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# Multiple System Atrophy: Genetic or Epigenetic?

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Multiple system atrophy (MSA) is a rare, late-onset and fatal neurodegenerative disease including multisystem neurodegeneration and the formation of  $\alpha$ -synuclein containing oligodendroglial cytoplasmic inclusions (GCIs), which present the hallmark of the disease. MSA is considered to be a sporadic disease; however certain genetic aspects have been studied during the last years in order to shed light on the largely unknown etiology and pathogenesis of the disease. Epidemiological studies focused on the possible impact of environmental factors on MSA disease development. This article gives an overview on the findings from genetic and epigenetic studies on MSA and discusses the role of genetic or epigenetic factors in disease pathogenesis.

**Key words:** Multiple system atrophy,  $\alpha$ -synuclein, neurodegeneration, genetics, epigenetics

## INTRODUCTION

In 1969 Graham and Oppenheimer suggested the term “multiple system atrophy” (MSA) to describe and combine a set of different disorders, including olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND) and Shy-Drager syndrome [1]. MSA is nowadays considered to be a rare, late-onset and fatal neurodegenerative disease with a largely unknown etiopathogenesis. Prevalence ranges from 1.9 to 4.9 per 100,000 inhabitants, incidence is about 0.6 per 100,000 per year or rather 3 per 100,000 per year in the population over 50 years [2, 3]. Patients show an average disease onset of 60 years (SD=9; range: 34 to 83 years), affecting males and females equally [4]; mean disease duration is between 7 to 9 years after clinical presentation [5]. This movement disorder is clinically represented by atypical parkinsonism, cerebellar ataxia, pyramidal signs, and always accompanied by autonomic failure; pathologically MSA

is characterized by selective wide spread neuronal cell loss, gliosis and oligodendroglial cytoplasmic inclusions (GCIs) affecting several structures of the central nervous system [3, 6, 7].

Neuronal loss in MSA affects the striatum, substantia nigra pars compacta (SNpc), cerebellum, pons, inferior olives, central autonomic nuclei and the intermediolateral column of the spinal cord [8]. Microglial and astroglial activation (gliosis) affecting several regions of the MSA brain could partly be triggered by oligodendroglial  $\alpha$ -synuclein pathology, but the exact pathogenic mechanisms need to be further clarified [9-12]. GCIs represent the major pathological hallmark of the disease [7] and are mostly containing misfolded, hyperphosphorylated (affecting residue Ser129) and fibrillar  $\alpha$ -synuclein [13-15]. GCIs also contain tau, 14-3-3 protein, LRRK2, parkin, heat shock protein family members Hsp70 and Hsc70, p25 $\alpha$ ,  $\alpha$ -tubulin,  $\beta$ -tubulin, microtubule associated proteins and cyclin dependent kinase 5 (cdk5) among others [16-23]. The mechanisms of GCI formation in MSA remain unclear; two hypotheses try to explain. The first suggests that active uptake of  $\alpha$ -synuclein from neighboring neurons by oligodendroglia could take place. Whereas the second hypothesis states that there could be a selective increase of  $\alpha$ -synuclein expression in oligodendroglial cells in MSA [24]. Disturbed protein degradation may further contribute to the accumulation of

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$\alpha$ -synuclein in MSA oligodendrocytes [25]. Since the etiology and pathogenesis of MSA are not completely understood, no effective therapies have been established up to date to cure MSA. In 2009, the discovery of  $\alpha$ -synuclein gene (SNCA) variants association with an increased risk for MSA especially in Caucasians suggested an important lead in the role of genetic predisposition in MSA [26]. Along with the fact that MSA has always been considered to be a sporadic disease [27], this was thought to be a great breakthrough. Since then, many studies have been performed with the aim to detect disease-causing or disease-linked genes and gene variants. Other studies focused on environmental risk factors and epigenetic mechanisms, since MSA shares common features with other neurodegenerative disorders that have proven role of epigenetic modifications in their pathogenesis [28]. Within this article, we provide an update on recent studies concerning genetic and epigenetic factors that might be involved in MSA etiology and pathogenesis.

## GENETIC FACTORS IN MSA

### *Familial MSA*

MSA is a typically sporadic neurodegenerative disease [27], but rare cases exist presenting a family history of MSA [29-33]. The ancestry arrangement in two of those family cases – probable MSA in one German and one Japanese family – [30, 32, 33] is consistent with typical autosomal dominant inheritance. Four different Japanese families with multiple affected siblings show probable autosomal recessive inheritance [29]. In 2012, a case of two sisters from the US was reported, presenting similar syndromes of MSA and thereby suggesting autosomal dominant inheritance [31]. Recently, two Japanese siblings (affected with either probable MSA-C and definite MSA-P) were described. Inheritance was found to be autosomal recessive, even though no consanguineous marriage took place and no genetic mutations were identified [34]. So far, no disease-causing and heritable mutations have been definitely identified in MSA.

### *Potential genetic “hotspots”*

#### **SNCA – mutations, multiplications, SNP variants and the possible risk to develop MSA**

Since the pathological hallmark of MSA is represented by GCIs [7] containing mostly  $\alpha$ -synuclein among other components, MSA together with Parkinson's disease (PD) and Dementia with Lewy bodies (DLB) is considered to be an  $\alpha$ -synucleinopathy [13]. The fundamental role of  $\alpha$ -synuclein in MSA pathogenesis leads to the suggestion that there might be a connection between possible

SNCA variants and a risk for developing MSA. Several genetic approaches have been undertaken addressing this particular question.

Discovered in 1997, A53T has been the first SNCA point mutation identified in families with autosomal dominant PD [35-49]. This was followed by the identification of A30P [35, 44, 50, 51] and E46K point mutations of the SNCA gene in familial PD cases [52]. *In vitro* as well as *in vivo* experiments in PD models showed that those mutations promote the aggregation of  $\alpha$ -synuclein [53-55]. *In silico* experiments demonstrated that A18T and A29S were associated with sporadic forms of PD and similarly accelerate  $\alpha$ -synuclein aggregation [56]. Recently two novel substitutions in SNCA, H50Q [57-61] and G51D [59, 60, 62, 63], have been described. H50Q was associated with increased  $\alpha$ -synuclein aggregation, secretion and extracellular toxicity [59-61]. Interestingly, G51D has an opposite effect on the aggregation behavior of  $\alpha$ -synuclein, thereby reducing aggregation effects, accompanied with impaired membrane binding and enrichment of the mutant in the nuclear compartment [59, 63]. Consequently, different groups attempted to detect an association between SNCA gene mutations and MSA, but these efforts remained futile. It was suggested that transcriptional alterations of SNCA using bigger sample sizes with higher statistical power should be investigated [64-67]. Yet, no mutations in the coding region of SNCA have been identified in pathologically proven MSA cases [64]. A patient with the G51D substitution showed clinical, genetic and neuropathological characteristics of an  $\alpha$ -synucleinopathy including PD and MSA-like features including widespread neuronal and GCI-like oligodendroglial inclusions, neuronal loss in substantia nigra, locus coeruleus, hippocampal CA2/3 subregions, frontal and temporal cortices, dorsal motor nucleus of the vagus and striatum [62]. The observed features were found to be similar to those in cases with A53T mutations and SNCA polymorphism cases [68, 69]. It was therefore suggested that the G51D substitution of the SNCA gene could be a possible link between PD and MSA. This idea was further supported by the detection of the novel A53E SNCA substitution in a Finnish patient presenting both atypical PD as well as MSA features [70]. In relation to the findings of SNCA multiplications in PD, Fuchs and colleagues found that duplications and triplications of SNCA are leading to MSA-like features in autosomal dominant PD [71]. However, a targeted search of SNCA multiplications in 58 pathologically confirmed MSA cases failed to confirm the role in MSA [66].

In 2009, the single nucleotide polymorphism (SNP) study in SNCA by Scholz and colleagues suggested the first genetic SNCA variants that were associated with increased MSA risk

in Caucasian patients. Two SNPs at the SNCA locus were found: rs11931074 (p-value in recessive model =  $1.4 \times 10^{-11}$ ) and rs3857059 (p-value in recessive model =  $4.9 \times 10^{-6}$ ) with increased frequency in MSA. The authors stated that those variants might lead to pathogenic  $\alpha$ -synuclein accumulation by alteration of the SNCA splicing pattern and/or SNCA messenger RNA processing and/or by other genetic factors [26]. Interestingly, both SNCA variants are considered to be PD risk factors [72, 73]. Two further studies subsequently replicated the results from Scholz and colleagues [74, 75]. Another study focusing on Korean MSA patients failed to replicate the findings by Scholz and colleagues (p-value of rs11931074 in recessive model = 0.77) [76], suggesting a certain degree of heterogeneity within different ethnicities.

SNCA-linked genetic predisposition seems to play an important role in MSA but further studies are needed to identify the possible mechanisms underlying these interactions.

### COQ2 mutations and MSA

COQ2 gene encodes the enzyme parahydroxybenzoate-polyprenyl transferase, which is important for the biosynthesis of coenzyme Q<sub>10</sub> (CoQ<sub>10</sub> or ubiquinone) [77]. Recently, the Multiple-System Atrophy Research Collaboration published an association between COQ2 mutations and an increased risk for developing MSA. By whole genome sequencing two mutations, M128V-V393A/M128V-V393A (homozygous) and R337X/V393A (heterozygous variant), were identified in two multiplex families with MSA. The V393A variant was shown to be common in sporadic MSA cases, Japanese patients only (allele frequency = 1.6 to 2.2%), thereby suggesting that it could serve as a potential risk factor for MSA-C. Finally it was concluded that mutations in the COQ2 gene would theoretically impair the mitochondrial respiratory chain and lead to less tolerance to oxidative stress, further resulting in a predisposition to MSA. The authors suggest possible efficacy of oral treatment with coenzyme Q<sub>10</sub> in MSA [78, 79], since COQ2 mutations cause a lack of coenzyme Q<sub>10</sub> [80]. Several studies in European and Korean MSA patients failed to detect COQ2 mutations [79, 81-83], thereby contradicting the findings of the MSA Research Collaboration with a Japanese lead. Additionally, a very recent case report on two MSA affected Japanese siblings also failed to identify any COQ2 mutations, neither the homozygous (M128V-V393A/M128V-V393A) nor the heterozygous (R337X/V393A) variant [34, 79]. It is assumed that COQ2 mutations may cause a higher vulnerability of the cerebellum to damages, including dysfunction and loss of oligodendrocytes in MSA [84], but the exact role on MSA etiology remains unclear and requires further investigation. In summary, it seems that the evidence of a direct association between COQ2

mutations and MSA is currently weak.

### Genes related to spinocerebellar ataxias and MSA

MSA patients show overlapping features with autosomal dominant spinocerebellar ataxias (SCAs), including prominent ataxia, dysmetria and abnormal eye movement [85]. For this reason the investigation of possible SCA genocopies in MSA patients has been of great interest. Since 1996, many studies focused on the possible clinical overlap of SCAs and MSA [86-90]. Gilman et al. investigated four members of a family with SCA1 mutations presenting dominantly inherited progressive ataxia, dystonia, autonomic dysfunction and peripheral neuropathy. Several unusual SCA1 but MSA-like symptoms were found including neurodegeneration of the basal ganglia, cerebellum, brainstem and the intermediolateral columns of the spinal cord as well as tau- and ubiquitin-positive GCIs. Yet, unusual MSA features like early disease onset, cerebellar and autonomic features in the absence of pyramidal or extrapyramidal signs were also detected. It was concluded that SCA1 gene mutations might only lead to a disorder mimicking MSA [86]. Although cases of SCA2 were identified to present with glial cytoplasmic inclusions these were  $\alpha$ -synuclein-negative [91, 92]. A SCA3 patient showed additional neurodegenerative disorders resembling the pathological features of cerebellar MSA (MSA-C). The patient presented  $\alpha$ -synuclein positive GCIs and neurodegeneration in the olivopontocerebellar, striatal and pyramidal motor regions [87], thereby meeting the criteria for definite MSA-C diagnosis [93]. A case-control study on Caucasian MSA patients (n=80) failed to confirm the presence of SCA3 expansions, highlighting that MSA is an autonomous disease, not related to SCA-gene mutations [94]. Further studies found SCA6, SCA8 and SCA17 genes to be related to MSA [88, 95-97], but others state that those as well as the SCA 1, 2, 3, 7 and 12 genes do not contribute to MSA etiology [97, 98]. Patients with FXTAS, which is caused by a CGG expansion in the X mental retardation 1 gene (FMR1) [99], often show clinical features that look like those of MSA-C [100, 101]. A possible connection between MSA and premutations (55-200 repeats) in the FMR1 gene was investigated in a study on Japanese MSA patients, but failed to support the initial assumption [102]. Additionally, the European MSA study group is not recommending FMR1 genotyping to diagnose MSA [90].

### Other genetic risk loci and MSA

Several studies on mutated genes associated with MSA-related neurodegenerative disorders failed to identify a direct genetic link to MSA. Negative findings included: *Parkin* and *PTEN-induced putative kinase 1 (PINK1)* mutations causing autosomal recessive

early-onset PD [103-105], genetic variants of MAPT encoding for the microtubule-associated protein tau [106-108], PD risk factors *LRRK2* and *GBA* genes [26, 65, 109-114] and other mutations in genes coding for apolipoprotein E, dopamine  $\beta$ -hydroxylase, ubiquitin C-terminal hydrolase-1 (UCH-1), fragile x mental retardation 1, leucine-rich kinase 2 (LRRK2), progranulin (PRGN) [115-118], dopamine- $\beta$ -hydroxylase (DBH) [119], CYP2D6 [120-122], BDNF, CNTF, IGF1, HLA and hiGIRK [94], PITX3 [123] and rs1572931 polymorphisms in the *RAB7L1* gene [124].

Since gliosis accounts to MSA pathogenesis [6], several genes involved in inflammatory processes have been investigated. Microglia activation leads to the production of cytokines, including interleukin-1- $\alpha$  (IL-1- $\alpha$ ), IL-1- $\beta$ , IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), as well as chemokines such as IL-8 and the inflammatory intercellular-adhesion molecule-1 (ICAM-1) [125]. Association with an increased risk to develop MSA was found in relation to gene polymorphisms in *IL-1- $\alpha$*  [126], *IL-1- $\beta$*  [127], *IL-8* and *ICAM-1* [128],  *$\alpha$ -1-antichymotrypsin* [98] and tumor necrosis factor genes [129]. Unfortunately, those studies include small patient numbers but they point out the possible pathogenic role of inflammation in MSA pathogenesis.

Since oxidative as well as nitrative stress are implicated in the progression of  $\alpha$ -synucleinopathies, related factors have been tested and a link to MSA was found for *SLC1A4*, *SQSTM1* and *EIF4EBP1* [130].

Genetic variability in alcohol dehydrogenase (ADH) gene risk factors was investigated in MSA. *ADH1C* G78X mutation was associated with MSA in British but not in German cohorts [131], whereas no connection of *ADH7* variants has been found [132]. In 2009, a MSA patient was reported to have “muscular” pain, similar to myotonic dystrophy type 2 (DM2). Since this disease is associated with parkinsonism, DNA analyses were performed revealing mutations in the *ZNF9* gene. However, no other MSA patients carrying this mutation have been reported so far [133, 134], thereby further studies are needed. For several years, there has been an ongoing discussion whether neurodegenerative diseases are prion-like diseases [135], supported by the finding of an intriguing MSA case with sporadic prion-like features. Genetic screening did not detect mutations in the prion protein gene (*PRNP*), but carried a well-established risk factor for Creutzfeldt-Jakob disease (M129V polymorphism in *PRNP*). A case control study investigated this risk factor and revealed an association with increased risk for MSA, when compared to PD, but not to the control group [136]. Very recently, hexanucleotide repeat expansions in C9orf72 were reported in a family presenting both MSA and amyotrophic lateral sclerosis (ALS), thereby highlighting a phenotypic variability of those expansions [137]. Sasaki and

colleagues suggested a causal link between a copy number loss of (Src homology 2 domain containing)-transforming protein 2 (SHC2) and MSA [138-140]. However, Ferguson and colleagues contradicted these finding when examining MSA patients from the US [141].

In conclusions, the genetic studies in MSA to date do not support the use of genetic factors like SNCA, COQ2, SCAs expansions etc. to reliably diagnose MSA. Several gene polymorphisms have been linked to an increased risk for developing MSA, but many of the findings have been contradictory dependent on the high heterogeneity of the MSA patients. Further genetic analysis involving larger patients cohorts are warranted to provide reliable information on the role of selected genes in the etiopathogenesis of MSA.

## EPIGENETIC AND ENVIRONMENTAL FACTORS IN MSA

### *Epigenetics and disease*

Given the fact that it is still unclear whether genetics have a predisposing role in the etiology of MSA, several studies focused on the investigation of risk factors that could lead, together with genetic predisposition to disease development. Epigenetics includes transcriptional as well as post-transcriptional, reversible and heritable changes to DNA that do not alter DNA sequence itself and regulate gene expression. The epigenetic machinery acts via different mechanisms. DNA-methylation includes the addition of a methyl group to the 5' carbon of cytosines, which are located to CpG islands in promoter regions (regions with high content of the bases cytosine and guanine) and associated with gene silencing. Histone modifications (acetylation, phosphorylation, methylation, ubiquitination or sumoylation) are carried out at the N-termini of the core histones that protrude from the nucleosome modulating gene expression and chromatin structure. RNA-mediated silencing pathways include non-coding RNAs as well as non-coding anti-sense RNAs, RNA interference and microRNAs (miRNAs). Together these epigenetic mechanisms form the “epigenetic landscape” being very dynamic, in contrast to irreversible genetic mutations, and can be influenced during life through environmental stimuli. Destruction of the epigenetic balance leads to several distinct diseases [142, 143]. Many disorders have already been connected to epigenetic alterations including cancer [144], cardiovascular diseases [145, 146], autoimmune disorders [147], metabolic diseases [148, 149], myopathies [150], learning and memory deficits [151, 152] and some neurodegenerative diseases [153].

There has been emerging evidence that neurodegenerative diseases are linked to exposure to chronic neurotoxic substances

and other risk environmental factors resulting in a higher risk of disease development [154]. For example the risk to develop multiple sclerosis is increased when being infected with Epstein-Barr virus and smoking cigarettes, whereas vitamin D is protective [155]; Alzheimer's disease is associated with lead (Pb) exposure resulting in higher amounts of  $\beta$ -amyloid, stress and traumatic brain injuries [156-160]; higher risk to develop PD was linked among others to exposure to metals (Pb and others), certain chemicals and magnetic fields [161].

Given that MSA is a neurodegenerative disease as well as  $\alpha$ -synucleinopathy with unclear genetic background, MSA patients have been investigated with regard to identify the role of environmental and epigenetic factors including stress, occupational and daily habits and exposure to toxins, metals, solvents, plastic monomers or additives, as well as history of farming.

#### ***Putative environmental risk factors in MSA***

Exposures to metal dusts and fumes, plastic monomers and additives, organic solvents and pesticides have been linked significantly to a higher vulnerability of the nervous system supporting disease onset of MSA [162]. Recently, one case report supported the role of intensive and extended contact with organic solvents as a risk factor in MSA, as reported when examining a long-term professional painter [163]. A putative association to environmental toxins with MSA-like disorders has been shown, including inorganic mercury, methanol, carbon tetrachloride, carbon disulfide, cyanide, and manganese after heavy occupational exposure [164, 165]. Control studies confirmed the findings by detecting increased total iron levels in MSA and PD brains, but failed to detect alterations in manganese levels [166-168].

Epidemiological studies investigated the influence of farming on MSA, involving exposure to different chemicals and factors (pesticides, solvents, mycotoxins, dust, fuels, oils, fertilizers, animals) and a certain lifestyle (consumption of well water, rural living, diet and physical activity) [169]. Especially pesticides have been continuously associated with an increased risk of developing MSA, supported by independent studies [162, 170, 171]. So far, there is only one study contradicting these findings and stating that only plant and machine operators and assemblers develop an increased risk for MSA that is increasing with time of exposure [172].

The influence of smoking on MSA has been investigated already in 1986 and studies showed an inverse association with MSA [170, 173, 174]. Vanacore and colleagues also investigated effects of smoking together with farming on MSA concluding that those two risk factors are not interacting with the disease development

(ever-smokers compared with never-smokers) [171]. In contrast to those findings, one MSA patient was reported recently having severe nicotine sensitivity. Interestingly, Graham and Oppenheimer described a similar case in 1969, but further studies are needed in order to investigate the prevalence of those cases in MSA [1, 175]. Regarding education, MSA patients seemed to have a lower educational level when compared to healthy controls [170, 172]. Concerning food habits, the consumption of meat has been associated with a higher risk of developing MSA. Other habits including drinking alcohol, aspirin use and fish or seafood consumption were found to be more common in healthy controls and are considered being protective factors. The same study was not able to confirm an effect of herbal tea or tropical fruits consumption, as it was suggested previously [172].

Until now, several risk factors have been associated with MSA. However, epidemiological studies display some limitations. Those studies are often affected by a certain recall bias (over-reporting of exposures) and selection bias (patients with severe disease are less able to participate) that influences the outcomes [176]. Therefore, further epidemiological studies of expanded cohorts are needed to get more data on potential MSA risk factors.

#### ***What is the evidence that epigenetics may play a role in MSA: recent findings***

It has been shown that nutrients and environmental toxins, especially metals, are able to cause DNA methylation changes, histone modifications and RNA interference [177]. Together with findings on maternal nutrition that modulates gene expression already in the embryo supporting the possible development of later life diseases [178], this is pointing out the powerful influence of environmental factors on the epigenetic landscape and supporting the idea of a certain gene-environment interaction. Unfortunately not much is known about epigenetic modulations in MSA that could be provoked by environmental risk factors.

As mentioned, the epigenetic landscape is shaped by several mechanisms. DNA methylation changes have not been reported in MSA yet. Histone modifications can include acetylation, phosphorylation, methylation, ubiquitination or sumoylation of the four core histone proteins (H2A, H2B, H3, and H4) of the nucleosome. None of these has been studied in MSA patients to our knowledge. Specifically histone acetylation is controlled by a pair of antagonistic enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) that carry out acetylation and deacetylation at the N-termini of the nucleosomes, thereby modifying the histones. Histone deacetylation by HDACs influences gene expression, cell cycle regulation, chromatin structure and developmental events [179-181]. 18 different HDAC

families are known in mammals. The representative family members can be subdivided into zinc-dependent (HDAC1-11) and nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent (sirtuin 1-7) enzymes [182]. Miki and colleagues showed that patients with PD and dementia with Lewy bodies (DLB) show a co-localization of HDAC6 with Lewy bodies and also HDAC6 co-localized with GCIs in MSA brains [183], indicating a putative role of HDAC6 in MSA. Despite its name, the role of HDAC6 in histone deacetylation directly is unclear. HDAC6 is unique to a certain extent, since it possesses two functional catalytic sites at the N-terminus in combination with an ubiquitin-binding domain at the C-terminus. Although shuttling between the cytoplasm and the nucleus has been proposed, HDAC6 is found mainly in the cytoplasm, which is suggesting a histone-independent function [184].

The very first indications of a changed epigenetic landscape in MSA were provided just recently, by studies describing an altered expression of microRNAs in MSA. MicroRNAs (miRNAs) are small non-coding RNAs that are able to regulate gene expression post-transcriptionally [185] and important for the survival of mature neurons and their functions [186]. Ubhi and colleagues found an upregulation of the microRNA miR-96 in MSA patients, which is connected to a down-regulation of miR-96 target genes, including family members of the solute carrier protein family SLC1A1 and SLC6A6 [187]. A previous genetic association of SLC1A4 with MSA is supporting this finding [130]. Expression of miR-202 is upregulated in the cerebellum of MSA patients, consistent with reduced Oct1 protein expression. By that, miR-202 and the Oct1 pathway are thought to participate in sporadic cerebellar neurodegeneration representing a novel putative therapeutic target in MSA. The authors suggest that decreased Oct1 levels lead to higher vulnerability of neurons to oxidative stress [188], since this mechanism is involved in cerebellar neurodegeneration [189]. Next to miR-202, other microRNAs show downregulation (miR-129-3p, miR-129-5p, miR-337-3p, miR-380, miR-433, miR-132, miR-410, miR-206 and miR-409-5p) or upregulation (miR-199a-5p) in the cerebellum, but those findings need to be re-evaluated and confirmed in future studies [188]. A further study was able to identify circulating microRNAs (cimRNAs) to be differentially expressed in MSA and PD patients. MSA patients are distinguished from PD patients and healthy controls by an up-regulation of miR-24, miR-34b and miR-148b, whereas miR-339-5p is downregulated. [190]. The role of these changes is still unclear, however similar they show definite link to neurodegeneration. Previous studies showed that miR-339-5p is expressed at low levels in mature neurons and connected to axon guiding [191]; miR-24 is upregulated in multiple sclerosis

and myocardial ischemia [192, 193]; miR-34b is connected to Huntington's disease, PD and Dementia with Lewy Bodies [194, 195]; miR-148b is downregulated in the parietal lobe cortex and hippocampal as well as medial frontal gyrus of Alzheimer's patients [196, 197].

## CONCLUSIONS

So far, the underlying mechanisms of MSA etiopathogenesis are still elusive. Several familial MSA cases exist, but no heritable mutations have been found supporting hereditary disease. COQ2 mutations have been proposed to associate with familial and sporadic MSA, however this observation could not be replicated in different patient cohorts. Investigations of other genetic "hotspots" linked SNCA polymorphisms with an increased risk of developing MSA in Caucasians. Further studies associated gene polymorphisms in *IL-1- $\alpha$* , *IL-1- $\beta$* , *IL-8*, *ICAM-1*,  *$\alpha$ -1-antichymotrypsin*, tumor necrosis factor genes, *SLC1A4*, *SQSTM1* and *EIF4EBPI* with MSA predisposition, but failed to detect other disease-causing mutations. The genetic background of MSA thereby remains unclear, very much population-specific, and needs to be investigated further. Epidemiological studies investigated the potential influence of environmental factors on MSA pathogenesis. Exposures to metal dusts and fumes, plastic monomers and additives, organic solvents, pesticides and other environmental toxins have already been linked to a higher risk of MSA by changing the epigenetic landscape. However, the mechanisms of environmental epigenetics are not studied in depth in MSA and need further investigation as supported by the emerging evidence [198]. Novel genetic or epigenetic clues linked to the primary oligodendroglipathy in MSA [199] may be crucial for understanding the pathogenesis of this disorder.

Therefore, MSA could be considered a disease that is related to a complex genetic and non-genetic interplay. Interaction of those factors could also contribute to the phenotypic variability of MSA (cerebellar or parkinsonian MSA in various combinations) among different populations, as it was discussed by Ozawa and colleagues [200]. How and whether certain risk factors contribute to MSA remains unclear, but the investigation of those factors is a key topic for promising future research initiatives. Furthermore, epigenetic disease markers may prove a potential role as novel biomarkers in the early diagnosis of MSA.

## DISCLOSURE STATEMENT

The authors declare that there are no actual or potential conflicts of interest.

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