

CATECHOL-O-METHYL TRANSFERASE AND SCHIZOPHRENIA

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SUMMARY

Catechol-O-methyl transferase (COMT) is an enzyme involved in the degradation of dopamine. The most commonly examined polymorphism within the COMT gene is Val108/158Met polymorphism, which results in three to fourfold difference in COMT enzyme activity. It is particularly important in prefrontal cortex, since COMT activity is the most important regulator of the prefrontal dopamine function. Given the association between schizophrenia and decreased dopamine activity in the prefrontal cortex, it is not surprising that Val108/158Met polymorphism is among the most extensively investigated polymorphisms in schizophrenia. According to different studies, Val allele may be a small risk factor for schizophrenia. There is also some evidence that Val108/158Met polymorphism influences the age of onset of schizophrenia, cognitive function, severity of psychotic symptoms, as well as efficacy and adverse events of antipsychotics.

Heterogeneity of patient population has undoubtedly influenced the results of these studies. Interaction of Val108/158Met polymorphism with other genes and environmental factors is an important avenue for future research.

Key words: COMT Val108/158Met polymorphism – schizophrenia - response to antipsychotics

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INTRODUCTION

COMT is an enzyme involved in the degradation of important neurotransmitters dopamine, epinephrine, norepinephrine (Weinshilboum et al. 1999). It has long been hypothesized that heredity plays a role in the catechol-O-methyl transferase (COMT) activity (Weinshilboum & Raymond 1977), since its activity has bimodal distribution (Weinshilboum et al. 1974). This hypothesis was confirmed by the identification of a common genetic polymorphism which is associated with a three-to-four-fold variation in COMT enzyme activity (Lachman et al. 1996).

The COMT gene encoding COMT maps to chromosome 22q11.2. The most commonly examined polymorphism within the COMT gene is a common G>A polymorphism (rs4680) that produces a valine-to-methionine (Val/Met) substitution at position 158 (Val158Met) in the longer form of the enzyme (membrane-bound COMT), and at position 108 (Val108Met) in the shorter form of the enzyme (soluble COMT). This polymorphism is usually referred as the Val108/158Met. The amino acid change results in altered activity of COMT and has generally been thought to be a main source of genetic variation in COMT enzyme activity. The Val (variant G) and Met (variant A) alleles, respectively, confer high and low COMT activity. Namely, variations in COMT Val108/158Met polymorphism result in a three to fourfold difference in COMT enzyme activity (Lachman et al. 1996), which, in turn, is supposed to influence extracellular dopamine levels in the brain. The Val variant of COMT degrades dopamine four times more than the Met variant.

The synaptic concentration of dopamine is the result of dynamic process which involves its release and clearance. Dopamine degradation includes two major pathways:

- Reuptake of dopamine by dopamine transporter back to presynaptic terminal and consequent degradation by monoamineoxidase (MAO).
- Degradation of dopamine by COMT in the synaptic cleft

The importance of the effects of COMT on dopamine clearance and function varies according to the brain regions. In striatum and nucleus accumbens, COMT appears to play a minor role in dopamine clearance compared to neuronal synaptic uptake by the dopamine transporter and subsequent MAO metabolism in the presynaptic terminals. In contrast to these pathways, dopamine transporters are sparse in prefrontal cortex (PFC) and therefore, COMT activity is the most important regulator of the prefrontal dopamine function. The Val allele of the COMT is a high activity variant that codes for an enzyme with approximately three times higher physiological activity, and is supposed to be related to hypodopaminergic state and frontal lobe hypoactivity.

COMT AS A CANDIDATE GENE IN SCHIZOPHRENIA

COMT is a strong positional and functional candidate gene for schizophrenia.

- COMT is located (along with 47 other genes) on chromosome 22q11. An evidence of linkage between this region and schizophrenia has been reported (Lewis et al. 2003, Owen et al. 2003).

- According to dopamine hypothesis, schizophrenia is associated with the decreased dopamine activity in the prefrontal cortex, and dopamine hyperactivity in subcortical areas (Da Silva Alves et al. 2008).

In terms of position and function, there are presumably no genes with a better a priori case for the involvement in schizophrenia than COMT (Williams et al. 2007). In a recent study, dopamine D1 receptor (DRD1)-associated haplotypes were exclusively related to schizophrenia, but only in male Val homozygous subgroup of patients (Hoenicka et al. 2010). Inverse correlation between the membrane-bound COMT and DRD1 expression was found in post-mortem samples from the frontal lobe of both controls and groups of schizophrenic and bipolar patients (Abdolmaleky et al. 2006). This study reported that COMT promoter methylation may also affect the level of COMT activity and modulate the expression of the risk alleles (Abdolmaleky et al. 2006). Although direct evidence for epigenetic dysfunction in schizophrenia is still limited, the exciting studies ahead of us will focus on investigations of the molecular modifications of DNA and examinations of the mechanisms by which environmental factors bring about epigenetic changes in gene expression (Rutten and Mill, 2009).

The hypothesis that the Val allele of Val108/158Met polymorphism in COMT gene is a risk factor for schizophrenia has been extensively tested. According to the separate meta-analyses of existing case-control and family-based association studies, the Val allele may be a very small but reliable risk factor for schizophrenia, especially for people of the European ancestry (Glatt et al. 2003). Furthermore, minimal evidence was found that the Val allele is a susceptibility factor for schizophrenia in either European or Asian populations (Fan et al. 2005). In contrast to these findings, another large study reported that the Val allele of COMT does not increase susceptibility to schizophrenia in Europeans (Williams et al. 2005). However, in the aforementioned studies heterogeneity of patients was significant. In a small sample, the overall age of onset of schizophrenia in patients homozygous or heterozygous for the Val allele was 7 years younger compared to age in patients homozygous for the Met allele (Abdolmaleky et al. 2006). Moreover, patients with schizophrenia, carriers of the Val/Val genotype, showed a higher severity of the psychotic symptoms than carriers of other genotypes (Molero et al. 2007). In a small study, the Met/Met homozygotes were found to have significantly higher levels of hostility than patients with other genotypes of the COMT (Volavka et al. 2004).

There is also evidence of the influence of COMT Val108/158Met polymorphism on the brain volume. In both healthy subjects and schizophrenic patients, each copy of the COMT Met allele was associated with on average a 2.6% increase in the right amygdala volume, a 3.8% increase in the left amygdala volume and a 2.2% increase in the right hippocampus volume, with no influence on the whole brain or prefrontal cortex

(Ehrlich et al. 2009). On the other hand, subjects at a high genetic risk of schizophrenia, with the COMT Val allele, had reduced gray matter density in anterior cingulate cortex (McIntosh et al. 2007).

COMT AND COGNITIVE FUNCTION IN SCHIZOPHRENIA

Cognitive impairment is considered a central feature of schizophrenia. While the functioning in attention and spatial memory is deficient even at an early stage of schizophrenia, chronic patients are even more impaired, with deficits mainly related to psychomotor speed, pattern memory, and executive functioning (Braw et al. 2008). While healthy subjects with the Met/Met genotype performed better on Wisconsin Card Sort Test than those with the Val/Val genotype, no significant differences were found between COMT genotypes and cognitive function in schizophrenic patients, according to meta analysis of 12 studies (Barnett et al. 2007), or in the first episode patients (Mata et al. 2008). On the contrary, a linear relationship between the number of Val alleles and the scores on the cognitive deterioration index (i.e. more Val alleles were associated with more cognitive deterioration) was observed in patients treated with atypical antipsychotics (Mata et al. 2006).

Moreover, additional loci within the COMT have been found to have an effect on the gene function. In healthy subjects, subjects carrying the Val allele had less hippocampal volume than those homozygous for the Met allele. However, an u-shaped relationship between hippocampal volume and presumed COMT activity is proposed, describing that very low activity (COMT Met variant combined with the low activity G-allele of the P2 promoter) and very highly active COMT variants (Val158 on the ancestral P2-A allele) had larger hippocampal volumes than haplotypes with predicted intermediate COMT activity (P2-G allele and Val158, and P2-A allele and 158Met) (Honea et al. 2009). These findings suggest that both over- and under-stimulation with dopamine may result in an impaired neuronal survival and growth, implying that an optimum range for extracellular dopamine in cortex and hippocampus may exist for structural integrity (Honea et al. 2009).

COMT AND PHARMACOGENETICS

A limited number of studies have indicated that COMT Val108/158Met polymorphism might be associated with the response to antipsychotic medication. The Met allele carriers showed significant improvement of cognitive function compared to Val allele carriers after clozapine (Woodward et al. 2007) and olanzapine (Bertolino et al. 2004) treatment. Furthermore, the Met homozygotes showed also significantly better improvement of cognitive function during treatment with different antipsychotics, compared to the Val homozygotes, who in turn showed no improvement et all (Weickert et al. 2004). On the

other hand, while COMT Val108/158Met polymorphism was not associated with the response to risperidone, as determined by the change in the Positive and negative syndrome scale (PANSS) (Yamanouchi et al. 2003) and by Clinical Global Impressions (CGI) scale, it was significantly associated with seven COMT marker haplotypes (Gupta et al. 2009). In another study, patients with schizophrenia with the Val/Val genotype showed worse response to neuroleptic treatment than patients with other COMT genotypes, as determined by the CGI and by PANSS scores (Molero et al. 2007). Interestingly, in 47 patients a correlation between median total defined daily doses of antipsychotics, and COMT Val108/158Met polymorphism was found, being highest for the Met/Met genotype, intermediate for the Met/Val genotype and the lowest for the Val/Val genotype (Hagen et al. 2008). Similarly, daily neuroleptic dosage during the maintenance treatment was higher in patients with the low activity COMT genotype (i.e. the Met allele) compared to patients with other genotypes of the COMT (Inada et al. 2003). Similarly to other association studies, no such correlation was found in another study on 180 schizophrenic patients (Illi et al. 2007).

Furthermore, it has been shown that the low activity COMT allele or Met variant was protective against the extrapyramidal symptoms in bipolar patients (Lafuente et al. 2008), but did not influence prolactin concentration in schizophrenia patients treated with risperidone (Yasui-Furukori et al. 2008). A protective effect for the Val/Met and the Met/Met genotypes against tardive dyskinesia in schizophrenic patients was found in a meta-analysis (Bakker et al. 2008).

Apart from metabolizing dopamine, COMT catalyzes the O-methylation of a wide array of catechol-containing substrates (catecholamines and catechol estrogens,) as well as exogenous catechol substrates (bioflavonoids and tea catechins) (Bai et al. 2007). In turn, the catechol-containing tea catechins and bioflavonoids are strong inhibitors of human liver COMT-mediated O-methylation of catechol estrogens (Nagai et al. 2004).

CONCLUSION

The COMT Val108/158Met polymorphism is an almost irresistible target for genetic investigations, and combined worldwide, many thousands of cases and controls have now been studied (Williams et al. 2007), yielding positive and negative results. Heterogeneity of patient population has undoubtedly contributed to these inconsistent results. While the high activity *Val* allele is weakly, if at all, associated with the increased risk for schizophrenia, its interaction with other candidate genes, environmental factors, such as smoking, antipsychotic efficacy and adverse events, as well as its role in cognitive (dys)function is an exciting area for the future research.

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