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Original article

The lipidome in major depressive disorder: Shared genetic influence for ether-phosphatidylcholines, a plasma-based phenotype related to inflammation, and disease risk

E.E.M. Knowles [a,*], K. Huynh [b], P.J. Meikle [b], H.H.H. Göring [c], R.L. Olvera [d], S.R. Mathias [a], R. Duggirala [c], L. Almasy [c], J. Blangero [c], J.E. Curran [c], D.C. Glahn [a,e]

[a] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[b] Baker Heart and Diabetes Institute, Melbourne, Australia
[c] South Texas Diabetes and Obesity Institute, University of Texas Rio Grande Valley School of Medicine, Brownsville, TX, USA
[d] Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[e] Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital, Hartford, CT, USA

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ABSTRACT

Background: The lipidome is rapidly garnering interest in the field of psychiatry. Recent studies have implicated lipidomic changes across numerous psychiatric disorders. In particular, there is growing evidence that the concentrations of several classes of lipids are altered in those diagnosed with MDD. However, for lipidomic abnormalities to be considered potential treatment targets for MDD (rather than secondary manifestations of the disease), a shared etiology between lipid concentrations and MDD should be demonstrated.

Methods: In a sample of 567 individuals from 37 extended pedigrees (average size 13.57 people, range = 3–80), we used mass spectrometry lipidomic measures to evaluate the genetic overlap between twenty-three biologically distinct lipid classes and a dimensional scale of MDD.

Results: We found that the lipid class with the largest endophenotype ranking value (ERV, a standardized parametric measure of pleiotropy) were ether-phosphodatidylcholines (alkylphosphatidylcholine, PC(O) and alkenylphosphatidylcholine, PC(P) subclasses). Furthermore, we examined the cluster structure of the twenty-five species within the top-ranked lipid class, and the relationship of those clusters with MDD. This analysis revealed that species containing arachidonic acid generally exhibited the greatest degree of genetic overlap with MDD.

Conclusions: This study is the first to demonstrate a shared genetic etiology between MDD and ether-phosphatidylcholine species containing arachidonic acid, an omega-6 fatty acid that is a precursor to inflammatory mediators, such as prostaglandins. The study highlights the potential utility of the well-characterized linoleic/arachidonic acid inflammation pathway as a diagnostic marker and/or treatment target for MDD.

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1. Introduction

Major Depressive Disorder (MDD) is a common and potentially life-threatening disorder of mood [1]. It affects 16.2% of individuals in the US during their lifetime [2] and as such it incurs great economic cost ($83.1 billion per annum in the US) [3]. This is not to mention the personal cost where the impact of MDD on well being and functioning is in line with that seen in arthritis and diabetes mellitus [4]. Moreover, functional impairments remain after the remission of a depressive episode [5]. Unsurprisingly, the World Health Organization (WHO) cites MDD as a leading cause of disability worldwide [6]. However, despite decades of research, the etiology of the illness remains largely unknown.

Lipidomic alterations have been reported in numerous psychiatric disorders, including schizophrenia [7], autism [8,9], and bipolar disorder [10–12]. In particular, changes in the lipidome (the complete lipid profile of an organism) have been most consistently associated with MDD [13]. The first indication of this association came from early trials of statins, statins are

* Corresponding author.
E-mail address: emknowles@gmail.com (E.E.M. Knowles).

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cholesterol-lowering drugs prescribed to individuals with increased lipid levels [14]. During the statin trials, the lipid-lowering benefits of statin therapy (i.e. reduced cardiovascular disease risk) were offset, in some cases, by an increase in suicidality [15–20]. Though, it should be noted that others have reported beneficial effects of statins on depressive symptomatology when combined with anti-depressant medications including SSRIs [21,22]. The obvious overlap between suicidality and MDD led some to propose a direct link between lipids and MDD. Indeed, subsequent studies have reported differences between depressed and healthy subjects in the concentrations of fatty acids in both animal models of depression [23–27] and also in clinical populations of humans [28–31]; and also alterations in lipid classes including phospholipids (e.g., phosphatidylcholines [PCs], lysophosphatidylcholines [LPCs], lysophosphatidylethanolamine [LPEs], phosphatidylethanolamines [PEs], sphingolipids, and cholesterol esters) [32–35]. However, despite strong evidence linking lipid concentrations and MDD, it is currently unclear whether the lipidomic alterations observed in MDD are secondary to the manifestation of the illness or its treatment, or whether lipid concentrations are related to the genetic predisposition for depression. If the latter supposition were true, lipids could be considered a promising diagnostic and/or treatment target for MDD.

In the present study, we aimed to provide evidence for a shared etiology between lipidomic concentrations and MDD, and determine which lipid classes, and which species within those classes, might be most informative when attempting to isolate potential diagnostic and treatment targets for MDD. To achieve these aims we completed three steps:

- we ranked sum concentrations of twenty-three lipid classes by their genetic overlap with MDD and isolated those classes with the greatest degree of overlap;
- we took the top-ranked lipid classes and investigated the structure of the species within them using cluster analysis;
- we evaluated the degree of genetic overlap between each species cluster and MDD in an attempt to characterize the relationships between the lipids and MDD at the species level.

2. Methods

2.1. Participants

Lipidomic and psychiatric data were available from a total 567 participants from 37 families (average family size = 13.57, range = 3–80) the sample was 64% female and had a mean age of 49.47 years (SD = 13.31, range = 27–97). The lipidomic data was collected as part of the San Antonio Family Study (SAFS), diagnostic data were also available in these same individuals as part of assessments conducted in overlapping individuals as part of the Genetics of Brain Structure and Function (GOBS) study. GOBS data collection occurred between 2006 and 2016. Individuals from the SAFS cohort have actively participated in research for over 18 years. Participants were randomly selected from the community with the constraints that they were of Mexican American ancestry, part of a large family, and lived in the San Antonio, TX, region. All participants provided written informed consent in compliance with the institutional review board at the University of Texas Health Science Center of San Antonio [36].

2.2. Continuous index of MDD

All participants received the Mini-International Neuropsychiatric Interview (MINI) [37], a semi-structured interview augmented to include items on lifetime diagnostic history. Masters- and doctorate-level research staff, with established reliability for diagnosing affective disorders ($\kappa \geq 0.85$), conducted the interviews. All subjects with possible psychopathology were discussed in case conferences that included licensed psychologists or psychiatrists. Lifetime consensus diagnoses were determined based on available medical records, the MINI interview, and the interviewer's narrative. Consistent with previous work [38], all items from the Past Major Depressive Episode (A3a-g) section of the MINI were entered into a confirmatory factor analysis with a single factor, and maximum-likelihood estimates of the latent factor scores were used as the dimensional scale of MDD. In our previous study, we demonstrated that this continuous index conferred multiple advantages for gene-finding efforts over the conventional dichotomous (present-absent) diagnosis of MDD (for details, see [38]). Using conventional diagnoses, 216 individuals endorsed a major depressive episode in their lifetime while 115 had experienced two or more episodes (recurrent MDD).

2.3. Lipid extraction and analysis procedure

The lipid extraction procedure used in this sample has been described in detail elsewhere (see [39,40]). Briefly, the San Antonio Family study is part of an ongoing longitudinal observational investigation comprising four phases of data collection during a 23-year period. The plasma samples used for lipidomic analysis in the present study were collected during the first phase, between the years 1992–1996. The order of the plasma samples was randomized prior to lipid extraction and analysis. Quality control plasma samples were included at a ratio of 1:18. Total lipid extraction from a 10 mL aliquot of plasma was performed by a single phase chloroform:methanol (2:1) extraction after the addition of 15 μL of internal standard mix containing 16 non-physiological or stable isotope lipid standards (Supplementary Table 1) [41].

Lipid analysis was performed by liquid chromatography, electrospray ionisation-tandem mass spectrometry using an Agilent 1200 liquid chromatography system combined with an Applied Biosystems API 4000 Q/TRAP mass spectrometer with a turboionspray source (350 °C) and Analyst 1.5 data system [41]. Liquid chromatography was performed on a Zorbax C18, 1.8 μm, 50 $\times$ 2.1 mm column (Agilent Technologies) using the following gradient conditions (300 μL/min) 0% solvent B to 100% solvent B over 8.0 min, 2.5 min at 100% solvent B, a return to 0% solvent B over 0.5 min then 10.5 min at 0% solvent B prior to the next injection. Diacylglycerol (DG) and triacylglycerol (TG) species (1 μL injection) were analyzed in a separate chromatographic run using an isocratic flow (100 μL/min) of 85% solvent B over 6 min. Solvents A and B consisted of tetrahydrofuran:methanol:water in the ratio (30:20:50) and (75:20:5) respectively, both containing 10 mM ammonium formate. Columns were heated to 50 °C and the auto-sampler regulated to 25 °C. All other lipid species (5 μL injection) were separated under gradient conditions.

Multiple reaction monitoring (MRM) experiments were used to analyses lipid species in the following classes and subclasses: dihydroceramide (dhCer), ceramide (Cer), monohexosylceramide (MHC), dihexosylceramide (DHC), trihexosylcermide (THC), GM3 ganglioside (GM3), sphingomyelin (SM), phosphatidylcholine (PC), alkylphosphatidylcholine (PC(O)), alkenylphosphatidylcholine (plasmalogen, PC(P)), lysophosphatidylcholine (LPC), lysoalkylphosphatidylcholine (lysoplatelet activating factor, LPC(O)), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylglycerol (PG), cholesterol ester (CE), free cholesterol (COH), diacylglycerol (DG) and triaclyglycerol (TG) [41–43]. A total of 65 diacylglycerol and triacylglycerol species and 257 other lipid species were analyzed. The mass spectrometry conditions are shown in Supplementary Table 1. The listed abbreviations are used to refer to individual lipid species e.g.

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