Journal of Psychiatric Research xxx (2013) 1–9

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A genome-wide association study of a sustained pattern of antidepressant response

Aimee M. Hunter [a,*], Andrew F. Leuchter [a], Robert A. Power [b], Bengt Muthén [c], Patrick J. McGrath [d], Cathryn M. Lewis [b], Ian A. Cook [a], Holly A. Garriock [e,f], Peter McGuffin [b], Rudolf Uher [b,g], Steven P. Hamilton [e]

[a] Department of Psychiatry, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, USA
[b] Institute of Psychiatry, King's College London, UK
[c] UCLA Graduate School of Education & Information Studies, USA
[d] Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, USA
[e] Department of Psychiatry, Institute for Human Genetics, University of California, San Francisco, USA
[f] National Institute of Mental Health (NIMH), Division of Developmental Trajectories, USA
[g] Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

ARTICLE INFO

Article history:
Received 25 January 2013
Received in revised form
25 March 2013
Accepted 2 May 2013

Keywords:
Antidepressant
Genetics
STAR*D
GENDEP
Growth mixture modeling
Citalopram

ABSTRACT

Genome-wide association studies (GWAS) have failed to replicate common genetic variants associated with antidepressant response, as defined using a single endpoint. Genetic influences may be discernible by examining individual variation between sustained versus unsustained patterns of response, which may distinguish medication effects from non-specific, or placebo responses to active medication. We conducted a GWAS among 1116 subjects with Major Depressive Disorder from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial who were characterized using Growth Mixture Modeling as showing a sustained versus unsustained pattern of clinical response over 12 weeks of treatment with citalopram. Replication analyses examined 585 subjects from the Genome-based Therapeutic Drugs for Depression (GENDEP) trial. The strongest association with sustained as opposed to unsustained response in STAR*D involved a single nucleotide polymorphism (SNP; rs10492002) within the acyl-CoA synthetase short-chain family member 3 gene (*ACSS3*, p-value $= 4.5 \times 10^{-6}$, odds ratio $= 0.61$). No SNPs met our threshold for genome-wide significance. SNP data were available in GENDEP for 18 of the top 25 SNPs in STAR*D. The most replicable association was with SNP rs7816924 ($p = 0.008$, OR $= 1.58$); no SNP met the replication p-value threshold of 0.003. Joint analysis of these 18 SNPs resulted in the strongest signal coming from rs7816924 ($p = 2.11 \times 10^{-7}$), which resides in chondroitin sulfate N-acetylgalactosaminyltransferase 1 gene (*CSGALNACT1*). An exploratory genetic pathway analysis revealed evidence for an involvement of the KEGG pathway of long-term potentiation (FDR $= .02$). Results suggest novel genetic associations to sustained response.

1. Introduction

Treatment with antidepressant medications is associated with significant improvements in clinical symptoms of Major Depressive Disorder (MDD), as well as improvements in functional status and quality of life. However, there is marked heterogeneity of outcomes including a subset of patients who show unsustained response (Muthén et al., 2011; Quitkin et al., 1984). Inter-individual variation in antidepressant response is under genetic influence (Tansey et al., 2012a), yet no genetic marker has shown a consistent association with clinical outcome (Tansey et al., 2012b; Uher et al., 2013). Limited progress in predicting drug efficacy may be in part due to heterogeneity in MDD related to complex gene–environment etiology (Keers and Aitchison, 2011), or the inability to separate specific response to antidepressants from naturalistic course or placebo response (Malhotra, 2010; Malhotra et al., 2012), among other factors.

The discovery of predictors of clinical response may also depend critically on the classification of outcomes. MDD trials commonly define outcomes using a predetermined cutoff score assessed at a

* Corresponding author. Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Rm. 57-455, Los Angeles, CA 90024-1759, USA. Tel.: +1 310 206 2237.
E-mail address: amhunter@ucla.edu (A.M. Hunter).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.05.002

single primary endpoint. This approach fails to account for patterns of change in clinical symptoms over time (Muthén et al., 2008) and may not reflect clinically or physiologically meaningful distinctions (Uher et al., 2010a,b). Clinical changes over time are especially relevant when subjects exhibit alternating improvement and worsening of symptoms (Hunter et al., 2010) or a U-shaped pattern of outcome (Muthén et al., 2011; Quitkin et al., 1984). Unsustained response is clinically undesirable and may represent a "placebo" response rather than a "true drug" effect (Quitkin et al., 1984). Insofar as differences between sustained and unsustained response patterns may reflect a physiological substrate, it is of interest to examine these phenotypes for genetic association.

Advanced statistical modeling techniques have identified various response patterns, including unsustained response during acute antidepressant treatment. Growth mixture modeling (GMM) is a systematic, data-driven approach that utilizes symptom severity measures from all available time points to identify distinct trajectories of response; cluster analytic features are incorporated into GMM to reveal latent "classes" or patterns of change in symptom severity over time (Muthén and Asparouhov, 2009; Muthén and Shedden, 1999). Such techniques have been successfully applied to longitudinal data to identify response patterns of clinical relevance during pharmacotherapy interventions in MDD (Gueorguieva et al., 2011; Hunter et al., 2010; Muthén et al., 2011; Power et al., 2012; Uher et al., 2009, 2010a,b, 2011).

GMM was recently applied to data from the Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D) (Trivedi et al., 2006), a large open-label multi-site study that, because of its size and inclusion of "real world" patients, is especially well suited to this technique. Analyses that examined all available scores on the 16-item clinician-rated Quick Inventory of Depressive Symptoms (QIDS-C) (Rush et al., 2003b) obtained at baseline and over 12 weeks during Level 1 treatment with citalopram yielded fundamental trajectory shapes providing evidence of four classes: 'non-responders'; 'partial improvers'; 'sustained responders' (SUS) showing monotonic improvement culminating in response at week 12; and 'unsustained responders' (UNS), showing U-shaped response-level improvement by week 6 but with a return of baseline-level symptoms by week 12 (Fig. 1) (Muthén et al., 2011). SUS and UNS responder class sizes ranged from 32% to 45%, and 6% to19%, respectively, depending on the model (Muthén et al., 2011).

We hypothesize that sustained and unsustained response trajectories represent biologically distinct types of response to antidepressants. To test this hypothesis, we conducted a genome-wide association study (GWAS) contrasting STAR*D subjects in SUS versus UNS response trajectory classes to determine whether common DNA variation determines durability of response to antidepressant treatment. Identification of individuals unlikely to sustain antidepressant response would have great clinical utility, providing incentive for aggressive optimization of treatment in susceptible individuals.

2. Methods and materials

2.1. Overview

GWAS was conducted in the STAR*D dataset to test for association between single-locus SNP variants and durability of response ('sustained' versus 'unsustained' response class outcomes defined using GMM). SNPs with the strongest association were then examined prospectively for replication in subjects from the Genome-based Therapeutic Drugs for Depression (GENDEP) study. Secondary, gene-based analyses were conducted to determine the association between combined effects of SNPs within individual genes and response durability. A third, exploratory level of analysis examined: 1) the combined effects of SNPs in functionally related genes i.e., 'gene set enrichment analysis,' and 2) aggregate effects of SNPs (across genes) found in our STAR*D GWAS to have the strongest statistical association with the sustained-unsustained response phenotype, i.e., 'SNP profile scoring' analysis. This scoring algorithm was then tested in the GENDEP sample.

2.2. Subjects – STAR*D-based analysis

STAR*D enrolled treatment-seeking adults from primary care and psychiatric outpatient settings across the United States, meeting DSM-IV criteria for non-psychotic MDD and having a score ≥ 14 on the 17-item Hamilton Depression Rating Scale (HAM-D). Included were subjects having psychiatric and other medical comorbidities other than those which were either contraindicated by the protocol medications (e.g. bulimia nervosa), or would specify alternative treatment (e.g. primary obsessive compulsive disorder). Enrollees had a mean entry score > 21 on the HAM-D indicating moderate-to-severe depression (Trivedi et al., 2006). In Level 1, all subjects received flexible, manualized, measurement-based treatment with citalopram (60 mg/day maximum final dose) for up to 14 weeks based upon clinical response and side effects evaluated at weeks 2, 4, 6, 9, and 12. Patient care and evaluation were coordinated through investigators at 14 Regional Centers who provided protocol implementation oversight. Details of the STAR*D trial design and conduct (Fava et al., 2003; Rush et al., 2003a; Trivedi et al., 2006) have been described elsewhere. DNA samples were collected according to the STAR*D protocol as described previously (Kraft et al., 2007).

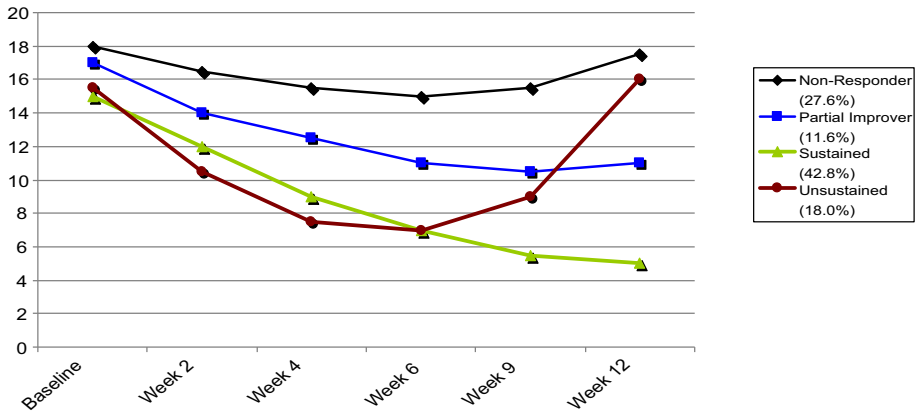

Fig. 1. Estimated mean QIDS-C scores (y-axis) across 12 weeks of citalopram treatment (x-axis) for four classes of subjects in STAR*D[2].

Please cite this article in press as: Hunter AM, et al., A genome-wide association study of a sustained pattern of antidepressant response, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.05.002