Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 36–42

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Genetic association studies between SNPs and suicidal behavior: A meta-analytical field synopsis

Anne H.E. Schild *, Jakob Pietschnig, Ulrich S. Tran, Martin Voracek

University of Vienna, School of Psychology, Department of Basic Psychological Research and Research Methods, Liebiggasse 5, 1010 Vienna, Austria

ARTICLE INFO

Article history:
Received 15 April 2013
Received in revised form 20 June 2013
Accepted 24 June 2013
Available online 2 July 2013

Keywords:
Association study
Genetics of suicide
Meta-analysis
Single nucleotide polymorphism
Suicidal behavior
Systematic review

ABSTRACT

The large number of published meta-analyses on the associations between single-nucleotide polymorphisms (SNPs) and suicidal behavior mirrors the enormous research interest in this topic. Although meta-analytic evidence is abundant and certain patterns are apparent, those have not been integrated into a general framework as of yet. In a systematic review, genetic association studies between SNPs and suicidal behavior were identified. Previously published meta-analyses for eight SNPs were updated and the results of the different meta-analyses were compared. Meta-analyses for 15 SNPs, which had not been subjected to meta-analysis before, were conducted. The present meta-analytical field synopsis showed five major similarities between new and published analyses: 1) Summary effect sizes were small and rarely statistically significant, 2) heterogeneity between studies was often substantial, 3) there were no time trends, 4) effects were easily swayed and were largely dependent on individual studies, and 5) publication bias does not play a role in this field of research. Meta-analytic data show once more that major contributions of single genes are unlikely. However, association studies and corresponding meta-analyses have been an important and necessary stepping stone in the development of modern and more complex approaches in the genetics of suicidal behavior.

1. Introduction

Family studies (Brent and Mann, 2005), adoption studies (Voracek, 2007), and twin studies (Voracek and Loibl, 2007) have kindled a large research interest in the genetics of suicidal behavior. The first genetic association study in this field was published nearly 20 years ago (Nielsen et al., 1994) and since then a large number of association studies have been conducted.

The serotonergic system has been the main focus of the majority of these studies (Antypa et al., 2013), although a variety of neurotransmitters have been implicated in suicidal behavior (see Ernst et al., 2009, for a review). Its apparent implication in the pathogenesis of suicide-related phenotypes, the positive effects of drugs targeting the serotonergic system, and altered 5-HIAA levels (5-Hydroxyindoleacetic acid, the main metabolite of serotonin) have made it a prime candidate in the search for the genetic underpinnings of suicide (Ernst et al., 2009).

Published meta-analyses on SNPs implicated in the serotonergic system have covered the serotonin synthesis (e.g., TPH1: Bellivier et al., 2004; Lalovic and Turecki, 2002; Li and He, 2006; Rujescu et al., 2003), reception (e.g., 5-HTR1A: Anguelova et al., 2003; Li and He, 2006), and re-uptake (e.g., 5-HTT: Anguelova et al., 2003; Li and He, 2007; Lin and Tsai, 2004). Close scrutiny of those meta-analyses reveals certain patterns and similarities which may be generalized to other neurotransmitter systems which have received far less attention (e.g., the dopaminergic system).

In the last decade, this large research interest has culminated in the publication of a considerable number of meta-analyses investigating associations between single-nucleotide polymorphisms (SNPs) and suicidal behavior. While it is clear that suicidal behavior has a considerable genetic component (Bondy et al., 2006; Brent and Mann, 2005), meta-analyses on single SNP association studies show no or marginal effects. This issue has been discussed in the framework of the missing heritability (Manolio et al., 2009; Zuk et al., 2012) and numerous explanations have been proposed.

While meta-analytic evidence is abundant in the genetics of suicide, a number of questions remain unanswered and no attempts have been made to review the field as a whole. In this regard, the present review aims at presenting a meta-meta-analysis in order to integrate the evidence into a general framework.

2. Methods

2.1. Literature search and study selection

The search string *suic** *AND gene** was entered into ISI Web of Knowledge, Medline, and Scopus. The initial search included all records

Abbreviations: SNP, Single nucleotide polymorphism; TPH, Tryptophan hydroxylase; 5-HT, 5-hydroxytryptamine (serotonin); 5-HIAA, 5-Hydroxyindoleacetic acid; 5-HTR1A, 5-HT_{1A} receptor; 5-HTT, Serotonin transporter; 5-HTTLPR, Serotonin-transporter-linked polymorphic region; GWAS, Genome-wide association study.

* Corresponding author. Tel.: +43 1 4277 471 24; fax: +43 1 4277 9 471.
E-mail addresses: anne.schild@univie.ac.at (A.H.E. Schild), J.Pietschnig@mdx.ac (J. Pietschnig), ulrich.tran@univie.ac.at (U.S. Tran), martin.voracek@univie.ac.at (M. Voracek).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.06.014

available in these databases up until May 2012 and yielded more than 40,000 hits, which were then screened for eligibility. Exclusion of irrelevant studies was performed in several steps (see Fig. 1 for an overview of the process of literature search and selection): 1) Duplicates were automatically identified, 2) studies referring to non-human subjects were automatically identified (using keywords such as *mouse*, *mice*, *monkey**, or *transgenic*), 3) studies pertaining to cancer research were automatically identified (using keywords such as *tumor**, *oncolog**, *metastas** or *cancer*). All automatic literature screening processes were conducted with the open-source software JabRef 2.6 (JabRef Development Team, 2010).

From the remaining 5548 records, studies were selected first by screening titles and abstracts and, if the study appeared to be relevant, full texts were reviewed. Studies were checked for inclusion by three researchers (AHES, UST, and JP). Reference lists of relevant meta-analyses were then screened manually for missing records.

2.2. Inclusion criteria

In order to be included in the meta-analyses four eligibility criteria had to be fulfilled. Studies had to a) be published in peer-reviewed journals, b) report genetic association studies of suicidal behavior using a case–control design, c) report data for suicidal cases (i.e., attempted or completed suicide), and d) report independent data.

2.3. Data extraction

Data on allele and genotype frequencies were extracted by three researchers (AHES, JP, and UST). Variables extracted as potential moderators included country of origin, ethnicity, phenotype of cases (attempted or completed suicide, non-violent or violent) and type of controls (clinical or healthy).

2.4. Statistical analysis

Data analyses were performed using the package metafor (Viechtbauer, 2010) in the open-source software R (R Development Core Team, 2012). The strength of association in individual two-by-two tables was calculated using odds ratios (*OR*s) with an *OR* greater than 1 indicating a positive association between the risk allele and suicidal behavior.

Individual allele-wise and genotype-wise meta-analyses were conducted for all SNPs. Heterogeneity was assessed using the *Q* statistic and I^2, with $I^2 < 25$ considered to be indicating low, $25 \geq I^2 \leq 75$ medium, and $I^2 > 75$ high heterogeneity, respectively (Huedo-Medina et al., 2006).

Random-effect models (DerSimonian and Laird) were adopted for all analyses, as the theoretical assumption of no heterogeneity was

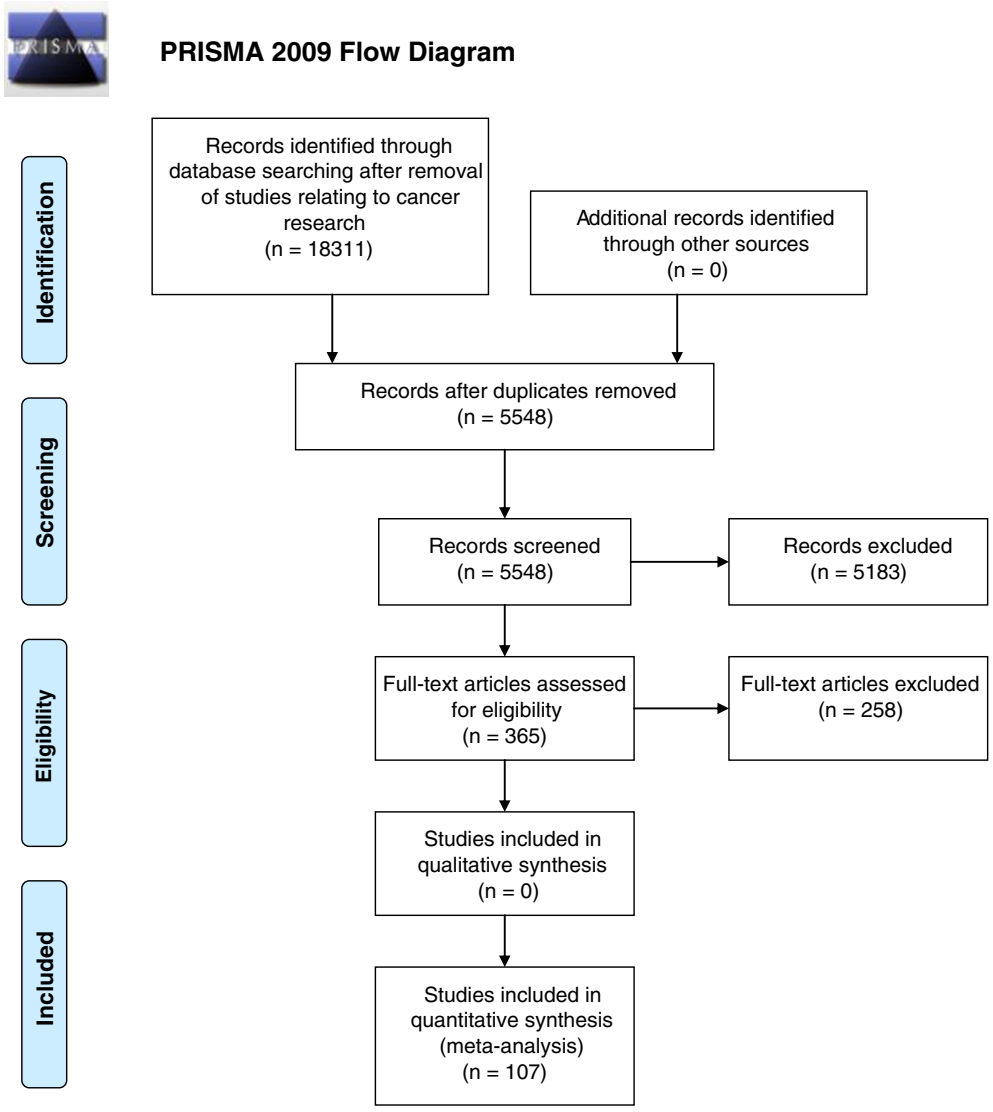

Fig. 1. Overview of the process of participant selection and inclusion.