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MINIREVIEWS

Gene × environment interaction in major depressive disorder

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Abstract

Major depressive disorder (MDD) is a multifactorial disorder, where multiple susceptibility genes interact with environmental factors, predisposing individuals to the development of the illness. In this article, we reviewed different gene × environment interaction (G×E) studies shifting from a candidate gene to a genome-wide approach. Among environmental factors, childhood adversities and stressful life events have been suggested to exert crucial impacts on MDD. Importantly, the diathesis-stress conceptualization of G×E has been challenged by the differential susceptibility theory. Finally, we summarized several limitations of G×E studies and suggested how future G×E studies might reveal complex interactions between genes and environments in MDD.

Key Words: Major depressive disorder; Gene × environment interaction; Diathesis-Stress model; Differential susceptibility Theory; Stressful life events; Childhood adversities

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Core Tip: The effects of environmental factors on the risk of developing major depressive disorder are likely to be moderated by genetic variants which confer a sensitivity to both positive and negative environmental factors.

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INTRODUCTION

Major depressive disorder (MDD) is a debilitating illness which severely restricts psychosocial function and diminishes quality of life. MDD is characterized by alterations in mood, interests, pleasure, neurovegetative function and cognition. The average 12-mo prevalence of MDD was estimated to be approximately 6%[1]. Lifetime MDD risk is typically threefold higher than the 12-mo prevalence, meaning MDD is common, with almost one in every six adults experiencing one episode at some point in their lifetime[2]. The World Health Organization ranked MDD as the third cause of burden of disease in 2008 and predicted that, by 2030, MDD will rank first and account for 13% of the total global burden of disease replacing cardiovascular disorders[3].

Although the pathophysiology of MDD is not yet fully understood, the presence of a genetic component to MDD has been established by family, twins, and adoption studies[4]. It has been known for more than a century that MDD shows family aggregation. There is a threefold increased risk of MDD among first-degree relatives, with a heritability risk that is quantified as approximately 35%[5]. Furthermore, genetic overlaps between MDD and other psychiatric disorders have been identified[6, 7].

However, identification of the main genetic effects in MDD so far has not revealed replicated significant findings[8]. One of the potential reasons for this weak genetic effect is the fact that an individual gene is likely to exert only a modest effect and individual genotypic variations may increase the risk of MDD only in the presence of exposure to adverse environmental circumstances, a phenomenon known as "gene×environment interaction (G×E)"[9] (Figure 1). This review will focus on studies that aimed to assess the joint contribution of gene and environment in the development of MDD.

GENETIC VULNERABILITY RISK FACTORS FOR MDD

To date, as a part of a concerted effort to investigate the genetic contribution to MDD, many G×E studies have been based on candidate genes. The serotonin transporter promoter short/Long polymorphism (*5-HTTLPR*) and a functional single nucleotide polymorphism (SNP) within the *FK506* binding protein 51 (*FKBP5*) gene were two of the most investigated examples of candidate G×E linking environments to MDD. Caspi and colleagues were the first to estimate the moderating effects of *5-HTTLPR* on MDD within a G×E framework, showing that individuals with a short allele of *5-HTTLPR* were at higher risk of MDD and suicidality as compared with those with homozygous or long alleles[10]. Since then, more than fifty studies have been conducted to replicate this finding, however, not all of them have achieved their aims [11]. G×E has been suggested to predict MDD in individuals exposed to negative environmental factors[12,13]. Similarly, many studies have found that a functional SNP within *FKBP5* interacted with environments to predict MDD[14-17].

The *5-HTTLPR* or *FKBP5* interacting with environments were based on hypothesis-driven studies which aimed to identify not only genetic variants that increased the risk of MDD, but also potential biological and molecular mechanisms underlying this increased risk. It was extensively discussed elsewhere that the hypothesis-driven approach could only discover a fraction of potential existing genetic variants. Genome-wide by environment interaction studies (GWEIS) using a hypothesis-free approach to identify genes associated with MDD are emerging, but enormous datasets with both environments and phenotype data are required. So far, three GWEIS have been performed in this regard. The first was conducted by Dunn and colleagues[18] who used data from the SNP Health Association Resource (SHARe) cohort of the Women's Health Initiative and investigated both genetic main effects and G×E effects in the development of depressive symptoms. The second was a pilot study and conducted in 320 subjects with no interactions reaching genome-wide significance[19]. The third used an omics-based approach to identify genetic variants with G×E effects in GWAS

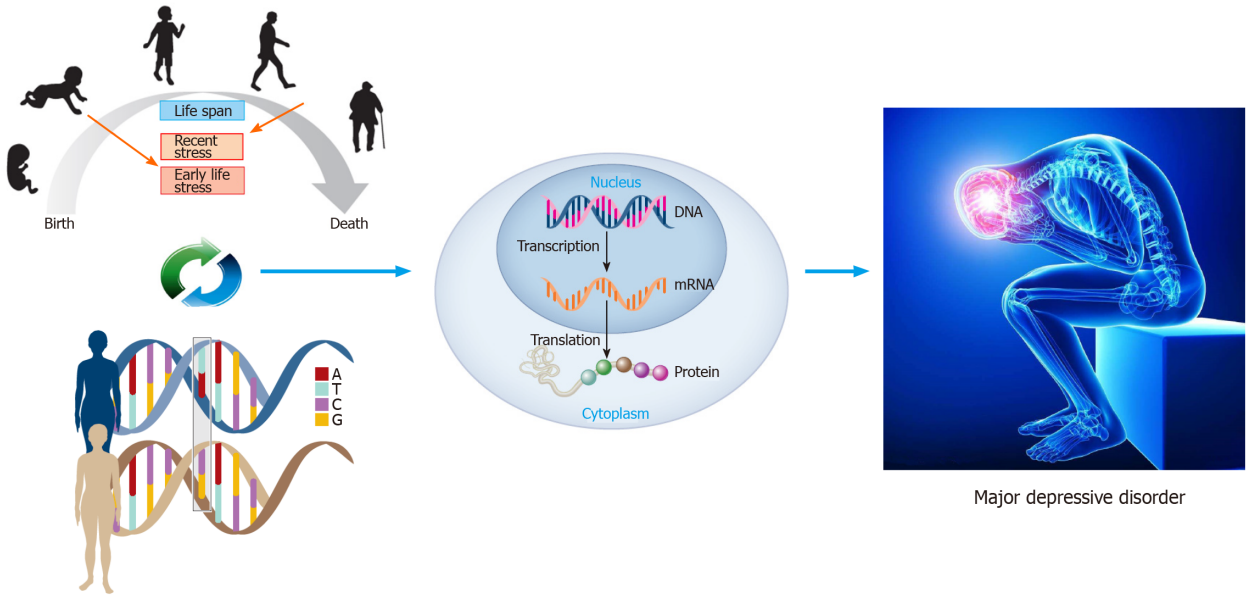

Figure 1 Interaction between genes and environments in major depressive disorder.

datasets and found three candidate genes associated with MDD[20].

ENVIRONMENTAL FACTORS IN MDD

Environmental factors are associated with a dramatic increase in the risk of developing MDD. A number of environmental factors contributing to MDD vulnerability have been identified, including lack of nutrients, social disadvantage, childhood adversities, maternal stress, and stressful life events[21-24]. Of these environmental factors, stressful life events and childhood adversities have been shown to exert crucial impacts on MDD[25,26]. Stressful life events are described as circumstances that have negative effects on an individual occurring close to the onset of MDD[27]. Childhood adversities are defined as stressful experiences which occur early in life. It is very important to differentiate distal environmental factors (childhood adversities) and proximal environmental factors (stressful life events) in G×E studies. Distal environmental factors are critical because they can increase the likelihood of the occurrence of proximal environmental factors. Proximal environmental factors are more relevant than distal environmental factors to the G×E effects on MDD.

Environmental influences on MDD also exhibit a cumulative effect[28,29]. The effect of a single environmental factor may be small, cumulative effects of multiple factors may be quite large, which can be described as a dose-response relationship between environments and phenotype[30]. Many powerful effects involved chains of environmental factors rather than a single factor at just one point in time. It was shown that a developmental cascade of negative experiences was a leading cause of MDD in women [31].

THEORETICAL FRAMEWORKS OF GENE×ENVIRONMENT INTERACTION

Traditionally, the Diathesis-Stress model was the leading conceptual framework for G×E studies, because most investigators usually focused on genetic influences moderated by environments[32]. Specifically, the Diathesis-Stress model hypothesizes that individuals with specific biological (*e.g.*, genetic) and/or psychological (temperament) traits are more vulnerable to adverse environmental influences, but that this inherent vulnerability is not sufficient to lead to psychopathology if such adverse environmental influences are absent. Furthermore, individuals who do not succumb to the negative effects of environmental factors, either as the function of not carrying genetic vulnerabilities or due to the presence of other protective factors, are deemed resilient.

However, the Diathesis-Stress model has been challenged by Stress Generation[33] and Differential Susceptibility Theory[34,35]. Stress Generation suggested that the Diathesis-Stress model of MDD was woefully inadequate because the model was unidirectional, with the environment predicting MDD in those with the diathesis. Stress Generation suggested that the reverse was also true: MDD patients caused stressful life events. Stressors might occur in an individual for random reasons, but many stressful life events are not random. It was shown that women with a history of MDD had higher levels of stressful life events compared with women without a history of MDD[36]. Differential Susceptibility Theory suggested that individuals differed in their general susceptibility to both negative and positive environmental influences. Specifically, individuals who were genetically more vulnerable to environmental influences might be more likely to develop MDD in response to stressful life events and childhood adversities. However, these individuals with higher genetic vulnerability might also be likely to benefit from positive and supportive environmental influences. In contrast to the Diathesis-Stress model, Differential Susceptibility Theory was an evolutionary-inspired developmental model taking into account both negative and positive effects on MDD. This evolutionary model may better account for the findings that most of candidate genes in G×E studies were "common" variants. Findings of these common variants indicated that they might have benefits that counteracted the negative influences of heightened vulnerability[37,38]. Hence, these variants might not merely infer negative effects, as proposed by the Diathesis-Stress model, but they also infer positive effects, as suggested by Differential Susceptibility Theory[39].

LIMITATIONS OF CANDIDATE G×E STUDIES

Although candidate G×E studies have made a critical contribution to the field of MDD, several limitations should also be acknowledged. First, a robust biological hypothesis is required to select appropriate candidate genes. Given the fact that knowledge regarding the specific biological mechanisms underlying MDD remain limited, there is a high risk of selecting inappropriate candidate genes and having publication bias[8,40]. Second, a recent discovery in MDD suggested that the genetic architecture of MDD was highly complex and polygenic[41]. In other words, MDD was influenced by many thousands of gene variants with very small effects rather than by several gene variants with large effects[13]. Third, it is difficult to replicate findings from G×E studies, which is a particular concern. Initial studies might use small sample sizes that were unable to provide statistical power required to detect G×E and, consequently, might increase the risk of false positive findings[42,43]. Finally, most G×E studies in MDD were based on the Diathesis-Stress model which ignored the positive effects of environmental influences[39,44]. The notion that selected candidate genes might be associated with heightened sensitivity to both environmental risk and protective factors, might also contribute to heterogeneous findings.

FUTURE DIRECTIONS

Genome-wide association studies have been conducted for decades to investigate genetic main effects and G×E studies should also be shifted from candidate genes to a genome-wide approach. In addition to collecting large samples required for GWEIS, high quality and more objective measures of environments are also important. The experience sampling method (ESM) may provide a novel approach to obtain more accurate self-report data on an individual's experience of their environments. The ESM has also been used to investigate individual difference in response to both positive and negative environments[45]. Empirical studies indicated that there were substantial aetiological overlaps between MDD and other psychiatric disorders[7]. The Transdiagnostic phenotypes may be more suited as outcomes in G×E studies than categorical and narrowly defined clinical diagnoses for psychiatric disorders[46]. G×E effects may differ across life span, with effects being stronger in early development. Genetically sensitive children who experienced a poor early environment showed increased sensitivity to stressful life events. Applying a developmental perspective may fully understand the role of G×E in the progress of MDD.

CONCLUSION

Despite the importance of candidate gene studies for G×E in MDD, to date, only a few candidate vulnerability genes explain little of the variance. GWEIS are needed for a more complete understanding of G×E in the pathophysiology of MDD.

Among environmental factors, stressful life events and childhood adversities have been recognized to have prominent roles in MDD. Environmental influences on MDD have a cumulative effect, and a dose-response relationship or interaction between stressful life events and childhood adversities may exist in the develop-ment of MDD.

Most G×E studies in MDD were guided by the Diathesis-Stress model which did not consider that individuals who were genetically more sensitive to negative environmental factors might also be more sensitive to positive ones as proposed by Differential Susceptibility Theory. The Differential Susceptibility Theory as a solid evolutionary theory may advance knowledge on interactions between genes and environments in the development of MDD.

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