Journal of Psychiatric Research xxx (2015) 1–7

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Identifying genetic loci associated with antidepressant drug response with drug–gene interaction models in a population-based study

Raymond Noordam [a, b], Nese Direk [b], Colleen M. Sitlani [c], Nikkie Aarts [a, b], Henning Tiemeier [b, d, e], Albert Hofman [b, j], André G. Uitterlinden [a, j], Bruce M. Psaty [f, g], Bruno H. Stricker [a, b, h, j, *], Loes E. Visser [a, b, i]

[a] Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[b] Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[c] Department of Medicine, University of Washington, Seattle, WA, USA
[d] Department of Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[e] Department of Child and Adolescent Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[f] Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA
[g] Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA
[h] Inspectorate of Health Care, The Hague, The Netherlands
[i] Apotheek Haagse Ziekenhuizen, HAGA, The Hague, The Netherlands
[j] The Netherlands Genomics Initiative-Sponsored Netherlands Consortium for Healthy Aging (NGI-NCHA), Leiden/Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 16 October 2014
Received in revised form
6 January 2015
Accepted 12 January 2015

Keywords:
Genome-wide association study
Serotonin uptake inhibitors
Pharmacogenetics
Gene–environment interaction
Drug response biomarkers

ABSTRACT

It has been difficult to identify genes affecting drug response to Selective Serotonin Reuptake Inhibitors (SSRIs). We used multiple cross-sectional assessments of depressive symptoms in a population-based study to identify potential genetic interactions with SSRIs as a model to study genetic variants associated with SSRI response. This study, embedded in the prospective Rotterdam Study, included all successfully genotyped participants with data on depressive symptoms (CES-D scores). We used repeated measurement models to test multiplicative interaction between genetic variants and use of SSRIs on repeated CESD scores. Besides a genome-wide analysis, we also performed an analysis which was restricted to genes related to the serotonergic signaling pathway. A total of 273 out of 14 937 assessments of depressive symptoms in 6443 participants, use of an SSRI was recorded. After correction for multiple testing, no plausible loci were identified in the genome-wide analysis. However, among the top 10 independent loci with the lowest p-values, findings within two genes (*FSHR* and *HMGB4*) might be of interest. Among 26 genes related to the serotonergic signaling pathway, the rs6108160 polymorphism in the *PLCB1* gene reached statistical significance after Bonferroni correction (p-value = 8.1e-5). Also, the widely replicated 102C > T polymorphism in the *HTR2A* gene showed a statistically significant drug–gene interaction with SSRI use. Therefore, the present study suggests that drug–gene interaction models on (repeated) cross-sectional assessments of depressive symptoms in a population-based study can identify potential loci that may influence SSRI response.

1. Introduction

Failure of antidepressant therapy is common in the treatment of depression (Trivedi et al., 2006), and is genetically inherited (Franchini et al., 1998; O'Reilly et al., 1994; Tansey et al., 2013). Most genetic variants associated with antidepressant response were identified within candidate gene studies, in which a predefined hypothesis was tested (Horstmann and Binder, 2009; Kato and Serretti, 2010). Beside genetic variation in Cytochrome P450 metabolizing enzymes (e.g. CYP2D6) and transporter

* Corresponding author. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands. Tel.: +31 10 70 44294; fax: +31 10 70 44657.
E-mail addresses: r.noordam@erasmusmc.nl (R. Noordam), n.direk@erasmusmc.nl (N. Direk), csitlani@uw.edu (C.M. Sitlani), n.aarts@erasmusmc.nl (N. Aarts), h.tiemeier@erasmusmc.nl (H. Tiemeier), a.hofman@erasmusmc.nl (A. Hofman), a.g.uitterlinden@erasmusmc.nl (A.G. Uitterlinden), pasty@u.washington.edu (B.M. Psaty), b.stricker@erasmusmc.nl (B.H. Stricker), l.e.visser@erasmusmc.nl (L.E. Visser).

http://dx.doi.org/10.1016/j.jpsychires.2015.01.005
0022-3956/

proteins (e.g. P-glycoprotein), which affects the pharmacokinetics of antidepressants, some genes encoding proteins that influence the pharmacodynamics of antidepressants also showed associations with the antidepressant drug response (Kato and Serretti, 2010). However, the heterogeneity between the studies in a meta-analysis was substantial, which complicates the interpretation of the research findings (Kato and Serretti, 2010). Indeed, some of the findings were, in more recent studies, not replicated or only observed in subtypes of depression, such as melancholic or psychotic depression (Arias et al., 2013; Zhao et al., 2012). In addition, Genome-Wide Association Studies (GWAS) have not been able to identify statistically significant associations between Single Nucleotide Polymorphisms (SNPs) and response to antidepressants (Garriock et al., 2010; Gendep Investigators et al., 2013; Ising et al., 2009; Uher et al., 2010).

Most studies used a treated-only design, in which patients with depression were followed over time from start of antidepressant therapy until relief of the depressive symptoms or the end of the study period. However, the use of this design has limitations, as it does not allow distinction between the drug response and the natural course of the disease (Laje and McMahon, 2011). In fact, loci observed within such studies might be associated with depressive symptoms rather than with the response to antidepressants (Avery et al., 2014). The uncertainty in the interpretation can be reduced when untreated participants are included in the analyses (Avery et al., 2014).

Prospective population-based studies might have data available that is suitable for research on antidepressant drug response (Hek et al., 2013). We hypothesized that if an association between a SNP and depressive symptoms differs between participants treated with Selective Serotonin Reuptake Inhibitors (SSRIs) and untreated participants, the SNP is possibly associated with drug response to SSRIs. Therefore, we studied whether genetic loci of potential interest for SSRI drug response can be identified in prospective population-based studies using drug–gene interaction models of repeated cross-sectional assessments of depressive symptoms.

2. Materials and methods

2.1. Setting of the Rotterdam Study

The current study was embedded in the prospective Rotterdam Study which aims to investigate the incidence of and risk factors for several age-related diseases. A more detailed description of the design and rationale of the study was published elsewhere (Hofman et al., 2013, 1991). From 1990 to 1993, all inhabitants aged 55 years and older from a district (Ommoord) located in Rotterdam, the Netherlands, were asked to participate in the original cohort (denoted hereafter as RS-I). In total, 7983 individuals agreed to participate (response rate 78%). An extension of the original cohort was initiated in 2000 (denoted hereafter as RS-II). Within this subcohort, all inhabitants from Ommoord aged 55 years and older, and not already participating in RS-I, were asked to participate in RS-II. In total, 3011 individuals agreed to participate (response rate 67%). Follow-up examinations were conducted approximately every 4–5 years after baseline. The Rotterdam Study has been approved by the medical ethics committee according to the “Wet Bevolkingsonderzoek ERGO” (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands and written informed consent was obtained from all study participants.

2.2. Study population

We included all participants from RS-I and RS-II who were successfully genotyped and completed at least one questionnaire about their current depressive symptoms (collecting started in the second follow-up round, 1997). Assessments of depressive symptoms at which participants were using tricyclic antidepressants or other antidepressants were excluded from the study.

2.3. Drug exposure

More than 99% of the participants have their drug prescriptions filled at seven fully computerized regional pharmacies. The available data included the Anatomical Therapeutical Chemical (ATC) code, the dispensing date, the total amount of drug units per prescription, the prescribed daily number of units, and the product name of the drug. SSRI drug exposure (ATC code: N06AB) was defined as ‘current’ if the center visit date fell within a prescription episode. The duration of the episode was calculated by dividing the total number of filled tablets/capsules/suspensions by the daily-prescribed number. Participants without a SSRI drug prescription at a center visit were considered as non-users. Ever users of antidepressants were defined based on the presence of at least one SSRI prescription between start of follow-up and December 31, 2011.

2.4. Genotyping

Genotyping of the polymorphisms in RS-I was performed with the Infinium II HumanHap 550K Genotyping BeadChip® version 3 (Illumina, San Diego, CA, USA). For RS-II, genotyping was performed with the Infinium II HumanHap 550K + 610K Quad Genotyping GenomeStudio® (Illumina, San Diego, CA, USA). Polymorphisms were genotyped according to the instructions of the manufacturer. Quality controls and results of the genotyping are published elsewhere (Richards et al., 2008). The number of polymorphisms was increased by imputing surrounding SNPs using the Caucasian Hapmap population (release 22) with MACH software version 1.0.15 (RS-I) and version 1.0.16 (RS-II) (International HapMap, 2003). Additive genetic models were used. SNPs located on the X chromosome were not considered for analyses.

2.5. Assessment of depressive symptoms

Current depressive symptoms were screened with a Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D). The questionnaire resulted in a score, ranging between 0 and 60, with higher scores indicative of more depressed feelings (Beekman et al., 1997; Radloff, 1977). The CES-D score was not normally distributed and therefore log transformed (ln(CES-D + 1)).

2.6. Statistical analyses

The CES-D questionnaire was completed at multiple center visits during follow-up. Therefore, all analyses adjusted for the within-person correlation of repeated measures. Specifically, we used Generalized Estimating Equations (GEE) (Zeger and Liang, 1986). However, the robust standard error estimates in GEE have an inflated type I error when the number of participants is small (Lipsitz et al., 1994). In our interaction analyses, many SSRI-SNP strata were small, so type I error was higher than the specified significance level. To reduce type I error, we modified the reference distribution to a *t*-distribution with degrees of freedom approximated via Satterthwaite's methods (Pan and Wall, 2002; Satterthwaite, 1946). Analyses were adjusted for age and sex.

Please cite this article in press as: Noordam R, et al., Identifying genetic loci associated with antidepressant drug response with drug–gene interaction models in a population-based study, Journal of Psychiatric Research (2015), http://dx.doi.org/10.1016/j.jpsychires.2015.01.005