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Associations of Matrix Metalloproteinase-9 and Tissue Inhibitory Factor-1 Polymorphisms With Parkinson Disease in Taiwan

Yi-Chun Chen, MD, Yih-Ru Wu, MD, Mina Mesri, and Chiung-Mei Chen, MD, PhD

Abstract: Matrix metalloproteinases (MMPs) function in the degradation of extracellular matrix and are considered to play a role in the pathogenesis of neurodegenerative diseases including Parkinson disease (PD). MMPs activities are modulated by tissue inhibitors of metalloproteinases (TIMPs). This study examined whether the genetic polymorphisms of *MMP-3*, gelatinase (*MMP-2* and *MMP-9*), *TIMP-2*, and *TIMP-1* were associated with PD in Taiwan.

A total of 359 PD patients and 332 controls were enrolled. The candidate genetic variants included *MMP-2* rs2285053 (−735 C > T), *MMP-3* rs3025058 (−1171 5A > 6A), *MMP-9* rs3918241 (−1831 T > A), rs17576 (G > A, R279Q), and rs3787268 (G > A, intron), *TIMP-1* rs4898 (T > C, F124F), and *TIMP-2* rs7503607 (−269 G > T). Associations were tested by logistic regression, adjusted with gender and age at onset.

Minor allele frequency of *TIMP-1* rs4898 (36.0%) was significantly lower in the male PD patients than in the male controls (51.2%) (χ^2 test, $P = 0.004$). When adjusted with gender and age at onset, *MMP-9* rs17576 AA genotype was associated with PD susceptibility in a recessive fashion (odds ratios [OR] = 2.28, 95% confidence intervals [95% CI] = 1.12–4.62, $P = 0.02$). In males, *TIMP-1* rs4898 C allele was associated with a protective effect on PD (OR = 0.75, 95% CI = 0.60–0.94, $P = 0.014$). We did not find association between the examined genetic variants of *MMP-2*, *MMP-3*, and *TIMP-2* and PD susceptibility.

This is the first study that demonstrated a protective effect of *TIMP-1* rs4898 C allele on male PD and a modest association of *MMP-9* rs17576 AA genotype with PD susceptibility in the Taiwan population. Further replication is needed for confirmation.

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Abbreviations: 6-OHDA = 6-hydroxydopamine, ADAMs = A disintegrin and metalloproteinase domains, BBB = blood–brain barrier, CGMH = Chang-Gung Memorial Hospital, CI = confidence interval, CSF = cerebrospinal fluid, ILs = interleukins, MAF = minor allele frequency, MMPs = matrix metalloproteinases, MPP^+ = 1-methyl-4-phenylpyridinium, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, NO = nitric oxide, OR = odds ratio, PD = Parkinson disease, PGE2 = prostaglandin E2, SNpc = Substantia nigra pars compacta, SNPs = single nucleotides polymorphisms, TIMPs = tissue inhibitors of metalloproteinases, TNF-α = tumor necrosis factor-alpha.

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disorder. The pathological hallmarks of PD include progressive loss of nigro-striatal dopaminergic neurons and the presence of α-synuclein-containing Lewy bodies in the substantia nigra pars compacta (SNpc) and other sites of the brain.[1] The majority of PD cases are sporadic with only ∼10% identified as familial.[2] In contrast, mutations in different genes and environmental factors collectively account for most of the sporadic PD. There is ample evidence to suggest that it most likely results from an elaborate interplay of various factors: genetic predispositions, modifying effects by susceptible alleles, environmental exposures, gene–environment interactions, and their direct impact on the developing and aging brain.[1–3] Several pathways have been linked to PD pathogenesis including the presence of inflammation in the SNpc, oxidative stress, mitochondrial dysfunction, accumulation of atypical or misfolded protein, malfunction of ubiquitin-proteasome pathway, impairment of autophagolysosomes, and alterations of synaptic function and endosomal trafficking.[1,4–7]

More recently, the role of inflammation in the pathogenesis of PD has gained rising attention.[8] Pathology of substantia nigra of postmortem PD has shown $CD8^+$ and $CD4^+$ T-cell infiltration, accumulations of microglia cells and astrocytes, and alterations in glial cell morphology and function.[9] Aggregated alpha-synuclein could activate microglia, which leads to disease progression in PD.[10] Direct injection of α-synuclein into the substantia nigra resulted in the upregulation of mRNA expression of proinflammatory cytokines and microglial activation.[11] Microglia are the resident innate immune cells in the central nervous system and produce several factors (interleukins [ILs], tumor necrosis factor-alpha [TNF-α], nitric oxide [NO], prostaglandin E2 [PGE2], matrix metalloproteinases [MMPs], etc). Among these factors produced by activated microglia, MMPs are also proinflammatory factors that are toxic to neurons.[12] Accumulating evidence suggests that MMPs are involved in the neuropathological processes such as inflammation, blood–brain barrier (BBB) damage and neuronal cell death, which lead to central nervous system disorders such as PD.[12] Inducers of MMP expression and activity, such as cytokines, NO, and reactive oxygen species are implicated in the pathophysiology

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From the Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and College of Medicine, Chang-Gung University, Taoyuan, Taiwan (Y-CC, Y-RW, C-MC); and Medicine and Surgery MBChB, School of Medicine, University of Liverpool, Liverpool, United Kingdom (MM).
Correspondence: Chiung-Mei Chen, Department of Neurology, Chang Gung Memorial Hospital, Chang-Gung University College of Medicine, Taipei, Taiwan (e-mail: cmchen@adm.cgmh.org.tw).
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of PD. Tissue inhibitors of metalloproteases (TIMPs) have inhibitory actions against most MMPs with some predilections: TIMP-1 mainly inhibits MMP-9, whereas TIMP-2 inhibits MMP-2 and, paradoxically, contributes to activation of pro-MMP-2.

In the 4 main categories of MMP family, MMP-3 (one of the stromelysins) has been reported to influence pathogenesis of PD by generation of specific aggregation-enhancing α-synuclein fragments resulting from limited proteolysis.[13] MMP-3 was induced and activated in dopaminergic cells upon stress conditions.[14] In the postmortem brains of PD patients, α-synuclein and MMP3 were found to be co-localized in Lewy bodies.[14,15] MMP-3 contributes to the loss of dopaminergic neurons in a mouse model of PD with BBB damage and infiltration of peripheral immune cells.[16] In addition, gelatinases (MMP-9 and MMP-2) have been shown to be related to PD. Reduced MMP-2 and increased TIMP-1 levels were shown in substantia nigra of postmortem brain of PD.[17] Increased TIMP-1 levels in cerebrospinal fluid (CSF) of PD patients were also shown.[18] Although these findings pointed towards a possible link between MMPs and TIMPs and pathogenesis of PD, the associations between genetic polymorphisms of the MMP/TIMP pathway and the susceptibility to PD are largely unknown in the Taiwan population. A prior report showed no association between *MMP-3* − 1171 (5A/6A) and PD risks in Finns;[19] however, the sample number was small. A significant association between the −1562 C > T polymorphism in the *MMP-9* gene and risk of PD has been reported in Chinese.[20] The study herein is a case–control study that examines whether the single nucleotides polymorphisms (SNPs) of *MMP-3*, gelatinase (*MMP-2* and *MMP-9*), and their counter-proteins (*TIMP-2* and *TIMP-1*) are associated with PD susceptibility in the Taiwan population.

METHODS

Subjects

A total of 359 PD patients and 332 controls were enrolled in this study. Patients (mean age at onset 61.0 ± 11.5 years, age at recruitment 68.4 ± 10.8 years, 49.6% women) diagnosed with PD were recruited from the neurology clinics of Chang-Gung Memorial Hospital (CGMH). All patients were diagnosed with probable sporadic PD according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria.[21] Controls were recruited from unrelated healthy adult volunteers (age at recruitment 67.4 ± 8.1 years, 50.3% women) matched for age, gender, and ethnicity. This study was approved by the Institutional Review Board of CGMH. All subjects gave informed consent for the study.

Polymorphism Selection and Detection

The cytogenetic location of *MMP-2* is at 16q12. We selected a promoter variant rs2285053 (−735 C > T) which increased *MMP-2* transcription.[22] The cytogenetic location of *MMP-3* is at 11q22. The common polymorphism rs3025058 (−1171 5A/6A) in the promoter of *MMP-3* gene affected the *MMP-3* gene expression, in which the 5A allele was associated with higher transcriptional activity compared to 6A allele.[23] The SNPs of *MMP-9*, located at 20q13, were selected based on international HapMap data on NCBI Build 36 assembly for Asian population and our prior experience,[24] including rs3918241 (−1831 T > A, promoter), rs17576 (G > A, missense variant R279Q, exon6), and rs3787268 (G > A, intron). For the *TIMP-1* gene (cytogenetic location at Xp11.23), we selected rs4898 (T > C, synonymous, F124F, exon5) which is a strong tag SNP for Han Chinese. For the *TIMP-2* gene (cytogenetic location at 17q25.3), we selected *TIMP-2* rs7503607 (−269 G > T) which is 8 base pairs away from −261 G > A and fits the condition for TaqMan® SNP Assays. Genomic DNA was extracted from peripheral blood mononuclear cells by standard protocols. Polymorphisms were genotyped by the TaqMan® SNP Assays using the ABI Prism 7900HT Sequence Detection System (Table 1). All the SNPs are in Hardy–Weinberg equilibrium with significance level set at 0.05 to control SNP quality.

Statistical Analysis and Power Estimation

The differences in allele frequencies of SNPs between PD patients and controls were analyzed by the χ^2 test and Fisher exact test where appropriate. Multivariable logistic regression was used to analyze the phenotype-genotype associations of PD first under the additive genetic model and then the recessive model based on the distribution of genotypes. Covariables included age and gender.

Given the observed allele frequency in the present case–control study, at the 0.05 significance level, we had power >0.8 to identify an association of each genetic variant with PD susceptibility when the per-allele genetic effect was greater than an odds ratio of 1.4. Analyses were performed using SAS software version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

The allele frequency distributions of the examined polymorphisms in PD patients and controls are displayed in Table 2. Minor allele frequency (MAF) of *TIMP-1* rs4898 (36.0%) were significantly lower in the male PD patients, compared with that in the male controls (51.2%) (χ^2 test, $P = 0.004$). The frequency of minor allele in all of the other examined genetic variants was not different between PD patients and controls. The distributions of genotypes of the candidate variants and the associations of individual genetic variant with PD risk are displayed in Table 3. When adjusted with gender and age of onset, we found that *MMP-9* rs17576 AA genotype was associated with PD susceptibility in a recessive fashion (odds ratios [OR] = 2.28, 95% confidence intervals [95% CI] = 1.12–4.62, $P = 0.02$). In men, *TIMP-1* rs4898 C allele was associated with a protective effect on PD (OR = 0.75, 95% CI = 0.60 to 0.94, $P = 0.014$). The association between *TIMP-1* rs4898 and PD was not observed in the women. We did not find association between the examined variants of *MMP-2*, *MMP-3*, and *TIMP-2* and PD susceptibility. In addition, pairwise haplotype analysis of the 3 polymorphisms of MMP-9 showed no additional information regarding PD susceptibility.

DISCUSSION

This is the first study showing associations of *MMP-9* and *TIMP-1* variants with PD susceptibility. For *MMP-9,* a prior study showed a significant association between −1562 C > T (rs3918242) polymorphism in the *MMP-9* gene and PD risk in Chinese.[20] Although we did not find association between PD risk and rs3918241, the selected polymorphism at *MMP-9* promoter, we discovered association between rs17576 AA genotype (missense variant R279Q, exon 6) and PD risk. For the *TIMP1* gene, the tag SNP rs4898 is considered to represent a complete haplotype block covering the whole *TIMP1* gene,

TABLE 1. Primers for Genotyping of Single Nucleotides Polymorphisms (SNPs) Using the TaqMan SNP Assays

SNP	Clone ID	Annealing Temperature	Forward Primers (F) and VIC-Probe	Reverse Primer (R) and FAM-Probe
MMP-2 rs2285053	C__26734093_20	60°C	VIC-TCATCCTGTGACCGAGAATGCGGA CCCTCCTGGGAGTGCAGCCCAGCAGGT	FAM-TCATCCTGTGACCGAGAA TGCGGACTCTCCTGGGAGTG CAGCCCAGCAGGT
MMP-3 rs3025058	AHFA947 (Custom)	63°C	F-TCAATGTGGCCAAATATTTTCCCTGTA VIC-ACATGGTTTTTTCCCC	R-ATTCTATGGTTCTCCATTCC TTTGATGG FAM-ACATGG TTTTTCCCC
MMP-9 rs17576	C__11655953_10	60°C	VIC-CTCCTCGCCCCAGGACTCTACACCC AGGACGGCAATGCTGATGGGAAACCC	FAM-CTCCTCGCCCCAGGAC TCTACACCCGGGACGGC AATGCTGATGGGAAACCC
MMP-9 rs3787268	C___7499592_10	60°C	VIC-GGCCATAGAGGATGTCGCTTAAAA CAAAAAAGAAGAAGAAGAAAGTCCTGT	FAM-GGCCATAGAGGATGT CGCTTAAAACGAAAAAGAA GAAGAAGAAAGTCCTGT
MMP-9 rs3918241	C__29689865_10	60°C	VIC-AACTTCAACTTTTCTGTAAAGGAAGA TAATTATCTCCATCTCACAGTCTCA	FAM-AACTTCAACTTTTCTGT AAAGGAAGTTAATTATCT CCATCTCACAGTCTCA
TIMP-1 rs4898	C__11175659_10	60°C	VIC-TCTTGCACATCACTACCTGCAGTTT CGTGGCTCCCTGGAACAGCCTGAGCT	FAM-TCTTGCACATCACTA CCTGCAGTTTTGTGGCT CCCTGGAACAGCCTGAGCT
TIMP-2 rs7503607	AHLJ0X8 (Custom)	58°C	F- GCGCAAACTTTCTCTCCTCTTT VIC-CTCGGCGGCCGCG	R- GCAGCAAACACATCCGT AGAAG FAM-TCTCGGC TGCCGCG

SNP = single nucleotides polymorphisms.

based on international HapMap data on NCBI Build 36 assembly for Asian population.[24] We found that carriers of minor allele T of *TIMP1* rs4898 might be protected from PD risk in the male group. For *MMP-2* and *TIMP-2*, we did not find associations between the selected polymorphisms and PD. For *MMP-3*, this study supported the prior Finns research which demonstrated no association between *MMP-3* and PD.[19] Because the significance of the discovered associations is weak, further replication study with larger sample size is needed to confirm our findings.

Recently, increasing attention has been drawn to the role of inflammation in the pathogenesis of PD. Metalloproteinases are a large family of important proteases that include MMPs and proteins with a disintegrin and metalloproteinase domains (ADAMs). MMPs and ADAMs play an important role in neuroinflammmation. MMPs produced by activated microglia are proinflammatory factors and have been implicated to contribute to the pathogenesis of neurodegenerative diseases including PD.[24] Microglia stimulated by alpha-synuclein induced the expression of MMP-1, -3, -8, and -9 and inhibition of MMP-3, -8, or -9 suppresses the production of NO and other proinflammatory cytokines in primary microglia.[25] Overexpression of alpha-synuclein in rat primary astrocytes or glia increased MMP-9 activity.[26] 6-Hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP^+) increased MMP-9 gene expression by inducing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) binding to the MMP-9 promoter in human neuroblastoma cells.[27] All of these suggest

TABLE 2. Comparison of Minor Allelic Frequency Between Parkinson Disease (PD) Cases and Controls

		MAF (95% CI) %	
SNP/Cytogenetic Location	PD N = 359	Controls N = 332	*P*
MMP-2 16q12/rs2285053	24.2 (21.1, 27.4)	24.2 (20.9, 27.4)	0.97
MMP-3 11q22/rs3025058	16.3 (13.6, 19.0)	14.0 (11.4, 16.6)	0.24
MMP-9 20q13/rs3918241	13.7 (11.1, 16.3)	11.0 (8.7, 13.3)	0.12
rs17576	22.4 (19.1, 25.7)	22.0 (18.8, 25.1)	0.83
rs3787268	40.5 (36.9, 44.1)	43.6 (39.7, 47.4)	0.25
TIMP-1 Xp11/rs4898 in males	36.0 (28.9, 43.0)	51.2 (43.5, 59.0)	0.004
TIMP-1 Xp11/rs4898 in females	44.7 (39.5, 49.8)	47.5 (42.1, 53.0)	0.45
TIMP-2 17q25/rs7503607	16.9 (14.2, 19.6)	14.5 (11.8, 17.1)	0.21

Comparisons between PD cases and controls were analyzed by the χ^2 test.
CI = confidence interval, MAF = minor allele frequency, PD = Parkinson disease, SNP = single nucleotides polymorphisms.

TABLE 3. The Distributions of Genotypes of the Candidate Variants and the Associations of Individual Genetic Variant With PD Risk

SNP	Genotype	PD	Control	OR (95% CI), P^* (model)
MMP-2 rs2285053	CC	206	187	
	CT	132	122	1.01 (0.73, 1.41), 0.94*
	TT	21	18	1.06 (0.75, 1.50), 0.75*
				1.03 (0.80, 1.34), 0.82 (additive)
MMP-3 rs3025058	6A6A	250	245	
	6A5A	101	81	1.18 (0.83, 1.70), 0.36*
	5A5A	8	6	1.12 (0.63, 1.99), 0.69*
				1.17 (0.86, 1.60), 0.33 (additive)
MMP-9 rs3918241	TT	268	260	
	TA	82	71	1.23 (0.84, 1.80), 0.29*
	AA	8	1	2.89 (0.97, 8.59), 0.06*
				1.39 (0.98, 1.97), 0.07 (additive)
rs17576	GG	225	197	
	GA	107	118	0.81 (0.58, 1.14), 0.22*
	AA	27	13	1.46 (1.02, 2.10), 0.04*
				2.28 (1.12, 4.62), 0.02 (recessive)
rs3787268	GG	127	105	
	GA	173	159	0.90 (0.63, 1.28), 0.55*
	AA	59	63	0.85 (0.68, 1.07), 0.18*
				0.86 (0.69, 1.08), 0.20 (additive)
TIMP-1 rs4898 in males	T	116	80	
	C	65	84	0.75 (0.60, 0.94), 0.014*
TIMP-1 rs4898 in females	TT	53	45	
	TC	91	81	0.95 (0.57, 1.59), 0.85*
	CC	34	37	0.91 (0.66, 1.26), 0.57*
				0.91 (0.66, 1.25), 0.55 (additive)
TIMP-2 rs7503607	GG	246	235	
	GT	103	86	1.06 (0.74, 1.52), 0.74*
	TT	9	4	1.47 (0.79, 2.75), 0.23*
				1.16 (0.84, 1.56), 0.39 (additive)

Adjust age at onset and gender by logistic regression in the additive model or recessive model where appropriate.
CI = confidence interval, OR = odds ratio, PD = Parkinson disease, SNP = single nucleotides polymorphisms.
*Odds ratios of the at-risk genotype were calculated by comparing each value to the common genotype and under additive or recessive genetic models.

the expression of MMPs may contribute the pathogenesis of PD and expression of MMPs may influence the risk of PD.

The promoter regions of the inducible genes encoding MMPs generally contain binding sites for transcription factors such as activator proteins and NF-κB.[28] Activation of the NF-κB that controls target genes encoding proinflammatory cytokines, adhesion molecules, chemokines, and inducible enzymes, has been shown in PD brain.[29] Reduced MMP-2 and increased TIMP-1 have been shown in substantia nigra of postmortem brain from PD patients.[17] Increased TIMP-1 levels in CSF of PD patients were also reported.[18] Our study further provides evidence of link between MMPs/TIMPs and PD, although this study demonstrates only modest significant association of *MMP-9* and *TIMP-1* polymorphisms with PD susceptibility. This study identified rs17576 AA genotype of *MMP-9* as a risk of PD susceptibility. Missense variation of rs17576 causes change in the catalytic domain and pexin-like domain of the MMP-9 enzyme, leading to polarity and functional change, which may thus contribute to enhanced inflammatory process.[30] There are limitations in our study. First, the protective genetic effect of rs4898 C allele of *TIMP1* and the risk imposed by rs17576 AA genotype of *MMP-9* on PD were not strong, and it is worth mentioning that the weak significance of the discovered associations might not survive during statistic correction of multiple testing. In addition, this study does not exclude association of PD with other SNPs within genes *MMP2*, *MMP3*, and *TIMP2*. Finally, the biological relevancies of the rs4898 C allele of *TIMP1* and AA genotype of *MMP-9* are not clear, which remains to be investigated. Further replicated studies with large sample size are needed to confirm our results before these candidate SNPs can be viewed as independent predictors of PD.

In summary, this is the first study that demonstrated modest association of *MMP-9* rs17576 AA genotype with PD susceptibility and a protective effect of *TIMP-1* rs4898 C allele on PD. The MMP/TIMP pathway posing a risk factor for PD may not be disease-specific, given that these polymorphisms could be risk factors for other medical conditions.[17,20,24,28] Further functional studies are needed to clarify the pathophysiology underlying the association between *MMP-9* and *TIMP-1* and PD risk and provide the additional functional information to support our findings.

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