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Depression and the role of genes involved in dopamine metabolism and signalling

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ABSTRACT

Major depressive disorder (MDD) is a common psychiatric disorder and leading cause of disability worldwide. It is associated with increased mortality, especially from suicide. Heritability of MDD is estimated around 40%, suggesting that genotyping is a promising field for research into the development of MDD. According to the dopamine theory of affective disorders, a deficiency in dopaminergic neurotransmission may play a role in the major symptoms of MDD. Specific polymorphisms in genes that affect dopamine transmission could increase susceptibility to MDD. To determine the extent to which these genes influence vulnerability to MDD, we discuss genes for crucial steps in dopamine neurotransmission: synthesis, signalling and inactivation. The val158met polymorphism of the COMT gene exemplifies the lack of consensus in the literature: although it is one of the most reported polymorphisms that relates to MDD vulnerability, its role is not corroborated by meta-analysis. Gene–gene interactions and gene–environment interactions provide more explanatory potential than single gene associations. Two notable exceptions are the DRD4 and DAT gene: both have variable tandem repeat polymorphisms which may have a "single gene" influence on susceptibility to MDD.

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Abbreviations: bp, base pair; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DBH, dopamine-β-hydroxylase; DDC, dopa decarboxylase; HVA, homovanillic acid; MAO, monoamine oxidase; MDD, major depressive disorder; MDE, major depressive episode; RFLP, restriction fragment length polymorphism; rs, reference SNP; SNP, single nucleotide polymorphism; TH, tyrosine hydroxylase; UTR, untranslated region; VNTR, variable number tandem repeat.

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1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder that has been predicted to become the second leading cause of disability worldwide by 2020 (Murray and Lopez, 1996). It is associated with increased mortality, especially from suicide (Harris and Barraclough, 1998; Schneider et al., 2001). In order to develop new pharmacotherapeutic strategies it is crucial to comprehensively understand the aetiology of MDD. Part of the phenotypic variation of MDD is genetic: twin studies estimate the heritability of MDD around 40% (Sullivan et al., 2000) or even higher (Kendler et al., 2001). Therefore, genetics are a promising field for research into aetiology of MDD.

On the longer term, knowledge of genetic variance associated with MDD might aid treatment strategies. The concept of personalised medicine (Langreth and Waldholz, 1999), originally formulated for oncological drugs, recommends that people be treated with drugs that suit their personal genotype. This might also be of relevance in psychiatry as a poor treatment response often results from giving every patient the same treatment (Lin et al., 2008). It has even been shown that patient stratification based on genetically determined aspects of personality could be employed to maximize the response to antidepressant treatment (Joyce et al., 1994). In sum, specific genotyping is important in the battle against MDD for two main reasons: (i) generation of a good model of MDD aetiology and (ii) patient stratification in the framework of personalised medicine.

Most genetic studies in MDD have until now focused on genes regulating the serotonergic neuromodulatory system. A meta-analysis on genetic association studies in MDD (Lopez-Leon et al., 2008) showed however that of the genes involved in serotonergic neurotransmission only one (the serotonin transporter gene, SLC6A4) showed a significant association. However, this area continues to be contentious (Risch et al., 2009).

1.1. Dopamine and the MDD phenotype

Despite the large focus on the serotonin system, already in 1965 it was postulated that dopamine is involved in MDD (Schildkraut, 1965) and since then the idea that prominent symptoms of MDD arise at least in part from disturbances in dopamine neurotransmission has been reiterated in the literature many times (Brown and Gershon, 1993; Diehl and Gershon, 1992; Dunlop and Nemeroff, 2007; Schildkraut, 1974; Schildkraut and Kety, 1967). Indeed, a considerable body of historical and recent evidence is consistent with this idea. First, to meet the criteria of a major depressive episode (MDE), at least five symptoms need to be present during the same 2-week period. These symptoms are listed in Table 1 (American Psychiatric Association, 2007).

Strikingly, disturbances in processes regulated by dopamine are known to lead to similar symptoms. Dopamine regulates the reward system (Lippa et al., 1973; Wise, 1978), specifically mood (Ashby et al., 1999), motivation (Blackburn et al., 1992; Wise and Bozarth, 1984), attention (Nieoullon, 2002), decision making (Assadi et al., 2009), and psychomotor speed (Poirier et al., 1975). Dopamine release in the ventral striatum is also correlated with the euphoric response to amphetamines (Drevets et al., 2001). Euphoria is the opposite feeling of dysphoria and dysphoria is an important symptom of a MDE. Therefore, dysphoria may be linked to dopamine neurotransmission. Amphetamines are used as pharmacological drug in the treatment of narcolepsy and obesity (Berman et al., 2009), which underscores the role of dopamine in weight control and sleep regulation. Second, antidepressants that are precursors in the biosynthesis of dopamine, dopamine agonists and dopamine re-uptake inhibitors all improve depressive symptoms (Kapur and Mann, 1992). For example, the dopamine agonist pramipexole was found to have antidepressant effects in MDD and bipolar disorder (Corrigan et al., 2000; Goldberg et al., 2004; Zarate et al., 2004). Conversely, dopamine depletors and antagonists reduce motivation and mood and induce a depressed

Table 1
Diagnostic criteria of major depressive episode, reproduced verbatim (except for page references) from the DSM IV-TR.

Diagnostic criteria for major depressive episode
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. *Note*: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). *Note*: In children and adolescents, can be irritable mood
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. *Note*: In children, consider failure to make expected weight gains
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation