Neuroscience and Biobehavioral Reviews xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

# Gene environment interaction studies in depression and suicidal behavior: An update

Laura Mandelli*, Alessandro Serretti

*Psychiatry Section, Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy*

ARTICLE INFO

*Article history:*
Received 16 April 2012
Received in revised form 8 July 2013
Accepted 10 July 2013

*Keywords:*
Major depression
Suicide
Genetics
Environment
Stressful life events
Gene × environment interaction

ABSTRACT

Increasing evidence supports the involvement of both heritable and environmental risk factors in major depression (MD) and suicidal behavior (SB). Studies investigating gene–environment interaction (G × E) may be useful for elucidating the role of biological mechanisms in the risk for mental disorders. In the present paper, we review the literature regarding the interaction between genes modulating brain functions and stressful life events in the etiology of MD and SB (G × E studies) and discuss their potential added benefit compared to genetic studies. Within the context of G × E investigation, thus far, only a few reliable results have been obtained, although some genes have consistently shown interactive effects with environmental risk in MD and, to a lesser extent, in SB. Further investigation is required to disentangle the direct and mediated effects that are common or specific to MD and SB. Since traditional G × E studies overall suffer from important methodological limitations, further effort is required to develop novel methodological strategies with an interdisciplinary approach.



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*Abbreviations:* ABCG1, ATP-binding cassette subfamily G member 1; ACE, angiotensin-converting enzyme; APOE, apoliprotein E; AVPR1B, argivanine vasopressin receptor 1B; BDNF, brain-derived neurotrophic factor; CNR1, cannabinoid receptor 1; COMT, catechol-O-methyltransferase A; CRH, corticotrophin-releasing hormone; CRHBP, corticotrophin-releasing hormone binding protein; CRHR1, corticotrophin-releasing hormone receptor 1; CRHR2, corticotrophin-releasing hormone receptor 2; DBH, dopamine beta-hydroxylase; DRD1, dopamine receptor D1; DRD2, dopamine receptor D2; DRD3, dopamine receptor D3; DRD4, dopamine receptor D4; DRD5, dopamine receptor D4; FKBP5, FK506-binding protein 5; FMR1, fragile-X mental retardation protein; G × E, gene–environment interaction; GABRA1, gamma-aminobutyric acid receptor alpha1; GABRA2, gamma-aminobutyric acid receptor alpha2; GABRA5, gamma-aminobutyric acid receptor alpha5; GABRG1, gamma-aminobutyric acid receptor gamma1; GABRG2, gamma-aminobutyric acid receptor gamma2; GAD1g, lutamate decarboxylase 1; GLULg, lutamate-ammonia ligase (glutamine synthase); GPX1, glutathione peroxidase; GRIA1g, lutamate receptor ionotropic AMPA 1 (glutamate receptor 1); GRIN2Ag, lutamate receptor ionotropic 2A (glutamate receptor 2A); GRIN2Bg, lutamate receptor ionotropic 2B (glutamate receptor 2B); GRIN2C, glutamate receptor ionotropic 2C (glutamate receptor 2C); GRIN2D, glutamate receptor ionotropic 2D (glutamate receptor 2D); GRIN3A, glutamate receptor ionotropic 3A (glutamate receptor 3A); GRIN3B, glutamate receptor ionotropic 3B (glutamate receptor 3B); GRM7, glutamate receptor metabotropic 7; GSK3B, glycogen-synthase 3beta; HTR1A, serotonin receptor 1A; HTR1B, serotonin receptor 2B; HTR2A, serotonin receptor 2A; HTR2C, serotonin receptor 2C; HTR3A, serotonin receptor 3A; IL10, interleukin 10; IL18, interleukin 18; MAOA, monoamine-oxidase A; MD, major depression; NPY, neuropeptide Y; NR3C1, nuclear receptor sub family 3 group c member 1 (glucocorticoid receptor); NTRK2, neurotrophic tyrosine kinase receptor 2; ODC1, ornithine decarboxylase 1; OXTR, oxytocin receptor; RGS2, regulator of G-protein signaling 2; SB, suicidal behavior; SLC6A2, solute carrier 6 A2 (noradrenalin transporter; SLC6A3, solute carrier 6 A3 (dopamine transporter); SLC6A4, solute carriers 6A (serotonin transporter); SLEs, stressful life events; TNF, tumor necrosis factor; TPH1, tryptophan hydroxylase; TPH2, neuronal tryptophan hydroxylase.

* Corresponding author at: Psychiatry Section, Department of Biomedical and Neuromotor Sciences, University of Bologna, V.le C. Pepoli 5, 40123 Bologna, Italy. Tel.: +39 51 6584233; fax: +39 51 521030.
*E-mail address:* laura.mandelli@unibo.it (L. Mandelli).

0149-7634/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.neubiorev.2013.07.011

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## 1. Introduction

Major depression (MD) and suicidal behavior (SB) are important public health issues because of their high prevalence and incidence in the population (Borges et al., 2010; Gelenberg, 2010). According to the World Health Organization (WHO) (see also Kessler et al., 2005), between 10% and 15% of the general population will experience a clinical depressive episode in their lifetime, and 5% of men and 9% of women will experience a depressive disorder in a given year (Hirschfeld, 2012). With regard to SB, in 2005, the overall suicide rate in the United States was 11/100,000 (National Center for Injury Prevention and Control (NCIPC), 2005), whereas, according to the WHO, the worldwide rate is 900,000/year (World Health Organization, 2001), with global rates of 17.7/100,000 for females and 10.7/100,000 for males (Mathers et al., 2006).

Although SB can occur in different psychopathological conditions (personality disorders, severe anxiety disorders, Schizophrenia and other major psychosis), patients affected by depressive disorders have the highest risk of attempting or committing suicide. Indeed, a meta-analysis of approximately 250 studies, spanning over 30 years, found that mood disorders (both unipolar and bipolar forms) carry the highest risk of SB compared to any other psychiatric and medical illness (Harrison and Burnet, 1997). Extensive literature has documented a substantial overlap between MD and SB with regard to familial risk, treatment (antidepressants and lithium salts are efficacious for MD and reduce SB risk) and environmental risk factors. Moreover, it has also been reported that SB may aggregate in families independently from the familial transmission of MD (Brent and Mann, 2006), suggesting that independent genetic risk factors for SB may exist.

MD has largely been recognized as a heritable disease (McGuffin and Katz, 1986). The estimated risk of disease in first-degree relatives of a proband is 3-times higher than that in the general population, although some studies have reported a 10-fold increased risk in siblings, when a more stringent definition of depression is applied (Farmer et al., 2000). Population-based studies support a heritability for depression of 30–40% (Kendler et al., 1992). Twin studies in bipolar disorder showed an increased rate concordance of both unipolar and bipolar mood disorders, with an estimated heritability of 80% (Bertelsen et al., 1977; McGuffin et al., 2003). With regard to SB, less evidence has been reported, since it mostly occurs within the context of diverse psychopathological conditions. However, twin studies have consistently documented genetic influences in SB, even when accounting for the effects of psychopathology. Concordance rates ranging from 6% to 35% have been reported in different studies of identical twins (see Pedersen and Fiske, 2010).

A number of biological factors and candidate genes have been tested in MD and SB (see Elder and Mosack, 2011; Mandelli et al., 2009; Rujescu et al., 2007; Tsai et al., 2011). However, to date, only a few consistent findings have been reported. One major challenge has been that SB and MD are complex and heterogeneous disorders that are caused by a combination of variations in multiple genes, each exerting a small effect on both disease risk and symptomatologic aspects. Furthermore, consistent evidence supports a critical role of environmental factors in modulating or triggering a genetic predisposition to SB (Roy et al., 2009; Saveanu and Nemeroff, 2012). Indeed, both early adversity and recent acute/chronic stress (loss, separation, interpersonal or family problems, occupational stress/unemployment, poor social contacts/support, among others) have long been recognized to play a pivotal role in both MD and SB (Paykel, 1976). For this reason, in the early 2000s, investigators focused on studying the interplay between genetics and environmental risk factors. Gene × environment (G × E) studies are useful in identifying correlations or interactions between risk genes for a specific disease and environmental factors (Cooper, 2001). In addition to providing a better characterization of already identified genes involved in the disease, these studies may enable the identification of new genes, in which their effects are dependent on the level of exposure to a specific environment.

In the present article, after a brief review of the genetic factors involved in MD and SB, we review the studies focused on G × E in these disorders/behavioral disturbances, highlighting the major and interesting findings obtained thus far and discussing the potential added benefit of G × E investigations compared to simple genetic association studies. Furthermore, we will discuss the potential helpfulness of the G × E approach in the overall context of psychopathology, together with the need of novel methods of study within a multidisciplinary framework.

## 2. Methods

### 2.1. Literature search

Published G × E studies in MD and SB were screened using several literature search strategies. Up to January 2013, appropriate search terms (gene, genetics, heritability, suicide, suicide attempt, completed suicide, suicidality, suicidal behavior, suicidal ideation, suicide intent, major depression, depressive disorder, and mood disorders) were entered into the common scientific literature databases (PubMed, SCOPUS and ISI Web of Science). The same terms were also entered in conjunction with other terms for G × E studies (stress, trauma, life events, adverse events, sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect). The reference lists of all of the retrieved studies were reviewed in order to retrieve further relevant studies.

### 2.2. Study inclusion criteria

The literature search was limited to English-language reports. Any study reporting data on genetic polymorphisms and environmental risk in MD, depressive symptoms or a type of SB (with the exclusion of self-harm without intent to die), independent of the study design, was eligible for inclusion in the review.

## 3. Genetic basis of major depression (MD) and suicidal behavior (SB)

Hundreds of candidate genes in MD and, to a lesser extent, in SB have been tested in several studies (most frequently examining candidates related to monoamine signaling, neurotrophins, neuroendocrinology or immunology/inflammation processes). Genes that have been most consistently associated with MD and SB (i.e., found positive in 2 or more independent studies and/or reported as associated in large meta-analyses) are reported in Table 1.

Not surprisingly, several genes have been reported as risk genes for both MD and SB, since a large component of the genetic studies



Please cite this article in press as: Mandelli, L., Serretti, A., Gene environment interaction studies in depression and suicidal behavior: An update. Neurosci. Biobehav. Rev. (2013), http://dx.doi.org/10.1016/j.neubiorev.2013.07.011