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**Hypothesis**

# Matrix Metalloproteinase-9 (MMP9)—A I Enzyme in Cardiovascular Disease, Canc Neuropsychiatric Disorders

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## Abstract

Matrix metalloproteinase-9 (MMP9) has been implicated in num disorders and cancer. Recently, MMP9 has been shown to be in nervous system activity. Furthermore, a pathogenic role for this er disorders as schizophrenia, bipolar illness, and multiple sclerosi molecular-genetic studies on MMP9 that have been performed in Furthermore, I hypothesize that the *MMP9* gene, as shown by fur mediating the relationship of neuropsychiatric illnesses (schizophre are comorbid with cardiovascular disease and cancer.

## 1. Introduction

The matrix metalloproteinases (MMPs) are a large family of zinc-de substrates of which are proteins of the extracellular matrix and (MMP9), also known as gelatinase B, 92 kDa gelatinase, or 92 D and most complex member of this family) has recently been a subj

In recent years, MMPs have attracted interest as mediators of both system [2]. Concerning MMP9, a role for this enzyme in the p investigated in experimental studies [3]. Blocking of MMP9, eithe inhibits hippocampal late-phase long-term potentiation as well as endogenous inhibitor of MMP9, abolished MMP9-dependent long-t moving rats [5]. In addition, a pathogenic role has been proposed [6] and temporal lobe epilepsy [7].

The human MMP9 gene was mapped to the chromosome region this gene were identified. The 1562 C/T polymorphism (rs39182 transcription. This single nucleotide polymorphism (SNP) at 156 which results in the loss of binding of a nuclear protein to this r macrophages. In these cells, the C/C genotype leads to a low pro result in high transcriptional activity [9].

The molecular-genetic studies of the functional 1562 C/T interesting results in cardiovascular, cancer, and neuropsychiatric cancer showed that carriers of the T allele have an increased se cardiac mortality [11], and increased risk or more severe progr studies also demonstrated an association of this polymorphism w illness [15], and multiple sclerosis [16, 17].

Based on the results of these studies, hypothesize that the polymorphism, may mediate the epidemiological comorbidity of mood disorder, multiple sclerosis) with cardiovascular diseases and

## 2. MMP-9 in Cardiovascular Disease

In a large prospective study of middle-aged men (465 cases, 107 of serum MMP9 with the incidence of coronary heart disease in t recently been performed in middle-aged population by Swedish r MMP9 levels not only with cardiovascular [19] but also with psych depression) [20]. Related to these observations, an inverse relat and MMP9 was found in healthy subjects [21]. The higher level of been recently reported [22]. Higher MMP9 level was also a correlat increased mortality in patients with coronary artery disease [24].

The association of MMP9 status with a progression of coronary he genetic studies that used the functional 1562 C/T polymorphism the T allele had increased cardiac mortality [11], and more re infarction in patients with coronary heart disease was found [ demonstrated between the T allele of the 1562 C/T polymorph compatible with higher transcriptional activity of this allele in expe plasma MMP9 and the T allele of the 1562 C/T polymorphism wa [26].

Recently, Konstantino et al. [27] pointed out the prominent role rupture, and postulated that MMP9 levels may serve as a biomark MMP9 levels with atherosclerotic changes has been previously fou artery [28] and with chronic periodontitis [29]. Higher levels cardiomyopathy, which correlated with a worse prognosis [30]. functional 1562 C/T polymorphism of the MMP9 gene, it was increased severity of coronary atherosclerosis [10].

The available data also show a possible association of MMP9 with disease. Higher MMP9 level were found preclinically in spontan clinically in women with gestational hypertension [32]. In the gr Offspring Study, higher MMP9 concentrations were related to highe it was demonstrated that plasma MMP9 samples were inhibited b converting enzyme [34].

## 3. MMP-9 in Cancer

Sakata et al. [35] showed an overexpression of MMP9 in an epithel node metastases of ovarian carcinoma cells. Similarly, in patient expression of MMP9 was associated with a worse prognosis of the been reported in endometrial polyps, especially in those occurrin MMP9 levels were also observed in pulmonary lymphangio-l proliferation [38].

Molecular-genetic studies of the functional 1562 C/T polymorph association of T allele with an increased risk of some kinds of can and/or greater dynamics of metastases. Sugimoto et al. [12] endometrial carcinoma risk in a Japanese population. Other studies for oral squamous cell carcinoma in younger male areca users [3 cell carcinoma [40]. Kader et al. [41] demonstrated that s polymorphism) were associated with the risk of invasive cancer o has been found that the T allele of the 1562 C/T polymorphis phenotype of this tumor [42] and with a higher frequency of Przybylowska et al. [44] reported that the T allele of this polymor of tumors, and Hughes et al. [13] showed an association with the lymph node metastases in colorectal cancer was also found to be c

## 4. MMP-9 in Multiple Sclerosis

An upregulation of MMPs with a decrease of tissue inhibitors (TI patients and in an animal model of the disease has been found ir affecting MMPs for treatment of MS has been discussed [46]. A courses of MS has been found [47]. Also recently, Shinto et supplementation decreased MMP9 levels in relapsing-remitting MS.

In recent years, molecular-genetic studies have focused on the gene in MS. In the first study performed in Serbia, it was found severity of MS, and the T allele was found significantly less freq performed in the Czech Republic confirmed these findings, showir MS compared to healthy subjects, especially females [17].

Recently, epidemiological studies investigating the comorbidity published. The first study was performed on 9949 hospitalizations 2002. It was found that MS patients were less likely to be hosp infarction. However, they were more likely to be hospitalized for is MS population) [49]. A second study performed in Sweden estim and 203 951 individuals without MS using Swedish general popul a decreased overall cancer risk, however, an increased risk for brai

## 5. MMP-9 in Schizophrenia

Studies on the MMP9 levels in schizophrenia have not yet been illness, we genotyped the functional 1562 C/T polymorphism in healthy control subjects. Since MMP9 influences hippocampal and that a polymorphism of the *MMP9* gene is associated with the pa prefrontal cortex impairment is one of the most common patholo the C/C genotype and C allele, and the diminished frequency of th schizophrenia subjects compared to healthy controls [14].

As shown previously, in both cardiovasular disease and cancer, manifestations of these conditions [10–13]. Although the risk of to be similar to that of the general population [52], some studies s in such patients [53]. Also, compatible with our findings, a lower has long been postulated [54], and the results of some recent anal

## 6. MMP-9 in Bipolar Mood Disorder

Similar to schizophrenia, there are no studies measuring MMP9 investigate the status of the *MMP9* gene in this illness, we genot group of 416 patients with bipolar mood disorder, including 75 pati subjects. This approach has been substantiated by previous report prefrontal cortical activity and for aspects of brain functions su Patients with bipolar mood disorder had a significant preponder polymorphism of the *MMP9* gene compared to healthy control s especially evident in a subgroup of patients with bipolar disorder ty

Compatible with the finding that T allele carriers present more se disease and cancer [10–13] are findings from a recent epidemiol among patients with bipolar disorder [57]. A Swedish epidemic increased mortality rate from cardiovascular disease in bipolar pati

## 7. MMP-9 and Neuropsychological Tests

In view of the experimental studies showing an involvement of M also performed neuropsychological tests measuring this activity in in control subjects in relation to 1562 C/T polymorphism of MMP 84 female), mean age 29 years, 177 patients with bipolar illness (6 181 healthy subjects (86 male and 95 female), mean age 35 y computer version of the Wisconsin Card Sorting Test (WCST) wa memory and executive functions, depending primarily on prefronta A and B, and the Stroop test, A and B, were used.

In schizophrenia patients, no differences were found regarding ne various genotypes of the polymorphism (data not published). Amo C/C homozygotes ( ) were better on all domains of the WCST no differences were found in female patients. Bipolar males and f and years) or mean duration of illness ( years a and mean duration of the illness of C/C homozygotes were similar

In the only previous study measuring the impact of MMP9 gene o association between hippocampus-dependent episodic memory a *MMP9* gene in healthy subjects. Also, in control subjects studied genotypes did not reveal significant differences either in the who

difference was in Stroop test, part A, in male patients, where the
than other genotypes combined ( ). This difference in perfo
obtained in male bipolar patients on WCST domains. Healthy mal
years and years, resp.) [61].

These results suggest that in humans, neuropsychological function
correlation. Thus, increased activity of the MMP9 system was ass
experimental animals models [4, 5], also with neuropsychiatric il
[16, 17] and The results obtained in males with bipolar illness on
may suggest that under certain conditions, a correlation of higher
(connected with lower transcriptional activity for the MMP9 gene) r

## 8. Matrix Metalloproteinase-9 (MMP-9)— A Putative Disorder, Cancer, and Neuropsychiatric Disorders

Because of the functional implications of the 1562 C/T polym
cardiovascular disorders, cancer, and such neuropsychiatric illnes
multiple sclerosis can be hypothesized (Figure 1).

**Figure 1:** Epidemiological relationships betwe
multiple sclerosis, and bipolar mood disorder
*MMP9* gene.

Hence, the T allele of the 1562 polymorphism of MMP9 gene is re
and in cardiovascular illness and cancer to higher MMP-levels in bi
carrying of the T allele and/or higher MMP9 levels are related to a
heart disease (CHD) [25] increased atherosclerosis [10], an
Interestingly, in neuropsychiatric disorders with a lower frequer
suggest a more benign course of cardiovascular disease, for exam
hospitalizations in MS [49]. On the other hand, the phenomenon
mortality in patients with mood disorders (which have a higher
observed [58]. The proposed mediating factors include impairme
both in bipolar and unipolar depression [62] and, as hypothesized

In oncology, the carrying of the T allele of the 1562 C/T MMP9 ge
some kinds of cancer [12], more severe progression of tumor gro
In neuropsychiatric disorders, some epidemiological studies s
schizophrenia [56] and in MS [50] (both illnesses with a lower fr
morbidity in bipolar mood disorder [57]. Interestingly, an associat
been also found with respect to the levels of another metalloprot
[63, 64].

Nevertheless, it should be emphasized that in the central nervous
As Agrawal et al. [65] pointed out “the good guys may go bad” u
to this hypothesis. The majority of referred molecular genetic re
polymorphisms of MMP9 but the other polymorphisms have not
human blood levels of MMPs used to develop this hypothesis wer
[66]. Also, it should be acknowledged that there is a complex int
environmental factors of MMPs family and with a host of other gen
the *MMP9* gene is a mediating factor among cardiovascular disorc

and multiple sclerosis. This is may contribute to a better explanat
neuropsychiatric illnesses.

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