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Effects of common functional *MMP12* gene polymorphisms on PD in a Polish population

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ABSTRACT

The present study investigated associations of two functional *MMP12* polymorphisms with PD risk and cognitive impairment in PD. A total of 478 study subjects (241 PD and 237 age and sex matched controls) were included in the study. UPDRS score, Hoehn–Yahr staging and Schwab–England scale were used to assess motor abilities and activity during daily life. All patients were classified into groups with dementia (PDD, $n = 72$) and without dementia (nPDD, $n = 159$) based on the neuropsychological assessment. The two most common functional single nucleotide polymorphisms (SNPs) in *MMP12* gene were determined using TaqMan real-time PCR assays. Frequencies of evaluated *MMP12* rs2276109 alleles and genotypes were similar in PD and the controls, whereas rs652438G allele genotypes were significantly more frequent among healthy individuals ($p = 0.013$, OR 0.47 (0.26–0.85). The rs2276109 and rs652438 allele and genotype frequencies were not associated with dementia in PD patients.

The current results suggest that *MMP12* rs652438 but not *MMP12* rs2276109 may affect the risk for PD, as the minor G allele genotypes might be a protective factor.

1. Introduction

Neurodegenerative diseases like Parkinson's and Alzheimer's constitute one of the major health problems in the elderly population. The mechanism of neurodegeneration has not been well established yet, however, more recently the role of inflammation in the pathogenesis of PD gained ground [1]. The neuroinflammation, defined as inflammation of the nervous tissue, can protect the CNS against harmful stimuli, but the primary initiation of a cascade of events, such as production of

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cytokines, chemokines and free radicals, finally results in chronic inflammatory state. Microglia, the resident immune cells of the central nervous system, play an important role in maintaining homeostasis. Under physiological conditions, number and function of microglia are controlled by the local microenvironment. However, the process of neurodegeneration can promote microglial activation, also known as 'microglial priming', and switches them from a protective to an aggressive phenotype with enhanced synthesis of pro-inflammatory mediators, such as reactive oxygen species (ROS), nitric oxide (NO) and metalloproteinases (MMPs). It is interesting that a common feature of neurodegenerative disorders is the presence of activated microglia in areas of neuronal death [2]. Astrocytes appear to play a similar role to microglia in inflammatory responses of the CNS. They also produce different inflammatory mediators, for example, IL-2 and IL-1, thereby stimulating $CD4^+$ T helper cells to produce granulocyte-macrophage colony stimulating factor (GM-CSF), which contribute to recruitment of CD11b-positive myeloid cells and propagation of inflammation processes [3]. $CD4^+$ and $CD8^+$ T cells can secrete cytokines and MMPs that are not only toxic to neurons but also can lead to vascular leakage and consequently the blood-brain barrier (BBB) damage. The disrupted BBB permits the entry of immune cells from periphery, thus converting acute inflammation into a chronic inflammatory state.

The loss of dopaminergic neurons in PD is usually associated with glial reaction, particularly the activation of immunocompetent microglia cells. The post mortem examination of substantia nigra of PD patients has shown CD^+ T cell infiltration, accompanied by morphologically and functionally changed microglia cells and astrocytes. There is evidence that direct injection of α-synuclein into the substantia nigra leads to upregulation of mRNA expression of proinflammatory cytokines producing several factors, including MMPs [4].

Matrix metalloproteinases (MMPs) are a growing family of zinc-bound endopeptidases, divided into five subgroups that include collagenases, gelatinases, stromelysins, membrane-type (MT)-MMPs and others. Most MMPs are expressed at low levels under normal physiological conditions (MMP2, MMP9), and serve rather as neuroprotective factors. However, upregulation of certain MMPs has been reported in Parkinson's disease (PD) [5]. A number of studies have demonstrated that neuronal death in PD can be connected with two pathways, i.e. apoptosis and necrosis. Apoptotic cells trigger recruitment of phagocytic cells releasing chemoattractants. Cho et al., and Sugama et al., showed that microglia were rapidly activated by apoptotic dopamine neurons in the substantia nigra after axon transection, and that phagocytosis of apoptotic neurons by activated microglia occurred at early stages of apoptosis [6,7].

Macrophage metalloelastase (MMP12) was first identified as an elastolytic metalloproteinase secreted by inflammatory macrophages. The expression of MMP12 has been revealed in hypertrophic osteoclasts, vascular smooth muscle cells, and the CNS [8,9]. Crocker et al., and other authors showed constitutively high level of MMP12 in microglia in the CNS, and proved its contribution to neuroinflammation [10–13]. Similarly to other MMPs, MMP12 could play a dual role in the pathogenesis of inflammatory diseases. MMP12 was demonstrated to be involved in progression of spinal cord trauma, intracerebral hemorrhage by disrupting BBB functions or triggering macrophage recruitment into the CNS. On the other hand, MMP12 inhibited pathogenesis of experimental autoimmune encephalomyelitis by enhancing anti-inflammatory effects [14].

Genetic variations of pro- and anti-inflammatory cytokines' genes, located within promoter regions, are considered to be involved in PD. Bialecka et al., revealed that *TNF*308AA genotype might increase the risk of early onset of PD [15]. However, associations between genetic polymorphisms of MMP in relation to the risk of PD have not been extensively studied. Chen et al. examined the impact of the genetic polymorphisms of MMP3, MMP2, MMP9 and tissue inhibitors of metalloproteases (TIMPs) TIMP-2 and TIMP-1 coding genes with PD. They demonstrated modest association of *MMP9* rs17576 AA genotype with PD susceptibility and a protective effect of *TIMP1* rs4898C allele in PD [1]. Another study assessed the correlation between cerebral MMP12 expression in the aged brain. Result of the study conducted by Liu et al., suggested that upregulated cerebral MMP12 during aging enhanced aging associated with neuroinflammmation by facilitating recruitment of bone marrow-derived microglia into the brain [9]. Over the last few decades, several factors have been identified as main players of neurodegeneration in the nigrostriatal system. Cytokines such as IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ are increased in serum of PD patients. Consistent with the aforementioned events, genetically inherited changes in MMPs expression might contribute to upregulation of cytokines and influence susceptibility to PD. The present study aims to evaluate the most common functional *MMP12* gene polymorphisms associations with PD in a Polish population.

2. Materials and methods

2.1. Subjects

Consecutive 241 PD patients of Caucasian origin (127 males and 114 females), aged from 25 to 89 years (64.17 $\pm$ 10.13 years), PD diagnosed, and confirmed during follow-up visits, according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria were recruited in Outpatient Movement Disorder Clinics at two Polish centers (Gdansk, Szczecin) [16]. Clinical stage of the disease was rated according to Hoehn and Yahr and severity of motor symptoms was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (parts II–IV) [17]. All patients with clinical symptoms suggesting secondary causes of parkinsonian syndrome (vascular, drug-induced), with features suggestive of atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy and corticobasal syndrome) were excluded from final data analysis. Control samples were obtained from 237 randomly selected healthy individuals (112 males and 125 females), aged 25–88 years (64.86 $\pm$ 9.43 years) from the same geographical region as the patients, matched by sex, age and ethnicity (all of Caucasian origin) to avoid the influence of population stratification.

All participants were assessed with Mini-Mental State Examination (MMSE) and Beck Depression Inventory (BDI) to screen for dementia and depression [18,19]. The control

subjects were included if they were not depressed and not demented (≥25 in MMSE), did not demonstrate any parkinsonian symptoms on neurological examination, had no history of stroke and did not suffer from any liver and kidney dysfunction. All patients who met inclusion criteria underwent detailed neuropsychological examination described previously [20]. According to the results of investigations, patients were classified as non-demented (nPDD) and demented (PDD) according to Emre et al. criteria [21]. The demographic and clinical characteristics of the Parkinson's disease patients with or without dementia are shown in Table 1.

The protocol of the study was approved by the relevant local ethics committees, and study participants provided written informed consent.

2.2. Genetic study

Genomic DNA was extracted from buccal swab samples from 241 PD patients and 237 control subjects, using Quick Blood DNA Purification Kit (EurX, Poland), and subsequently standardized to equal concentrations of 10 ng/μl, based on spectrophotometric absorbance measurement (260/280 nm). Genotyping for a presence of *MMP12* rs2276109:A>G (located in gene promoter, −82A>G) and rs652438:A>G (exon 8, Asn357-Ser) single nucleotide polymorphisms (SNPs) was performed using pre-validated allelic discrimination TaqMan real-time PCR assays (assay IDs: C__15880589_10 and C____785907_10, Life Technologies, USA), and TaqMan GTXpress Master Mix (Life Technologies, USA). All reactions were run in a final volume of 12 μl. Fluorescence data was captured using ViiA7 Real-Time PCR System (Applied Biosystems, USA) after 40 reaction cycles. Specific genotypes were assigned to individual samples after analysis with TaqMan Genotyper Software (Thermo Fisher Scientific, USA).

2.3. Statistical analysis

Concordance of genotype distribution with Hardy–Weinberg equilibrium was assessed using the χ^2 exact test. Genetic case-control analyses between study groups were performed using the Fisher exact test. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using the Newcombe–Wilson method without the continuity correction. Data alignment with normal distribution was tested by means of Shapiro–Wilk test, and further analyses were performed by means of *t*-Student test or Mann–Whitney *U*-test. The General Linear Model (GLM) was used for multivariate analysis. A p level of less than 0.05 was considered statistically significant. Calculations were performed using the Statistica 9.1 software package (StatSoft, Krakow, Poland).

3. Results

3.1. Demographic and clinical characteristics of PD patients

In the group of 241 PD patients enrolled to the study, 72 individuals fulfilled the criteria for dementia. nPDD and PDD did not differ in sex, mean age, age at disease onset, whereas the disease duration was significantly shorter in nPDD group (6.1 ± 4.8 vs. 8.3 ± 5.9, $p = 0.036$). The daily levodopa dosage was significantly lower in non-demented group (698 ± 439 mg) in comparison to PD with dementia (792 ± 427 mg, $p = 0.046$). Both Hoehn–Yahr disease stage and MMSE score were associated with dementia status (H–Y disease stage in nPDD group: 2.02 ± 0.74, in PDD group: 2.54 ± 0.95, $p < 0.0001$; MMSE score: 28.1 ± 1.9 in nPDD group and 23.6 ± 4.2 in PDD group, $p < 0.0001$).

3.2. MMP12 polymorphism in PD patients and controls

The observed distribution of *MMP12* genotypes was in concordance with the Hardy–Weinberg equilibrium, both in PD and control groups ($p > 0.1$). Frequency of *MMP12* rs2276109:A>G genotypes and alleles was similar in PD patients and healthy individuals (Table 2). In case of rs652438:A>G missense, minor G allele (357Ser) was found with significantly lower frequency in PD group, compared to the controls (3.7% vs. 7.6%, $p = 0.011$), and minor allele carrier

Table 1 – Demographic and clinical characteristics of non-demented (nPDD) and demented (PDD) patients (mean ± SD).

Demographic and clinical data	nPDD ($n = 159$)	PDD ($n = 72$)	p value
Females/Males	84/75	37/35	n.s.*
Mean age and range (years)	62.1 ± 9.6 39–89	69.3 ± 8.8 35–85	$p = 0.441$**
Age at disease onset and range (years)	56.0 ± 11.0 28–87	60.9 ± 10.4 29–80	$p = 0.637$**
Disease duration (years)	6.1 ± 4.8	8.3 ± 5.9	$p = 0.036$**
Hoehn–Yahr disease stage	2.02 ± 0.74 ($n = 154$)	2.54 ± 0.95 ($n = 68$)	$p < 0.0001$***
Daily levodopa dosage (mg)	698 ± 439 ($n = 152$)	792 ± 427 ($n = 70$)	$p = 0.046$***
MMSE score	28.1 ± 1.9 ($n = 158$)	23.6 ± 4.2 ($n = 71$)	$p < 0.0001$***

ns – not significant.
* Fisher test.
** *t*-Student test.
*** p values were calculated according to the Mann–Whitney *U* test.

Table 2 – Frequencies of the studied SNPs in PD patients and healthy controls.

	PD patients $n = 241$		Healthy controls $n = 237$		p value	OR (95%CI)
	n	%	n	%		
MMP12 rs2276109:A>G						
AA	182	75.5	187	78.9		
AG	52	21.6	41	17.3	0.296	1.30 (0.82–2.06)
GG	7	2.9	9	3.8	0.799	0.80 (0.29–2.20)
AG or GG	59		50		0.385	1.21 (0.79–1.86)
Minor (G) allele freq.		13.7		12.4	0.631	–
MMP12 rs652438:A>G						
AA	223	92.5	202	85.2		
AG	18	7.5	34	14.3	0.018	0.48 (0.26–0.88)
GG	0	0.0	1	0.4	0.476	–
AG or GG	18	7.5	35	14.8	0.013	0.47 (0.26–0.85)
Minor (G) allele freq.		3.7		7.6	0.011	–

p values for alleles and genotypes calculated by means of Fisher exact test in relation to major allele or homozygotes for a major allele.

status (AG or GG genotype) was associated with over two-fold reduced odds for PD (OR = 0.47, $p = 0.013$, Table 2).

Performed linkage analysis have shown that the studied *MMP12* SNPs (rs2276109:A>G and rs652438:A>G) are in full linkage disequilibrium ($D' = 1.000$, $r2 = 0.009$), and minor alleles are never observed simultaneously on the same chromosome in the studied population, leading to the presence of only 3 (from 4 potentially possible) haplotypes (i.e. A–A, G–A and A–G). The A–G haplotype has been found with significantly lower frequency among PD patients (Table 3) and the A–A/A–G diplotype determined 2-fold lower risk for PD than the most common A–A/A–A diplotype (OR = 0.5, $p = 0.031$, Table 3).

3.3. *MMP12 polymorphism in nPDD and PDD patients*

When *MMP12* genotypes were analyzed in PD patients divided into two groups, based on the aforementioned diagnostic criteria for dementia, no significant differences in the genotypes distribution nor in allele frequencies were observed (Table 4).

4. Discussion

The influence of genetic factors on Parkinson's disease has been proposed and the search for their definition is ongoing [22]. Currently, PD ethiopathogenesis is described as the interaction of variety of factors, including aging, environmental, immunological and genetic factors. Recently, the review of current publications, has once again drawn the attention to neuroinflammation and its connections with autoimmune mechanisms underlying the process of α-synuclein accumulation in the midbrain of PD patients. A significant level of cytokines such as IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ in the SN (substantia nigra) and CSF of PD patients has been reported, however, it has not been clearly established whether neuroinflammation protects or promotes the neurodegeneration [23]. Matrix metalloproteinases, including MMP12, may be one of the important players in the cascade of SN degeneration. The level of MMPs is increased in the presence of an external trigger, and activated MMPs can influence many factors, such

Table 3 – MMP12 Haplotypes and diplotypes in PD patients and control group.

	PD patients $n = 241$		Healthy controls $n = 237$		p value	OR (95%CI)
	n	%	n	%		
MMP12 diplotype						
A-A/A-A	165	68.5	154	65.0	0.438[a]	1.17 (0.80–1.70)
A-A/G-A	51	21.2	39	16.5	0.473	1.22 (0.76–1.95)
A-A/A-G	17	7.1	32	13.5	0.031	0.50 (0.26–0.93)
G-A/G-A	7	2.9	9	3.8	0.613	0.72 (0.26–2.00)
G-A/A-G	1	0.4	2	0.8	0.612	0.47 (0.04–5.20)
A-G/A-G	0	0.0	1	0.4	0.484	–
MMP12 haplotype						
A-A	398	82.6	379	80.0	0.320[a]	–
G-A	66	13.7	59	12.4	0.773	–
A-G	18	3.7	36	7.6	0.011	–

Haplotypes reconstructed from rs652438:A>G and rs2276109:A>G genotypes; p values for haplotypes and diplotypes calculated by means of Fisher exact test in relation to major haplotype or homozygotes for a major haplotype, except [a]calculated in relation to all other diplotypes/haplotypes.

Table 4 – Frequencies of the studied SNPs in PD patients with (PDD) and without dementia (nPDD).

	PDD patients $n = 72$		nPDD patients $n = 159$		p value	OR (95%CI)
	n	%	n	%		
MMP12 rs2276109:A>G						
AA	56	77.8	119	74.8	0.741[a]	1.18 (0.61–2.28)
AG	14	19.4	35	22.0	0.728	0.85 (0.42–1.70)
GG	2	2.8	5	3.1	1.000	0.85 (0.16–4.51)
Minor (G) allele freq.		12.5		14.1	0.664	–
MMP12 rs652438:A>G						
AA	69	95.8	145	91.2	0.281[a]	2.22 (0.61–7.98)
AG	3	4.2	14	8.8	0.281	0.45 (0.11–1.62)
GG	0	0.0	0	0.0	–	–
Minor (G) allele freq.		2.1		4.4	0.291	–

p values for alleles and genotypes calculated by means of Fisher exact test in relation to major allele or homozygotes for a major allele, except [a]calculated in relation to minor allele carriers.

as extracellular matrix, signaling molecules or growth factors. For example, MMP12 was suggested to function as TNF-α converting enzyme leading to liberation of active form of that pro-inflammatory cytokine by shedding it from the cell membrane, where the pro-form is typically bound [24]. In our study we hypothesized that different functional variants in *MMP12* gene, which are shown to affect the expression and activity of the enzyme, may be important in mediating susceptibility to PD and cognitive impairment development.

In the performed analysis, the frequencies of minor *MMP12* rs652438:G allele and G allele genotypes were significantly higher in the healthy subjects compared with the PD patients ($p = 0.011$ and $p = 0.013$, OR 0.47 (0.26–0.85)). It may suggest a protective role of the G allele, which seems to decrease more than 3-fold the activity of MMP12 due to missense change of asparagine to serine in haemopexin domain and alteration of substrate binding [25]. Our results are in line with the findings of Haq et al., who reported that the examined alteration in the aforementioned SNP was associated with severity of emphysema in lungs of patients with chronic obstructive pulmonary disease (COPD), with A/A homozygotes having more severe emphysema, in contrast to G allele carriers whose MMP12 exhibit lower activity [25]. In fact, MMP12 (−/−) knock-out mice were completely protected from development of emphysema and had impaired recruitment of monocytes/macrophages into the lung [26,27]. Moreover, Egeberg et al. investigated the risk of incident (new-onset) Parkinson disease in patients with rosacea. They showed not only a 2-fold increased risk of PD in patients diagnosed with ocular rosacea (adjusted IRR, 2.03 [95% CI, 1.67–2.48]), but also revealed that tetracycline therapy appeared to reduce the PD risk (adjusted IRR, 0.98 [95% CI, 0.97–0.99]) [28]. One of the possible explanations of those findings could be related to elevated matrix metalloproteinase activity. MMP12 seems to be a marker of inflammatory activation. The increased level of MMP12 was observed in chronic obstructive pulmonary disease, atherosclerosis and multiple sclerosis [27–30]. Chehaibi et al., investigated the association between MMP1-16071G/2G, MMP12-82A/G (rs2276109) and MMP12 1082A/G (N357S, rs652438G) (being also investigated in the present study) genotypes and haplotypes and the risk of ischemic stroke (IS) in patients with type 2 diabetes mellitus (T2DM). The −82G/1082G (rs652438:G, rs2276109:G) haplotype of *MMP12* was associated with higher risk of diabetes ($p = 0.029$) and of ischemic stroke in diabetic patients ($p = 0.032$), and thus *MMP12* polymorphism can be considered a potential marker of cerebrovascular disorders in diabetic patients [31]. In our study the A–G haplotype has been found with significantly lower frequency among PD patients, and may be considered as a protective factor for PD development than the A–A haplotype. Upregulation of MMP12 expression depends on MMP12 gene promoter, which contains an AP-binding site. TNF-α and IL-1β can induce, whereas TGF-β1 inhibits MMP12 expression. Liu et al. assessed changes in MMP12 concentration in 3-, 10-, and 18-month-old mice. Both MMP12 mRNA and protein expression were upregulated in aged brains. Moreover, they demonstrated that MMP12 deficiency reduced the ability of macrophages to cross the transwell membrane and decreased neuroinflammation in aged but not in young mice [9].

The predictors of PDD in the examined group of PD patients consisted of disease duration, advanced motor disability as well as daily levodopa dose. We failed to find any correlation between cognitive impairment and *MMP12* rs2276109:A>G polymorphism. Several similarities have been noticed in the pathogenesis of Parkinson's and Alzheimer's diseases, including abnormal protein aggregation. The relationship between amyloid-β peptide (Aβ) and MMP12 has been suggested. In the research performed by Ito et al., there was a significant increase in MMP12 mRNA as well as protein expression in the presence of Aβ1–42. However, it is inconclusive whether MMPs promote pathogenic plaque degradation, or contrarily, impair brain matrix, leading to progression of the disease [32]. In our study, we found no statistically significant impact of *MMP12* polymorphisms on the risk of dementia. Nevertheless, quantitative analyses, e.g. real time quantitative PCR, might have altered the results.

5. Conclusions

We provide one of the first reports evaluating the association of *MMP12* gene polymorphisms and PD. Our study suggests

that the rs652438:A>G SNP may influence the risk for sporadic Parkinson's disease, but not for dementia in the course of the disease. The minor G allele of the rs652438:A>G SNP can be considered as a protective factor against PD, probably because of decreased activity of MMP12. Future studies to evaluate interactions of other metalloproteinase genes' polymorphisms with Parkinson's disease would provide further valuable information about underlying pathophysiology of the disease.

Conflict of interest

None declared.

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REFERENCES

[1] Chen YC, Wu YR, Mesri M, Chen CM. Associations of matrix metalloproteinase-9 and tissue inhibitory factor-1 polymorphisms with Parkinson disease in Taiwan. Medicine (Baltimore) 2016;95(February (5)):e2672. http://dx.doi.org/10.1097/MD.0000000000002672

[2] Frank-Cannon TC, Alto LT, McAlpine FE, Tansey MG. Does neuroinflammation fan the flame in neurodegenerative diseases? Mol Neurodegener 2009;4(November):47. http://dx.doi.org/10.1186/1750-1326-4-47

[3] Lukens JR, Barr MJ, Chaplin DD, Chi H, Kanneganti TD. Inflammasome-derived IL-1β regulates the production of GM-CSF by CD4(+) T cells and γδ T cells. J Immunol 2012;188 (April (7)):3107–15. http://dx.doi.org/10.4049/jimmunol.1103308

[4] Couch Y, Alvarez-Erviti L, Sibson NR, Wood MJ, Anthony DC. The acute inflammatory response to intranigral α-synuclein differs significantly from intranigral lipopolysaccharide and is exacerbated by peripheral inflammation. J Neuroinflamm 2011;8(November):166. http://dx.doi.org/10.1186/1742-2094-8-166

[5] Brkic M, Balusu S, Libert C, Vandenbroucke RE. Friends or foes: matrix metalloproteinases and their multifaceted roles in neurodegenerative diseases. Mediat Inflamm 2015;2015:620581. http://dx.doi.org/10.1155/2015/620581

[6] Cho BP, Sugama S, Shin DH, DeGiorgio LA, Kim SS, Kim YS, et al. Microglial phagocytosis of dopamine neurons at early phases of apoptosis. Cell Mol Neurobiol 2003;23(October (4–5)):551–60.

[7] Sugama S, Cho BP, Degiorgio LA, Shimizu Y, Kim SS, Kim YS, et al. Temporal and sequential analysis of microglia in the substantia nigra following medial forebrain bundle axotomy in rat. Neuroscience 2003;116(4):925–33.

[8] Niu H, Li Y, Li H, Chi Y, Zhuang M, Zhang T, et al. Matrix metalloproteinase 12 modulates high-fat-diet induced glomerular fibrogenesis and inflammation in a mouse model of obesity. Scient Rep 2016;6(January):20171. http://dx.doi.org/10.1038/srep20171

[9] Liu Y, Zhang M, Hao W, Mihaljevic I, Liu X, Xie K, et al. Matrix metalloproteinase-12 contributes to neuroinflammation in the aged brain. Neurobiol Aging 2013;34(April (4)):1231–9. http://dx.doi.org/10.1016/j.neurobiolaging.2012.10.015

[10] Crocker SJ, Frausto RF, Whitton JL, Milner R. A novel method to establish microglia-free astrocyte cultures: comparison of matrix metalloproteinase expression profiles in pure cultures of astrocytes and microglia. Glia 2008;56(August (11)):1187–98. http://dx.doi.org/10.1002/glia.20689

[11] Power C, Henry S, Del Bigio MR, Larsen PH, Corbett D, Imai Y, et al. Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. Ann Neurol 2003;53(June (6)):731–42. http://dx.doi.org/10.1002/ana.10553

[12] Vos CM, van Haastert ES, de Groot CJ, van der Valk P, de Vries HE. Matrix metalloproteinase-12 is expressed in phagocytotic macrophages in active multiple sclerosis lesions. J Neuroimmunol 2003;138(May (1–2)):106–14.

[13] Toft-Hansen H, Nuttall RK, Edwards DR, Owens T. Key metalloproteinases are expressed by specific cell types in experimental autoimmune encephalomyelitis. J Immunol 2004;173(October (8)):5209–18.

[14] Weaver A, Goncalves da Silva A, Nuttall RK, Edwards DR, Shapiro SD, Rivest S, et al. An elevated matrix metalloproteinase (MMP) in an animal model of multiple sclerosis is protective by affecting Th1/Th2 polarization. FASEB J 2005;19(October (12)):1668–70.

[15] Bialecka M, Klodowska-Duda G, Kurzawski M, Slawek J, Gorzkowska A, Opala G, et al. Interleukin-10 (IL10) and tumor necrosis factor alpha (TNF) gene polymorphisms in Parkinson's disease patients. Parkinsonism Related Disord 2008;14(December (8)):636–40. http://dx.doi.org/10.1016/j.parkreldis.2008.02.001

[16] Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. Archiv Neurol 1993;50(February (2)):140–8.

[17] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(May (5)):427–42.

[18] Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(November (3)):189–98.

[19] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archiv Gen Psychiatry 1961;4(6):561–71. http://dx.doi.org/10.1001/archpsyc.1961.01710120031004

[20] Sławek J, Roszmann A, Robowski P, Dubaniewicz M, Sitek EJ, Honczarenko K, et al. The impact of MRI white matter hyperintensities on dementia in Parkinson's disease in relation to the homocysteine level and other vascular risk factors. Neuro-degenerat Dis 2013;12(1):1–12. http://dx.doi.org/10.1159/000338610

[21] Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22 (September (12)):1689–707. http://dx.doi.org/10.1002/mds.21507. quiz 1837

[22] Redenšek S, Trošt M, Dolžan V. Genetic determinants of parkinson's disease: can they help to stratify the patients based on the underlying molecular defect? Front Aging Neurosci 2017;9(February):20. http://dx.doi.org/10.3389/fnagi.2017.00020

[23] De Virgilio A, Greco A, Fabbrini G, Inghilleri M, Rizzo MI, Gallo A, et al. Parkinson's disease: autoimmunity and neuroinflammation. Autoimmun Rev 2016;15(October (10)):1005–11. http://dx.doi.org/10.1016/j.autrev.2016.07.022

[24] Churg A, Wang X, Wang RD, Meixner SC, Pryzdial EL, Wright JL. Alpha1-antitrypsin suppresses TNF-alpha and MMP-12 production by cigarette smoke-stimulated macrophages. Am J Respir Cell Mol Biol 2007;37(August (2)):144–51. http://dx.doi.org/10.1165/rcmb.2006-0345OC

[25] Haq I, Lowrey GE, Kalsheker N, Johnson SR. Matrix metalloproteinase-12 (MMP-12) SNP affects MMP activity,

lung macrophage infiltration and protects against emphysema in COPD. Thorax 2011;66:970–6. http://dx.doi.org/10.1136/thx.2011.159087

[26] Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science 1997;277:2002–4.

[27] Garbacki N, Di Valentin E, Piette J, Cataldo D, Crahay C, Colige A. Matrix metalloproteinase 12 silencing: a therapeutic approach to treat pathological lung tissue remodeling? Pulmon Pharmacol Therapeut 2009;22(August (4)):267–78. http://dx.doi.org/10.1016/j.pupt.2009.03.001

[28] Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Exploring the association between Rosacea and Parkinson disease: a Danish nationwide cohort study. J Am Med Assoc Neurol 2016;73(May (5)):529–34. http://dx.doi.org/10.1001/jamaneurol.2016.0022

[29] Ramella NA, Rimoldi OJ, Prieto ED, Schinella GR, Sanchez SA, Jaureguiberry MS, et al. Human apolipoprotein A-I-derived amyloid: its association with atherosclerosis. Public Libr Sci One 2011;6(7):e22532. http://dx.doi.org/10.1371/journal.pone.0022532

[30] Mirowska-Guzel D, Gromadzka G, Czlonkowski A, Czlonkowska A. Association of MMP1, MMP3, MMP9, and MMP12 polymorphisms with risk and clinical course of multiple sclerosis in a Polish population. J Neuroimmunol 2009;214(September (1–2)):113–7. http://dx.doi.org/10.1016/j.jneuroim.2009.06.014

[31] Chehaibi K, Hrira MY, Nouira S, Maatouk F, Ben Hamda K, Slimane MN. Matrix metalloproteinase-1 and matrix metalloproteinase-12 gene polymorphisms and the risk of ischemic stroke in a Tunisian population. J Neurol Sci 2014;342(July (1–2)):107–13. http://dx.doi.org/10.1016/j.jns.2014.04.036

[32] Ito S, Kimura K, Haneda M, Ishida Y, Sawada M, Isobe K. Induction of matrix metalloproteinases (MMP3, MMP12 and MMP13) expression in the microglia by amyloid-β stimulation via the PI3K/Akt pathway. Exp Gerontol 2007;42 (June (6)):532–7.