participants did not have active medical or neurologic illness at time of enrollment in the study based on history, physical examination, and a battery of standard laboratory tests. History of suicide attempt, defined as a self-destructive act in context of some intent to die (Posner, Oquendo, Gould, Stanley, & Davies, 2007), was assessed using the Columbia Suicide History form (Oquendo, Halberstam, & Mann, 2003). Case and control ascertainment and clinical evaluations were standardized between sites as described previously (Baca-Garcia, Oquendo, Saiz-Ruiz, Mann, & de Leon, 2006). Genetic data from subsets of these research participants have been used in previous studies with different research objectives (Almoguera et al., 2011; Almoguera et al., 2013a, 2013b; Alonso et al., 2008; Baca-Garcia et al., 2005; Baca-Garcia et al., 2003; Baca-Garcia, Vaquero, Diaz-Sastre, Garcia-Resa, et al., 2004; Baca-Garcia, Vaquero, Diaz-Sastre, Jimenez-Trevino, et al., 2004; Baca-Garcia et al., 2002; Baca-Garcia et al., 2007; Baca-Garcia et al., 2010;

Bermudo-Soriano et al., 2009; Blasco-Fontecilla et al., 2013; Costas et al., 2010; Fernandez-Navarro et al., 2012; Gratacos et al., 2009; Lopez-Castroman et al., 2009; Lorenzo et al., 2007; Penas-Lledo et al., 2012; Perroud et al., 2010; Sublette et al., 2008; Vaquero et al., 2004; Vaquero Lorenzo et al., 2006; Vaquero-Lorenzo et al., 2008; Vaquero-Lorenzo et al., 2014; Vaquero-Lorenzo et al., 2009).

Genetic analyses

Genomic DNA was extracted from peripheral blood samples collected from patients and controls using standard protocols (Gnome Whole Blood Kit and BIO 101, Qiogene, Carlsbad, CA, USA). The SNPs were genotyped using high throughput multiplex assays with VeraCode Technology (Illumina®) at the Centro Nacional de Genotipado (CeGen, Madrid, Spain). In addition to our study samples, 90 cell-line DNA samples obtained from the Coriell Institute for Medical Research (Camden, NJ, USA; <http://www.coriell.org/>) were used as internal controls (in duplicate) for the accuracy and validity of the multiplex genotyping. Their genotypes and haplogroup affiliations had previously been determined in the HapMap Project. This control step also had the ability to detect cross-contamination, as sample and replication were located in the same plate in different positions. An additional control step, NTC (Non-Template Control), was also applied to ensure the accuracy of PCR amplification and to detect possible contamination by PCR reagents, employing all the reagents with nuclease-free water instead of DNA samples.

Statistical analyses

Statistical analyses were performed using IBM-SPSS-Statistics (version 22 [Apple, Inc., Cupertino, CA]), and PLINK software version 1.07 (Purcell et al., 2007) (<http://pngu.mgh.harvard.edu/~purcell/plink/download.shtml>; Boston, MA, USA) for association analysis. The association analysis procedure was performed as described previously (Clarke et al., 2011). Briefly, *FADS*-related SNPs were identified from the literature (Schaeffer et al., 2006). Two major hypotheses were tested: (1) To assess whether participants with MDD exhibited differences in *FADS* variants compared with healthy volunteers, separate logistic regression analyses were performed using the 18 identified SNPs as predictors and diagnostic group as outcome. (2) Similarly, to test for suicide attempt-related differences in *FADS* variants within the MDD group, separate logistic regression analyses were performed using the 18 identified SNPs as predictors and suicide attempt group as outcome (suicide attempters vs nonattempters). For each hypothesis, additional separate models were run using the Cochran-Mantel-Haenszel test (2×2×2) including location and sex as covariates. Significance levels were set a priori at $\alpha = 0.05$ after Bonferroni correction for 18 comparison SNPs ($p < 0.003$).

Results

Sample characteristics

Population characteristics are shown in Table 1. In this sample, 72% were from Madrid, the remainder from New York, with an average age of 38.5 yrs in the combined population. The majority of depressed study participants were female (64%), reflecting the gender distribution of the illness, in contrast to 42% of healthy volunteers.

Association Analyses

We genotyped 18 SNPs (see Table 2) identified from public databases and literature concerning *FADS1-FADS2* (Hester et al., 2014; Schaeffer et al., 2006) as potentially relevant based on known associations with human health. All SNPs had minor allele frequencies of at least 5%.

No associations were observed between any of the 18 SNPs and diagnosis of MDD or suicide attempt status, after controlling for location and sex. Statistical power to detect a 15% difference in SNP frequency between depressed and healthy groups was 0.98.

Discussion

Low levels of n-3 LC-PUFAs have been implicated in the pathophysiology of major depression (Lin et al., 2010) and suicidal behavior (Huan et al., 2004; Lewis et al., 2011; McNamara et al., 2013; Sublette et al., 2006), relevant to public health as the dietary intake of n-3 LC-PUFA is currently low in many countries (Hibbeln, Nieminen, Blasbalg, Riggs, & Lands, 2006), including Spain and the United States. Therefore, the conversion of short-chain to LC-PUFA, a compensatory, failsafe mechanism for maintaining EPA and DHA levels in times of deficiency, assumes potential importance. Both psychopathologies and this conversion are partly heritable. Our finding that the presence of *FADS1-FADS2* polymorphisms did not differentiate depressed from healthy volunteer groups, does not support the hypothesis that genetically determined inefficient conversion of precursors to n-3 LC-PUFAs is a major contributor to the incidence of MDD or suicidal behavior. Although our study appears to be adequately powered, we cannot rule out the possibility that there may be subgroups of depressed patients in whom effects of *FADS1-FADS2* polymorphisms have a more profound effect on LC-PUFA status. We sought to reduce stratification effects that may obscure a disease association by confining the subjects and controls to Caucasians and by inclusion of location in the statistical model because New York ethnicities were likely to be more heterogeneous, compared with Spain. Other factors could conceivably confound the *FADS1-FADS2* differences between depressed and controls. For instance, LC-PUFA status is also a determinant of cardiovascular disease via effects on total cholesterol, HDL, LDL and triglyceride concentrations (Standl et al., 2012), and thus the efficacy of $\Delta 5$ and $\Delta 6$ desaturases could be low in atherosclerotic controls as well as in depressed patients, obscuring group differences. A similar confound has been seen in a *postmortem* study (McNamara et al., 2013), in which adult depressed suicides exhibited lower brain DHA concentrations than controls only when controls with cardiovascular disease were excluded. Given the mean age of 38 years in our study population, one might expect that those with genetic predispositions to cardiovascular disease may still be asymptomatic and thereby included in our study.

Limitations

This study did not measure dietary intake or blood levels of PUFA, which could be a confound, since effects of low functioning of $\Delta 5$ and $\Delta 6$ desaturases on depression could be mitigated by high dietary intake of n-3 LC-PUFA. Additionally, it is possible that alternative

SNPs in the FADS1-FADS2 locus, not previously identified as functionally relevant and therefore not measured by us, may impact MDD or suicide risk.

Conclusions

Although the ability for endogenous conversion of short-chain to LC-PUFA has been shown to maintain brain LC-PUFA in times of low dietary LC-PUFA supply, *FADS1-FADS2* genetic polymorphisms known to influence LC-PUFA levels were not associated with MDD or suicide attempts. Thus associations of low n-3 LC-PUFA levels with MDD and suicide risk are likely governed mostly by low dietary availability or other mechanisms such as higher metabolism or epigenetic regulation of biosynthesis.

Acknowledgments

Funding:

This work was funded in part by MH48514 (PI:Oquendo); MH062185 and MH040695 (PI:Mann); and MH079033 (PI:Sublette); Juan de la Cierva Programme JCI-2011-11050 (PI:Vaquero-Lorenzo); National Alliance for Research of Schizophrenia and Affective Disorders (NARSAD) and the Spanish Health Ministry (Instituto de Salud Carlos III PI13/02200 (PI:Baca-Garcia), CIBERSAM (PI:Baca-Garcia).

References

- Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, Dorado P, Lopez-Rodriguez R, Fernandez-Navarro P, Ayuso C. ATA homozygosity in the IL-10 gene promoter is a risk factor for schizophrenia in Spanish females: a case control study. *BMC Med Genet*. 2011; 12:81.10.1186/1471-2350-12-81 [PubMed: 21658228]
- Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, Dorado P, Vaquero-Lorenzo C, Fernandez-Piqueras J, Ayuso C. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. *Pharmacogenomics J*. 2013a; 13(2):197–204.10.1038/tpj.2011.57 [PubMed: 22212732]
- Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, Dorado P, Vaquero-Lorenzo C, Fernandez-Piqueras J, Ayuso C. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. *Pharmacogenet Genomics*. 2013b; 23(11):627–630.10.1097/FPC.0b013e3283659a94 [PubMed: 24026091]
- Alonso P, Gratacos M, Menchon JM, Saiz-Ruiz J, Segalas C, Baca-Garcia E, Estivill X. Extensive genotyping of the BDNF and NTRK2 genes define protective haplotypes against obsessive-compulsive disorder. *Biological Psychiatry*. 2008; 63(6):619–628.10.1016/j.biopsych.2007.06.020 [PubMed: 17884018]
- Baca-Garcia E, Oquendo MA, Saiz-Ruiz J, Mann JJ, de Leon J. A pilot study on differences in aggression in New York City and Madrid, Spain, and their possible impact on suicidal behavior. *Journal of Clinical Psychiatry*. 2006; 67(3):375–380. [PubMed: 16649822]
- Baca-Garcia E, Salgado BR, Segal HD, Lorenzo CV, Acosta MN, Romero MA, de Leon J. A pilot genetic study of the continuum between compulsivity and impulsivity in females: the serotonin transporter promoter polymorphism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2005; 29(5):713–717.10.1016/j.pnpbp.2005.04.019 [PubMed: 15908092]
- Baca-Garcia E, Vaquero C, Diaz-Sastre C, Ceverino A, Saiz-Ruiz J, Fernandez-Piquera J, de Leon J. A pilot study on a gene-hormone interaction in female suicide attempts. *European Archives of Psychiatry and Clinical Neuroscience*. 2003; 253(6):281–285.10.1007/s00406-003-0441-6 [PubMed: 14714116]
- Baca-Garcia E, Vaquero C, Diaz-Sastre C, Garcia-Resa E, Saiz-Ruiz J, Fernandez-Piqueras J, de Leon J. Lack of association between the serotonin transporter promoter gene polymorphism and impulsivity or aggressive behavior among suicide attempters and healthy volunteers. *Psychiatry Research*. 2004; 126(2):99–106.10.1016/j.psychres.2003.10.007 [PubMed: 15123389]

- Baca-Garcia E, Vaquero C, Diaz-Sastre C, Jimenez-Trevino L, Saiz-Ruiz J, Fernandez-Piqueras J, de Leon J. Lack of association between polymorphic variations in the alpha 3 subunit GABA receptor gene (GABRA3) and suicide attempts. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2004; 28(2):409–412.10.1016/j.pnpbp.2003.11.004 [PubMed: 14751442]
- Baca-Garcia E, Vaquero C, Diaz-Sastre C, Saiz-Ruiz J, Fernandez-Piqueras J, de Leon J. A gender-specific association between the serotonin transporter gene and suicide attempts. *Neuropsychopharmacology*. 2002; 26(5):692–695.10.1016/S0893-133X(01)00394-3 [PubMed: 11927194]
- Baca-Garcia E, Vaquero-Lorenzo C, Diaz-Hernandez M, Rodriguez-Salgado B, Dolengevich-Segal H, Arrojo-Romero M, Saiz-Ruiz J. Association between obsessive-compulsive disorder and a variable number of tandem repeats polymorphism in intron 2 of the serotonin transporter gene. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2007; 31(2):416–420.10.1016/j.pnpbp.2006.10.016 [PubMed: 17174018]
- Baca-Garcia E, Vaquero-Lorenzo C, Perez-Rodriguez MM, Gratacos M, Bayes M, Santiago-Mozos R, Oquendo MA. Nucleotide variation in central nervous system genes among male suicide attempters. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B(1):208–213.10.1002/ajmg.b.30975 [PubMed: 19455598]
- Bermudo-Soriano CR, Vaquero-Lorenzo C, Diaz-Hernandez M, Perez-Rodriguez MM, Fernandez-Piqueras J, Saiz-Ruiz J, Baca-Garcia E. SAT-1 -1415T/C polymorphism and susceptibility to schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2009; 33(2):345–348.10.1016/j.pnpbp.2008.12.015 [PubMed: 19162121]
- Blanchard H, Boulrier-Monthean N, Legrand P, Pedrono F. The 51kDa fatty acid desaturase 3 (FADS3) is not microsomal but secreted in the extracellular matrix of hepatocytes and blood in rat. *Journal of Cellular Biochemistry*. 2014; 115:199–207.10.1002/jcb.24651 [PubMed: 23966218]
- Blasco-Fontecilla H, Penas-Lledo E, Vaquero-Lorenzo C, Dorado P, Saiz-Ruiz J, Llerena A, Baca-Garcia E. CYP2D6 Polymorphism and Mental and Personality Disorders in Suicide Attempters. *J Pers Disord*. 2013; 10.1521/pedi_2013_27_080
- Burdge GC, Finnegan YE, Minihane AM, Williams CM, Wootton SA. Effect of altered dietary n-3 fatty acid intake upon plasma lipid fatty acid composition, conversion of [¹³C]alpha-linolenic acid to longer-chain fatty acids and partitioning towards beta-oxidation in older men. *British Journal of Nutrition*. 2003; 90(2):311–321. [PubMed: 12908891]
- Caspi A, Williams B, Kim-Cohen J, Craig IW, Milne BJ, Poulton R, Moffitt TE. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proc Natl Acad Sci USA*. 2007; 104(47):18860–18865.10.1073/pnas.0704292104 [PubMed: 17984066]
- Chiu C. Polyunsaturated fatty acid deficit in patients with bipolar mania. *European Neuropsychopharmacology*. 2003; 13(2):99–103.10.1016/S0924-977X(02)00130-X [PubMed: 12650953]
- Cho HP, Nakamura M, Clarke SD. Cloning, expression, and fatty acid regulation of the human delta-5 desaturase. *Journal of Biological Chemistry*. 1999; 274(52):37335–37339. [PubMed: 10601301]
- Cho HP, Nakamura MT, Clarke SD. Cloning, expression, and nutritional regulation of the mammalian Delta-6 desaturase. *Journal of Biological Chemistry*. 1999; 274(1):471–477. [PubMed: 9867867]
- Clarke GM, Anderson CA, Pettersson FH, Cardon LR, Morris AP, Zondervan KT. Basic statistical analysis in genetic case-control studies. *Nat Protoc*. 2011; 6(2):121–133.10.1038/nprot.2010.182 [PubMed: 21293453]
- Costas J, Gratacos M, Escaramis G, Martin-Santos R, de Diego Y, Baca-Garcia E, Sanjuan J. Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women. *Journal of Psychiatric Research*. 2010; 44(11):717–724.10.1016/j.jpsychires.2009.12.012 [PubMed: 20092830]
- Emken EA, Adlof RO, Gulley RM. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. *Biochimica et Biophysica Acta*. 1994; 1213(3):277–288. [PubMed: 7914092]
- Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. Prostaglandins, leukotrienes, and essential fatty acids. 2003; 69(6):393–399.

- Fernandez-Navarro P, Vaquero-Lorenzo C, Blasco-Fontecilla H, Diaz-Hernandez M, Gratacos M, Estivill X, Baca-Garcia E. Genetic epistasis in female suicide attempters. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2012; 38(2):294–301.10.1016/j.pnpbp.2012.04.014 [PubMed: 22554588]
- Ferno J, Raeder MB, Vik-Mo AO, Skrede S, Glambek M, Tronstad KJ, Steen VM. Antipsychotic drugs activate SREBP-regulated expression of lipid biosynthetic genes in cultured human glioma cells: a novel mechanism of action? *Pharmacogenomics J*. 2005; 5(5):298–304.10.1038/sj.tpj.6500323 [PubMed: 16027736]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002a.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York: Biometrics Research, New York State Psychiatric Institute; 2002b.
- Gillingham LG, Harding SV, Rideout TC, Yurkova N, Cunnane SC, Eck PK, Jones PJ. Dietary oils and FADS1-FADS2 genetic variants modulate [13C]alpha-linolenic acid metabolism and plasma fatty acid composition. *American Journal of Clinical Nutrition*. 2013; 97(1):195–207.10.3945/ajcn.112.043117 [PubMed: 23221573]
- Gratacos M, Costas J, de Cid R, Bayes M, Gonzalez JR, Baca-Garcia E, Carracedo A. Identification of new putative susceptibility genes for several psychiatric disorders by association analysis of regulatory and non-synonymous SNPs of 306 genes involved in neurotransmission and neurodevelopment. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B(6):808–816.10.1002/ajmg.b.30902 [PubMed: 19086053]
- Harslof LB, Larsen LH, Ritz C, Hellgren LI, Michaelsen KF, Vogel U, Lauritzen L. FADS genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants. *American Journal of Clinical Nutrition*. 2013; 97(6):1403–1410.10.3945/ajcn.113.058685 [PubMed: 23636240]
- Hester AG, Murphy RC, Uhlson CJ, Ivester P, Lee TC, Sergeant S, Chilton FH. Relationship between a Common Variant in the Fatty Acid Desaturase (FADS) Cluster and Eicosanoid Generation in Humans. *Journal of Biological Chemistry*. 2014; 289(32):22482–22489.10.1074/jbc.M114.579557 [PubMed: 24962583]
- Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. *American Journal of Clinical Nutrition*. 2006; 83(6 Suppl):1483S–1493S. [PubMed: 16841858]
- Hong SH, Kwak JH, Paik JK, Chae JS, Lee JH. Association of polymorphisms in FADS gene with age-related changes in serum phospholipid polyunsaturated fatty acids and oxidative stress markers in middle-aged nonobese men. *Clin Interv Aging*. 2013; 8:585–596.10.2147/CIA.S42096 [PubMed: 23818766]
- Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. *Schizophrenia research*. 1994; 13(3):195–207. [PubMed: 7841132]
- Huan M, Hamazaki K, Sun Y, Itomura M, Liu H, Kang W, Hamazaki T. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. *Biological Psychiatry*. 2004; 56(7):490–496. [PubMed: 15450784]
- Koletzko B, Demmelmair H, Schaeffer L, Illig T, Heinrich J. Genetically determined variation in polyunsaturated Fatty Acid metabolism may result in different dietary requirements. *Nestle Nutr Workshop Ser Pediatr Program*. 2008; 62:35–49. [pii]. 10.1159/000146246
- Lalovic A, Klempan T, Sequeira A, Luheshi G, Turecki G. Altered expression of lipid metabolism and immune response genes in the frontal cortex of suicide completers. *Journal of Affective Disorders*. 2010; 120(1–3):24–31.10.1016/j.jad.2009.04.007 [PubMed: 19443042]
- Lewis MD, Hibbeln JR, Johnson JE, Lin YH, Hyun DY, Loewke JD. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. *Journal of Clinical Psychiatry*. 2011; 72(4):4088/JCP.11m06879
- Li SW, Lin K, Ma P, Zhang ZL, Zhou YD, Lu SY, Liu SM. FADS gene polymorphisms confer the risk of coronary artery disease in a Chinese Han population through the altered desaturase

- activities: based on high-resolution melting analysis. PLoS ONE. 2013; 8(1):e55869.10.1371/journal.pone.0055869 [PubMed: 23383292]
- Lin PY, Huang SY, Su KP. A Meta-Analytic Review of Polyunsaturated Fatty Acid Compositions in Patients with Depression. *Biological Psychiatry*. 2010; 68(2):140–147. S0006-3223(10)00247-7 [pii]. 10.1016/j.biopsych.2010.03.018 [PubMed: 20452573]
- Liu Y, Jandacek R, Rider T, Tso P, McNamara RK. Elevated delta-6 desaturase (FADS2) expression in the postmortem prefrontal cortex of schizophrenic patients: relationship with fatty acid composition. *Schizophrenia Research*. 2009; 109(1–3):113–120.10.1016/j.schres.2008.12.027 [PubMed: 19195843]
- Lopez-Castroman J, Vaquero-Lorenzo C, Perez-Rodriguez MM, Diaz-Hernandez M, Fernandez-Piqueras J, Saiz-Ruiz J, Baca-Garcia E. Gender effect on association between DRD2 polymorphism and substance dependence in a Spanish sample. *Drug and Alcohol Dependence*. 2009; 101(3):210–212.10.1016/j.drugalcdep.2008.12.011 [PubMed: 19217722]
- Lorenzo CV, Baca-Garcia E, Hernandez MD, Martin CB, Perez-Rodriguez MM, Saiz-Gonzalez MD, de Leon J. No association between the Ser9Gly polymorphism of the dopamine D3 receptor gene and schizophrenia in a Spanish sample. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B(3):344–346.10.1002/ajmg.b.30331 [PubMed: 17171662]
- Malerba G, Schaeffer L, Xumerle L, Klopp N, Trabetti E, Biscuola M, Illig T. SNPs of the FADS gene cluster are associated with polyunsaturated fatty acids in a cohort of patients with cardiovascular disease. *Lipids*. 2008; 43(4):289–299.10.1007/s11745-008-3158-5 [PubMed: 18320251]
- Mann J. Neurobiology of suicidal behaviour. *Nat Rev Neurosci*. 2003; 4(10):819–828.10.1038/nrn1220 [PubMed: 14523381]
- Marquardt A, Stohr H, White K, Weber BH. cDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. *Genomics*. 2000; 66(2):175–183.10.1006/geno.2000.6196 [PubMed: 10860662]
- Martinelli N, Girelli D, Malerba G, Guarini P, Illig T, Trabetti E, Olivieri O. FADS genotypes and desaturase activity estimated by the ratio of arachidonic acid to linoleic acid are associated with inflammation and coronary artery disease. *American Journal of Clinical Nutrition*. 2008; 88(4):941–949. [PubMed: 18842780]
- McNamara RK, Jandacek R, Tso P, Dwivedi Y, Ren X, Pandey GN. Lower docosahexaenoic acid concentrations in the postmortem prefrontal cortex of adult depressed suicide victims compared with controls without cardiovascular disease. *Journal of Psychiatric Research*. 2013; 47(9):1187–1191.10.1016/j.jpsychires.2013.05.007 [PubMed: 23759469]
- Molto-Puigmarti C, Jansen E, Heinrich J, Standl M, Mensink RP, Plat J, Thijs C. Genetic variation in FADS genes and plasma cholesterol levels in 2-year-old infants: KOALA Birth Cohort Study. *PLoS ONE*. 2013; 8(5):e61671.10.1371/journal.pone.0061671 [PubMed: 23667444]
- Oquendo, MA.; Halberstam, B.; Mann, JJ. Risk factors for suicidal behavior: utility and limitations of research instruments. In: First, MB., editor. *Standardized Evaluation in Clinical Practice*. Vol. 22. Washington, D.C: APPI Press; 2003. p. 103-130.
- Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. *Journal of psychiatric research*. 1995; 29(3):227–232. [PubMed: 7473298]
- Penas-Lledo EM, Blasco-Fontecilla H, Dorado P, Vaquero-Lorenzo C, Baca-Garcia E, Llerena A. CYP2D6 and the severity of suicide attempts. *Pharmacogenomics*. 2012; 13(2):179–184.10.2217/pgs.11.146 [PubMed: 22141351]
- Perroud N, Salzmann A, Saiz PA, Baca-Garcia E, Sarchiapone M, Garcia-Portilla MP, Malafosse A. Rare genotype combination of the serotonin transporter gene associated with treatment response in severe personality disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B(8):1494–1497.10.1002/ajmg.b.31118 [PubMed: 20862697]
- Polymeropoulos MH, Licamele L, Volpi S, Mack K, Mitkus SN, Carstea ED, Lavedan C. Common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol supports a key role of lipid homeostasis in schizophrenia. *Schizophrenia Research*. 2009; 108(1–3):134–142.10.1016/j.schres.2008.11.025 [PubMed: 19150222]

- Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *American Journal of Psychiatry*. 2007; 164(7):1035–1043.10.1176/ajp.2007.164.7.1035 [PubMed: 17606655]
- Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*. 2007; 81(3):559–575.10.1086/519795 [PubMed: 17701901]
- Raeder MB, Ferno J, Vik-Mo AO, Steen VM. SREBP activation by antipsychotic- and antidepressant-drugs in cultured human liver cells: relevance for metabolic side-effects? *Molecular and Cellular Biochemistry*. 2006; 289(1–2):167–173.10.1007/s11010-006-9160-4 [PubMed: 16718372]
- Rapoport SI, Ramadan E, Basselin M. Docosahexaenoic acid (DHA) incorporation into the brain from plasma, as an in vivo biomarker of brain DHA metabolism and neurotransmission. *Prostaglandins and Other Lipid Mediators*. 2011; 96(1–4):109–113.10.1016/j.prostaglandins.2011.06.003 [PubMed: 21704722]
- Rapoport S, Rao J, Igarashi M. Brain metabolism of nutritionally essential polyunsaturated fatty acids depends on both the diet and the liver. *Prostaglandins Leukotrienes and Essential Fatty Acids*. 2007; 77(5–6):251–261.10.1016/j.plefa.2007.10.023
- Reardon HT, Hsieh AT, Park WJ, Kothapalli KS, Anthony JC, Nathanielsz PW, Brenna JT. Dietary long-chain polyunsaturated fatty acids upregulate expression of FADS3 transcripts. *Prostaglandins Leukotrienes and Essential Fatty Acids*. 2013; 88(1):15–19.10.1016/j.plefa.2012.02.003
- Rizzi TS, van der Sluis S, Derom C, Thiery E, van Kesteren RE, Jacobs N, Posthuma D. Genetic Variance in Combination with Fatty Acid Intake Might Alter Composition of the Fatty Acids in Brain. *PLoS ONE*. 2013; 8(6):e68000.10.1371/journal.pone.0068000 [PubMed: 23826354]
- Ross BM, Maxwell R, Glen I. Increased breath ethane levels in medicated patients with schizophrenia and bipolar disorder are unrelated to erythrocyte omega-3 fatty acid abundance. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010 S0278-5846(10)00463-X [pii]. 10.1016/j.pnpbp.2010.11.032
- Schaeffer L, Gohlke H, Müller M, Heid IM, Palmer LJ, Kompauer I, Heinrich J. Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. *Human Molecular Genetics*. 2006; 15(11):1745–1756.10.1093/hmg/ddl117 [PubMed: 16670158]
- Simopoulos AP. Evolutionary aspects of diet: the omega-6/omega-3 ratio and the brain. *Molecular Neurobiology*. 2011; 44(2):203–215.10.1007/s12035-010-8162-0 [PubMed: 21279554]
- Solakivi T, Kunnas T, Jaakkola O, Renko J, Lehtimäki T, Nikkari ST. Delta-6-desaturase gene polymorphism is associated with lipoprotein oxidation in vitro. *Lipids Health Dis*. 2013; 12:80.10.1186/1476-511X-12-80 [PubMed: 23721366]
- Sprecher H. Biochemistry of essential fatty acids. *Progress in Lipid Research*. 1981; 20:13–22. [PubMed: 7342077]
- Standl M, Lattka E, Stach B, Koletzko S, Bauer CP, von Berg A, Heinrich J. FADS1 FADS2 gene cluster, PUFA intake and blood lipids in children: results from the GINIplus and LISAplus studies. *PLoS ONE*. 2012; 7(5):e37780.10.1371/journal.pone.0037780 [PubMed: 22629455]
- Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, Martin NG. Suicidal behaviour: an epidemiological and genetic study. *Psychological Medicine*. 1998; 28(4):839–855. [PubMed: 9723140]
- Sublette ME, Baca-Garcia E, Parsey R, Oquendo M, Rodrigues SM, Galfalvy H, Mann JJ. Effect of BDNF val66met polymorphism on age-related amygdala volume changes in healthy subjects. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2008; 32(7):1652–1655.10.1016/j.pnpbp.2008.06.009 [PubMed: 18621091]
- Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *American Journal of Psychiatry*. 2006; 163(6):1100–1102. [PubMed: 16741213]
- van der Kemp WJ, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE. A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia. *Schizophrenia Research*. 2012; 141(2–3):153–161.10.1016/j.schres.2012.08.014 [PubMed: 22981812]

- Vaquero C, Baca-Garcia E, Diaz-Sastre C, Perez-Rodriguez MM, Navio Acosta M, Saiz-Ruiz J, Fernandez-Piqueras J. New GABAA receptor alpha5 subunit gene polymorphism that may confound genotyping. *Am J Med Genet B Neuropsychiatr Genet.* 2004; 129B(1):27–28.10.1002/ajmg.b.30048 [PubMed: 15274034]
- Vaquero Lorenzo C, Baca-Garcia E, Diaz-Hernandez M, Botillo-Martin C, Perez-Rodriguez MM, Fernandez-Ramos C, de Leon J. Association between the T102C polymorphism of the serotonin-2A receptor gene and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2006; 30(6):1136–1138.10.1016/j.pnpbp.2006.04.027 [PubMed: 16762472]
- Vaquero-Lorenzo C, Baca-Garcia E, Diaz-Hernandez M, Perez-Rodriguez MM, Fernandez-Navarro P, Giner L, Oquendo MA. Association study of two polymorphisms of the serotonin-2A receptor gene and suicide attempts. *Am J Med Genet B Neuropsychiatr Genet.* 2008; 147B(5):645–649.10.1002/ajmg.b.30642 [PubMed: 18163387]
- Vaquero-Lorenzo C, Lopez-Castroman J, Bermudo-Soriano CR, Saiz-Ruiz J, Fernandez-Piqueras J, Baca-Garcia E. Putative association between the -1415 T/C polymorphism of spermidine/spermine N1-acetyltransferase (SSAT1) gene and alcohol use disorders in women and men. *American Journal of Drug and Alcohol Abuse.* 2014; 40(3):240–243.10.3109/00952990.2014.891039 [PubMed: 24735382]
- Vaquero-Lorenzo C, Riaza Bermudo-Soriano C, Perez-Rodriguez MM, Diaz-Hernandez M, Lopez-Castroman J, Fernandez-Piqueras J, Baca-Garcia E. Positive association between SAT-1 -1415T/C polymorphism and anxiety. *Am J Med Genet B Neuropsychiatr Genet.* 2009; 150B(4):515–519.10.1002/ajmg.b.30850 [PubMed: 18759322]

Table 1

Characterization of the New York – Madrid study population.

	Madrid			New York			Total		
	Total	MDD	HV	Total	MDD	HV	Total	MDD	HV
Participants	791	377	414	324	258	66	1115	635	480
Suicide attempters (%)		203 (54%)	-		88 (34%)	-		291 (46%)	-
Male (%)	376 (48%)	134 (36%)	242 (58%)	126 (39%)	89 (34%)	37 (56%)	502 (45%)	223 (35%)	279 (58%)
Mean age (SD)	38.1 (13.3)	40.6 (12.6)	35.5 (14.6)	39.6 (13.1)	40.5 (14.7)	35.6 (11.3)	38.5 (13.3)	40.6 (13.9)	35.5 (11.8)

Table 2
Genotype frequencies of *FADS1 FADS2* polymorphisms in the New York – Madrid study populations.

Percentage of participants with genotype														
SNP	Major/minor Alleles (M/m)	MDD			MDD Suicide Attempters			MDD Suicide Non-attempters			Controls			Minor Allele Frequency ^d
		MM	Mm	mm	MM	Mm	mm	MM	Mm	mm	MM	Mm	mm	
<i>FADS1</i>														
rs174537	G/T	46.62	42.44	10.93	47.87	42.20	9.93	45.81	42.81	11.38	47.07	41.63	11.30	T=0.3029
rs174545	C/G	46.99	42.24	10.76	48.10	42.56	9.34	46.29	42.14	11.57	46.75	41.93	11.32	G=0.2979
rs174546	C/T	47.08	42.18	10.74	48.10	42.56	9.34	46.45	42.01	11.54	47.49	41.21	11.30	T=0.2975
rs174547	T/C	47.30	42.22	10.48	48.60	42.31	9.09	46.45	42.31	11.24	47.17	41.51	11.32	C=0.2979
rs174556	C/T	54.78	37.26	7.96	55.24	38.11	6.64	54.76	36.61	8.63	53.46	40.25	6.29	T=0.2796
rs174561	T/C	55.01	37.43	7.56	56.33	37.55	6.12	54.12	37.63	8.24	54.10	39.25	6.65	C=0.2796
<i>FADS2</i>														
rs174568	C/T	47.53	41.63	10.85	48.60	41.95	9.44	46.87	41.49	11.64	47.18	41.54	11.27	T=0.2961
rs174570	C/T	71.95	24.56	3.49	72.66	23.88	3.46	71.72	25.30	2.98	70.83	27.71	1.46	T=0.2282
rs174583	C/T	43.06	42.74	14.20	45.02	42.27	12.71	41.54	43.32	15.13	42.50	44.38	13.12	T=0.3686
rs174589	G/C	64.63	31.99	3.38	66.43	30.39	3.18	63.36	33.03	3.60	66.18	28.57	5.25	C=0.1344
rs174602	A/G	55.56	37.78	6.67	58.13	37.72	4.15	53.43	38.21	8.36	57.32	38.08	4.60	G=0.4229
rs174620	T/C	28.25	52.38	19.37	28.72	51.56	19.72	27.16	53.43	19.40	33.05	46.86	20.08	G=0.3411
rs2072114	A/G	76.74	20.89	2.37	77.24	20.34	2.41	76.49	21.43	2.08	74.53	24.42	1.05	G=0.1949
rs2524299	A/T	75.55	21.77	2.68	76.98	19.93	3.09	74.48	23.44	2.08	73.28	25.26	1.46	T=0.2057
rs526126	C/G	64.07	31.80	4.13	65.97	29.51	4.51	61.79	34.33	3.88	63.96	30.83	5.21	G=0.3199
rs968567	G/A	76.27	21.68	2.06	77.08	21.87	1.04	75.44	21.60	2.96	74.48	23.64	1.88	A=0.0527
rs99780	C/T	43.06	43.06	13.88	45.14	43.06	11.81	41.44	43.24	15.32	42.59	44.68	12.73	T=0.3974
<i>FADS2-FADS3 Intergenic</i>														
rs174627	C/T	78.21	20.35	1.43	79.86	18.06	2.08	76.72	22.39	0.90	75.73	23.43	0.84	T=0.0535

^aData obtained from <http://www.ncbi.nlm.nih.gov/snp>.