Drug and Alcohol Dependence 149 (2015) 259–263

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Short communication

Meta-analysis of six genes (BDNF, DRD1, DRD3, DRD4, GRIN2B and MAOA) involved in neuroplasticity and the risk for alcohol dependence

Diego A. Forero[a,*], Sandra López-León[b], Hyoung Doo Shin[c], Byung Lae Park[d], Dai-Jin Kim[e]

[a] Laboratory of NeuroPsychiatric Genetics, Biomedical Sciences Research Group, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia
[b] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[c] Laboratory of Genomic Diversity, Department of Life Science, Sogang University, Seoul, Republic of Korea
[d] Department of Genetic Epidemiology, SNP Genetics Inc., Seoul, Republic of Korea
[e] Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 17 November 2014
Received in revised form 12 January 2015
Accepted 12 January 2015
Available online 24 January 2015

Keywords:
Candidate genes
Neurogenetics
Addiction
Alcoholism

ABSTRACT

Background: Alcohol-related problems have a large impact on human health, accounting for around 4% of deaths and 4.5% of disability-adjusted life-years around the world. Genetic factors could explain a significant fraction of the risk for alcohol dependence (AD). Recent meta-analyses have found significant pooled odds ratios (ORs) for variants in the ADH1B, ADH1C, DRD2 and HTR2A genes.
Methods: In the present study, we carried out a meta-analysis of common variants in 6 candidate genes involved in neurotransmission and neuroplasticity: BDNF, DRD1, DRD3, DRD4, GRIN2B and MAOA. We carried out a systematic search for published association studies that analyzed the genes of interest. Relevant articles were retrieved and demographic and genetic data were extracted. Pooled ORs were calculated using a random-effects model using the Meta-Analyst program. Dominant, recessive and allelic models were tested and analyses were also stratified by ethnicity.
Results: Forty two published studies were included in the current meta-analysis: BDNF-rs6265 (nine studies), DRD1-rs4532 (four studies), DRD3-rs6280 (eleven studies), DRD4-VNTR (seven studies), GRIN2B-rs1806201 (three studies) and MAOA-uVNTR (eight studies). We did not find significant pooled ORs for any of the six genes, under different models and stratifying for ethnicity.
Conclusions: In terms of the number of candidate genes included, this is one of the most comprehensive meta-analyses for genetics of AD. Pooled ORs did not support consistent associations with any of the six candidate genes tested. Future studies of novel genes of functional relevance and meta-analyses of quantitative endophenotypes could identify further susceptibility molecular factors for AD.

1. Introduction

Alcohol-related problems have a large impact on human health (Schuckit, 2009), accounting for around 4% of deaths and 4.5% of disability-adjusted life-years around the world (Rehm et al., 2009). Genetic factors could explain a significant fraction of the risk for alcohol dependence (AD; Rietschel and Treutlein, 2013). Recent meta-analyses have found significant pooled odds ratios (ORs) for commonly studied variants in the following genes: alcohol dehydrogenase 1B (ADH1B), alcohol dehydrogenase 1C (ADH1C), aldehyde dehydrogenase 2 (ALDH2), ankyrin repeat and kinase domain containing 1 (ANKK1), serotonin receptor 2A (HTR2A), opioid receptor mu 1 (OPRM1), tryptophan hydroxylase 1 (TPH1) and serotonin transporter (SLC6A4) (Supplementary Table 1[1]; Cao et al., 2014; Li et al., 2011, 2012a, 2012b; Wang et al., 2013). In addition to the study of genes involved in alcoholism metabolism, such ALDH2 or ADH1B, there has been interest in the study of other molecules related to neural transmission and plasticity mechanisms (Cui et al., 2013; Hill, 2010). Of particular interest, several research groups have studied common variants in brain-derived neurotrophic

* Corresponding author. Tel.: +57 3132610427.
E-mail address: diego.forero@uan.edu.co (D.A. Forero).

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.01.017.

http://dx.doi.org/10.1016/j.drugalcdep.2015.01.017
0376-8716/

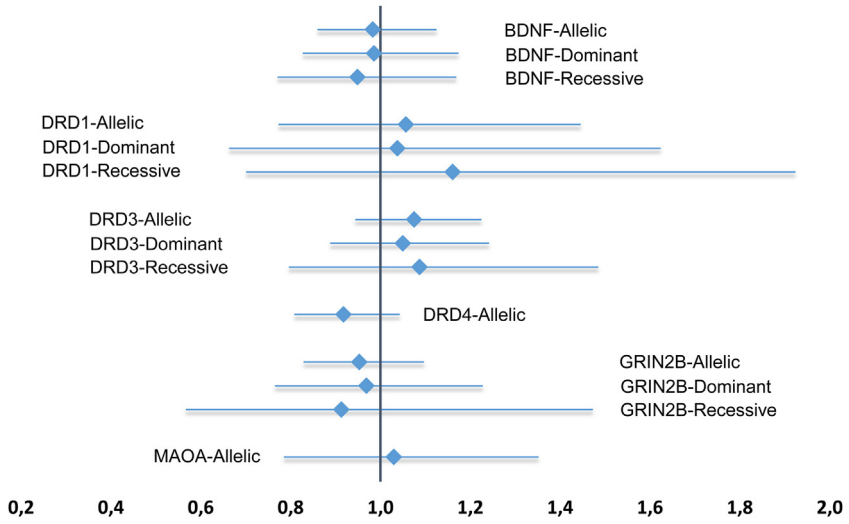

Fig. 1. Overview of the forest plots for the six candidate genes, testing different models, in alcohol dependence.

factor (BDNF, 11p14.1); dopamine receptor D1 (DRD1, 5q34-q35); dopamine receptor D3 (DRD3, 3q13.3), dopamine receptor D4 (DRD4, 11p15.5), glutamate receptor, ionotropic, *N*-methyl-D-aspartate 2B (GRIN2B, 12p13.1) and monoamine oxidase A (MAOA, Xp11.4-p11.3), with conflicting results (Bordukalo-Niksic et al., 2012; Cheah et al., 2014; Kang et al., 2014; Kim et al., 2006; Nedic Erjavec et al., 2014; Prasad et al., 2013). In the present study, we carried out a meta-analysis of common variants in six candidate genes involved in neurotransmission and neuroplasticity: BDNF, DRD1, DRD3, DRD4, GRIN2B and MAOA.

2. Methods

We followed the recommendations of the PRISMA statement (Moher et al., 2009) for reporting of meta-analyses. We used the Phenopedia tool from the HuGE navigator for an initial screening of eligible studies (Yu et al., 2010). We searched for genetic association studies analyzing polymorphisms in the BDNF (rs6265), DRD1 (rs4532), DRD3 (rs6280), DRD4 (variable number tandem repeat—VNTR), GRIN2B (rs1806201) and MAOA (uVNTR) genes in the PubMed database. We combined disease search terms "alcohol dependence or alcoholism" with the respective search terms for the genes of interest: "BDNF or brain-derived neurotrophic factor", "DRD1 or dopamine receptor D1", "DRD3 or dopamine receptor D3", "DRD4 or dopamine receptor D4", "GRIN2B or glutamate receptor, ionotropic, *N*-methyl-D-aspartate 2B" and "MAOA or monoamine oxidase A". In addition, we searched reference lists of relevant review and original papers and checked the supplementary files of high-throughput genetic association studies of AD to identify additional papers not covered by the electronic search of abstracts.

We included articles published in English in peer-reviewed journals that described results from case-control studies analyzing the association of the selected candidate polymorphisms with AD in different ethnic populations. Exclusion criteria were: studies of quantitative measures of alcohol consumption, response to medications or analyses of other markers (different from the selected candidate polymorphisms) in the candidate genes.

We extracted information about general features of the studies (sample sizes, age and gender distributions, genotyping methodologies, Hardy–Weinberg equilibrium—HWE) from each article. In all cases of missing data, we contacted the respective authors to ask for allele or genotype frequencies that were not available in the main text of the papers or in their supplementary files. Study selection and data extraction and synthesis were performed and checked by two independent investigators.

For the meta-analysis procedures, we used the freely available Meta-Analyst program (Wallace et al., 2009). It is cross-platform software that allows for the analysis of case-control association studies and other advanced approaches (e.g., implementation of fixed-effects or random-effects models, sensitivity analysis, cumulative meta-analysis, meta-regression and generation of forest plots). Following recommendations in the area, we used random-effects models for the calculations of the pooled odds ratios (ORs) and we calculated the I2 statistic for heterogeneity (Forero et al., 2009; Kavvoura and Ioannidis, 2008; Sagoo et al., 2009). We tested three different genetic models (allelic, dominant and recessive) and also carried out subanalyses of pooled ORs in specific ethnic groups (Caucasian or Asian groups). For BDNF, DRD1, DRD3, GRIN2B and MAOA, the alleles with the minor frequency were taken as the possible risk alleles (A, G, C, T and 3 repeat, respectively); for DRD4 it was the 4 repeat allele. A graphical overview of forest plots provided in Fig. 1 was generated as previously described (Neyeloff et al., 2012). This article does not contain any studies with human participants or animals performed by any of the authors.

3. Results

Forty two published studies were included in the current meta-analysis: BDNF-rs6265 (nine studies), DRD1-rs4532 (four studies), DRD3-rs6280 (eleven studies), DRD4-VNTR (seven studies), GRIN2B-rs1806201 (three studies) and MAOA-uVNTR (eight studies). Details of included studies are provided in Table 1 and complete list of references is included in the Supplementary file[2]. Some articles did not provide genotypic frequencies for cases and controls and it was not possible to include them for all the comparisons.

We applied random-effects meta-analyses to the available data and we did not find significant pooled ORs for any of the six genes, under the three different models (allelic, dominant and recessive; Fig. 1). We also stratified for ethnic groups (Caucasians and Asians) and did not find significant pooled ORs (Supplementary Table 2[3]).

[2] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.01.017.

[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.01.017.