

Review

Difference in MSA Phenotype Distribution Between Populations: Genetics or Environment?

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Abstract. The reasons for the differences in emphasis on striatonigral or olivopontocerebellar involvement in multiple system atrophy (MSA) remain to be determined. Semi-quantitative pathological analyses carried out in the United Kingdom and Japan demonstrated that olivopontocerebellar-predominant pathology was more frequent in Japanese MSA than British MSA. This observation provides evidence for a difference in phenotype distribution between British and Japanese patients with definite MSA. Studies of the natural history and epidemiology of MSA carried out in various populations have revealed that the relative prevalences of clinical subtypes of MSA probably differ among populations; the majority of MSA patients diagnosed in Europe have predominant parkinsonism (MSA-P), while the majority of MSA patients diagnosed in Asia have predominant cerebellar ataxia (MSA-C). Although potential drawbacks to the published frequencies of clinical subtypes and pathological subtypes should be considered because of selection biases, the difference demonstrated in pathological subtype is also consistent with the differences in clinical subtype of MSA demonstrated between Europe and Asia. Modest alterations in susceptibility factors may contribute to the difference in MSA phenotype distribution between populations. Synergistic interactions between genetic risk variants and environmental toxins responsible for parkinsonism or cerebellar dysfunction should therefore be explored. Further investigations are needed to determine the environmental, genetic, and epigenetic factors that account for the differences in clinicopathological phenotype of MSA among different populations.

Keywords: Multiple system atrophy, Parkinson's disease, spinocerebellar ataxia, genetic background, environmental factor

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Multiple system atrophy (MSA) is a rare neurodegenerative disorder with both clinical (MSA with predominant parkinsonism: MSA-P versus MSA

with predominant cerebellar ataxia: MSA-C) and pathological (striatonigral degeneration: SND versus olivopontocerebellar atrophy: OPCA) variants. Physicians and scientists investigating the aetiology of MSA have long been puzzled as to why some patients present primarily with parkinsonism whereas in others cerebellar ataxia predominates. MSA is characterized pathologically by glial (oligodendroglial) cytoplasmic inclusions (GCIs) [1, 2], which are composed of fibrillar α -synuclein [3–5] and other proteins. Recently, genetic studies of single nucleotide polymorphisms (SNPs) demonstrated that certain SNPs in the α -synuclein gene (*SNCA*) were significantly associated with increased risk of developing MSA in European cohorts [6, 7]. The discovery of *SNCA* risk variants for MSA provided useful information which may be relevant to the mechanism underlying the α -synuclein pathology in MSA. However, despite increased understanding of the pathological basis of MSA, the reasons for the differences in emphasis of striatonigral (StrN) or olivopontocerebellar (OPC) predominance in MSA remain to be determined. The natural history and epidemiology of MSA have been reported from many countries, and the variation in the phenotypic spectrum in different ethnic groups has recently attracted considerable attention.

The purpose of this review is to explore the factors that may underlie such phenotypic variation and to discuss any insights that these provide into the pathogenesis of MSA. We will summarize the results of neuropathological studies carried out in the United Kingdom (UK) [8] and Japan [9] which demonstrate that the spectrum of pathological involvement of the StrN and OPC systems differs between these two ethnically different populations and discuss the accumulating evidence that the relative clinical prevalences of MSA-P and MSA-C in Europe [10–17] may differ from those in Asia [18–21].

COMPARATIVE STUDY OF MSA PATHOLOGY IN TWO LARGE PATIENT COHORTS

In the past few years semi-quantitative pathological analyses of MSA have been carried out in the UK [8] and Japan [9] using autopsied brain material from 100 British (Caucasian) cases of MSA referred to the Queen Square Brain Bank, London, UK, and 50 cases of MSA referred to the Brain Research Institute, Niigata University, Japan. In this section, we summarize findings regarding MSA pathology that have been

reported separately in two papers [8, 9]. The first author (T.O.) of these studies performed semi-quantitative assessments of neuronal cell loss in 24 anatomical sites in the StrN and OPC regions (Fig. 1). For this, the following brain regions were selected for examination: (i) basal ganglia at the level of the nucleus accumbens and the anterior commissure; (ii) midbrain at the level of the red nucleus and also at the decussation of superior cerebellar peduncle; (iii) cerebellar vermis and hemisphere at the level of the dentate nucleus; (iv) rostral pons at the level of the locus coeruleus and caudal pons; and (v) medulla oblongata [8]. The semi-quantitative assessments of neuronal cell loss were performed using sections stained by haematoxylin and eosin (H&E) and Luxol fast blue/cresyl violet, and assigned one of four scores for the degree of neuronal loss (0, 1+, 2+, or 3+) in each anatomical site. There was a trend for the British cases to feature greater involvement of the basal ganglia, while in the Japanese cases the OPC region tended to be more severely affected than StrN structures (Fig. 2). The substantia nigra was found to be equally vulnerable in both the British and the Japanese MSA cases. Based on the data of the semi-quantitative assessments, the grading scale used to characterize StrN pathology was as follows. Grade 1: the SbN demonstrates 1+ or 2+ neuronal cell loss, and there is 0 or 1+ neuronal cell loss in globus pallidus, caudate nucleus or putamen. Grade 2: the SbN and putamen demonstrate 2+ or 3+ neuronal cell loss, and there is 1+ or 2+ neuronal cell loss in the caudate nucleus and globus pallidus (except for cases with 3+ neuronal cell loss in both SbN and putamen). Grade 3: the SbN and putamen demonstrate 3+ neuronal cell loss. The grading scale used to characterize OPC pathology was as follows. Grade 1: in the inferior olivary nucleus, pontine nuclei, cerebellar hemisphere or vermis, there is 0 or 1+ neuronal cell loss or one structure demonstrating 2+ neuronal cell loss, while the others have less than 1+ neuronal cell loss. Grade 2: in the inferior olivary nucleus, pontine nuclei, cerebellar hemisphere or vermis, there is either 2+ neuronal cell loss or one structure demonstrating 3+ neuronal cell loss, while the others have less than 2+ neuronal cell loss. Grade 3: more than two structures among the inferior olivary nucleus, pontine nuclei, cerebellar hemisphere or vermis demonstrate 3+ neuronal cell loss. If there were different degrees of pathology in the same structure (e.g., rostral pons 1+, caudal pons 3+), the worst (e.g., 3+) was used for the grading. Combinations of scores reflecting the grading for StrN and OPC neuronal loss were allotted to three categories: “StrN-predominant pathology”, “OPC-predominant pathology”, and “StrN and

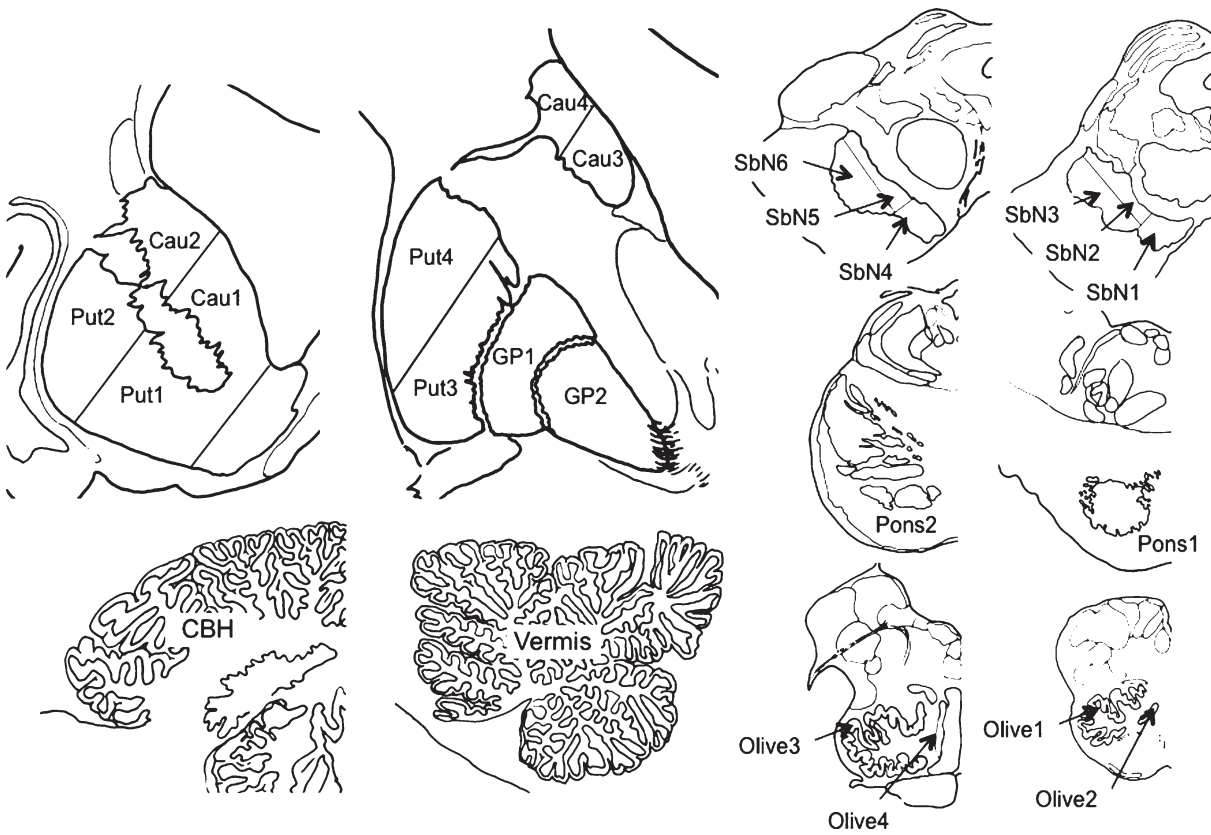


Fig. 1. The 24 anatomical sites in the striatonigral and olivopontocerebellar regions examined in a comparison of two large patient cohorts [8, 9]. Semi-quantitative assessment of neuronal loss in these anatomical regions was performed in autopsied brain samples from 100 British patients and 50 Japanese patients with multiple system atrophy. Put = putamen, Cau = caudate nucleus, GP = globus pallidus, SbN = substantia nigra, CBH = cerebellar hemisphere.

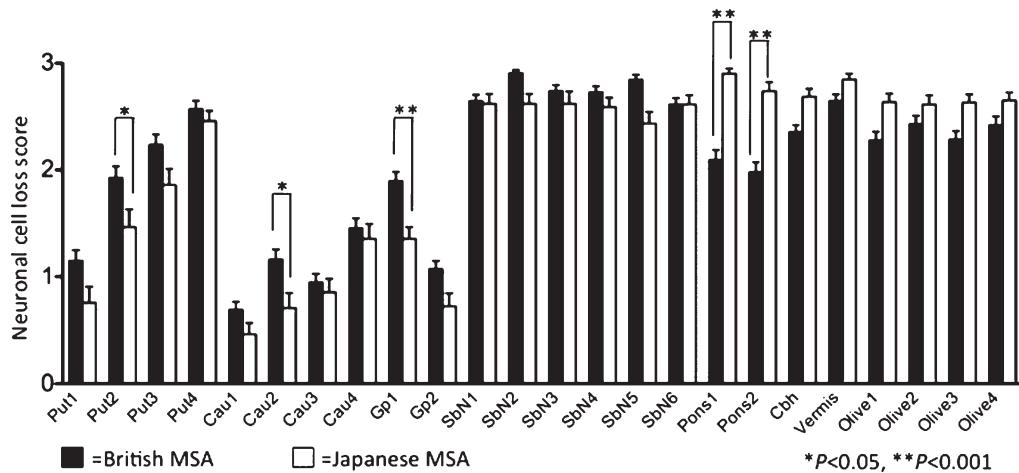


Fig. 2. Summary of the results of a comparative study of multiple system atrophy (MSA) cohorts carried out in the UK and Japan, which were presented separately in two papers [8, 9]. British MSA patients have significantly higher scores for neuronal loss in Put2, Cau2 and GP1 than do Japanese patients ($P < 0.05$, Bonferroni corrected). In Pons1 and 2, Japanese MSA patients have significantly higher scores for neuronal loss than British patients ($P < 0.001$, Bonferroni corrected). Generally, British MSA cases tended to feature greater involvement of the basal ganglia, while Japanese cases tended to feature greater involvement of the olivopontocerebellar region. The substantia nigra is equally vulnerable in both British and Japanese patients with MSA. Put = putamen, Cau = caudate nucleus, GP = globus pallidus, SbN = substantia nigra, Cbh = cerebellar hemisphere. Data are represented as mean \pm standard error of the mean.

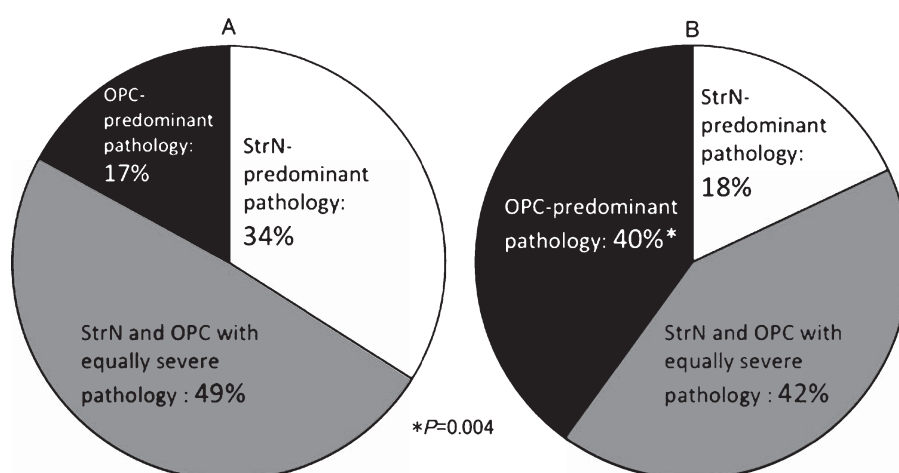


Fig. 3. Relative prevalence of striatonigral (StrN)- and olivopontocerebellar (OPC)-predominant pathology in British and Japanese multiple system atrophy (MSA), as presented separately in two papers [8, 9]. (A) In the British MSA cohort, the relative prevalence of pathological phenotypes was as follows: 17% had OPC-predominant, 34% StrN-predominant, and the remainder (49%) equivalent pathology. (B) In the Japanese cohort, 40% of cases had OPC-predominant pathology, 18% StrN-predominant pathology, and the remainder (42%) had equivalent pathology. The frequency of OPC-predominant pathology in the Japanese series was significantly higher than in the British series ($P=0.004$, Fisher's exact test).

OPC with equally severe pathology” [8]. In the British MSA cohort the relative prevalence of these phenotypes was as follows: 17% of cases had OPC-predominant pathology, 34% had StrN-predominant pathology, and the remainder (49%) had StrN and OPC with equally severe pathology (Fig. 3A) [8]. In the Japanese cohort, 40% of cases had OPC-predominant pathology, 18% had StrN-predominant pathology, and the remainder (42%) had equally severe StrN and OPC pathology (Fig. 3B) [9]. Thus the occurrence of OPC-predominant pathology in the Japanese series was significantly higher than that in the British series [9].

With regard to the clinicopathological correlations observed in the two studies, analyses of parkinsonism and cerebellar dysfunction demonstrated a reasonable correlation between clinical findings and neuropathology in both StrN- and OPC-predominant cases [8, 9]. Initial symptoms were quite variable in the patients with “StrN and OPC with equally severe pathology” groups [9], indicating that the clinical diagnoses of patients in this category include a mixture of MSA-P and MSA-C.

FREQUENCY OF LEWY BODY PATHOLOGY IN CAUCASIAN AND JAPANESE MSA

Lewy bodies have been identified in 8–12% of brains of normal individuals over age 60 years; this condition

is often termed incidental Lewy body disease and is thought to represent presymptomatic Parkinson's disease (PD) [22–24]. Only a few studies have examined the frequency of Lewy bodies in patients with MSA. Wenning and colleagues found that 3 of 35 MSA cases (8.5%) had Lewy bodies in cerebral cortex and substantia nigra [25]. Jellinger reported that 10 of 44 MSA cases (23%) had Lewy bodies mainly in the brainstem [26]. Ozawa and colleagues reported that 10 of 94 cases (10.6%) had Lewy bodies in the substantia nigra or the dorsal motor nucleus of the vagus [8]. All of these studies involved Caucasian cases. Regarding the frequency of Lewy bodies in Japanese cases of MSA, Ozawa and colleagues did not find Lewy bodies in the substantia nigra or the dorsal motor nucleus of the vagus in any of their 50 MSA cases [9]. However, Sone and colleagues reported that 4 of 26 MSA cases (15%) had a few Lewy bodies in the substantia nigra and the dorsal motor nucleus of the vagus [27]. Whilst it is of interest to compare the frequency of Lewy body pathology in MSA among various populations, there are some difficulties with investigating Lewy body pathology in MSA brains. Thus it can be difficult to differentiate Lewy bodies from α -synuclein-positive neuronal cytoplasmic inclusions (NCIs) [27], which have been described in the substantia nigra in MSA [28]. Also, as Lewy bodies occur in various anatomical sites the sampling strategy employed may influence their detection. In the context of MSA there are no guidelines for the diagnosis of concomitant PD or incidental Lewy body

Table 1
The relative frequencies of MSA-P and MSA-C in various populations

Author	Year	Population or regional study group	Total number of cases	Number of MSA-P (%)	Number of MSA-C (%)	Notes	Ref no
Wenning, et al.	1994	United Kingdom	100	82 (82)	18 (18)	The research center was located in London	13
Testa, et al.	1996	Italy	59	34 (57.6)	25 (42.4)	The research center was located in Milan	12
Watanabe, et al.	2002	Japan	230	75 (32.6)	155 (67.4)	The research center was located in Nagoya	19
Chrysostome, et al.	2004	France	50	35 (70)	15 (30)	The research center was located in Bordeaux	16
Benrud-Larson, et al.	2005	United States	99	62 (63)	25 (26)	Remaining 11 cases had equally severe findings of MSA-P and MSA-C. Racial breakdown was 96% Caucasian, 3% Asian/Pacific Islander, and 1% African-American	15
Yabe, et al.	2006	Japan	142	23 (16.2)	119 (83.8)	The research center was located in Sapporo	18
May, et al.	2007	North American MSA Study Group	67	(60)	(13)	The remaining cases (27%) had equally severe findings of MSA-P and MSA-C. The majority was non-Hispanic Caucasian	14
Kollensperger, et al.	2010	European MSA Study Group	437	298 (68.2)	139 (31.8)	This study involved 19 research centers in 10 countries (Germany, Austria, France, UK, Portugal, Spain, Italy, Sweden, Denmark, and Israel) Spanish data revealed 68% MSA-C	11
Seo, et al.	2010	South Korea	100	27 (27)	73 (73)	The research center was located in Seoul	20

disease. Thus, determining clinicopathological correlations of Lewy body pathology in MSA cases remains problematic.

DISTRIBUTION OF PATIENTS WITH MSA-P AND MSA-C IN VARIOUS POPULATIONS

We have reviewed articles detailing the natural history or epidemiology of MSA to determine the relative frequencies of MSA-P and MSA-C in various populations (Table 1). Studies with more than 50 patients with possible or probable MSA performed since the publication of the original Quinn diagnostic criteria [29], which analyzed the relative frequencies of MSA-P and MSA-C, were reviewed. Where more than 2 articles were published by the same group, the most recent publication was included. In Wenning and colleagues' study of 100 British patients with clinical MSA, 82% were MSA-P and 18% were MSA-C [13]. The interim report from the European MSA Study Group (EMSA-SG) involving research

groups in 11 countries (Germany, Austria, France, UK, Portugal, Spain, Italy, Sweden, Denmark, Slovenia and Israel) described 412 European patients with MSA had been entered into the registry by 2004, 63% of these patients were diagnosed with MSA-P and 34% with MSA-C, while the remaining cases (3%) did not meet criteria for MSA [10]. The final report from the EMSA-SG involving 437 MSA patients confirmed that the majority of patients exhibited MSA-P (68%); however, the Spanish group reported 69% MSA-C, probably due to the large number of cases emanating from the group of Berciano et al. in Santander that has a special interest in cerebellar disorders [11]. In Milan in Italy, Testa and colleagues studied 59 patients with MSA, including 34 (57.6%) with MSA-P and 25 (42.4%) with MSA-C [12]. Chrysostome and colleagues, studying 50 French patients with MSA, found that 35 (70%) had MSA-P and 15 (30%) had MSA-C [16]. In the United States, Benrud-Larson and colleagues reported that among 99 patients with MSA, 62 (63%) had MSA-P and 25 (26%) MSA-C -the remaining patients had equally severe findings of MSA-P and MSA-C ("equivalent"

MSA) [15]. The North American MSA Study Group (NAMSA-SG) enrolled 67 patients with MSA (the majority of patients were non-Hispanic Caucasian), and found that 60% were diagnosed with MSA-P and 13% with MSA-C, while the remaining patients (27%) had “equivalent” MSA [14]. Yabe and colleagues, studying 142 Japanese patients with MSA from the northern island of Japan, included 119 (83.8%) cases of MSA-C and 23 (16.2%) of MSA-P [18]. From the main island of Japan, Watanabe and colleagues enrolled 230 Japanese patients with MSA, 155 (67.4%) of whom had MSA-C and 75 (32.6%) had MSA-P [19]. In Korea Seo and colleagues, studying 100 Korean patients with MSA, noted that MSA-C patients accounted for 73% of their cohort [20]. There are some studies with fewer than 50 MSA patients that nevertheless should be mentioned in this review. A Singaporean study involving 33 cases [21], the only study from South East Asia, revealed that MSA-C patients accounted for 67% of the cohort. A study from a centre in Germany with a special interest in cerebellar disorders enrolled 32 patients that included 11 (34.4%) patients with MSA-P and 21 (64.6%) patients with MSA-C [17]. In summary, in studies from Asia, the majority of patients exhibited features of MSA-C, whereas in studies from Europe and North America MSA-P patients predominated; however, there are a few isolated studies presenting contrasting results. As suggested above, published frequencies of MSA-P and MSA-C are influenced by selection biases determined by the clinical interest of the investigators in either parkinsonism or cerebellar dysfunction. Nevertheless, the comparative study of MSA pathology in two large patient cohorts mentioned above [8, 9] demonstrated that OPC-predominant pathology seems to be more frequent in Japanese MSA than British MSA, and this finding is consistent with the trend that MSA-C patients are more frequent in Asian populations (East and Southeast Asian countries) than in European populations (of Europe and North America). This points to the need for further investigation to elucidate biological factors determining this regional difference in distribution of clinicopathological phenotypes of MSA.

Given the difference demonstrated in clinical subtype of MSA between Europe and Asia, its treatment also presumably differs between Europe and Asia. In Europe, the majority of patients presenting with MSA-P indicates the importance of treatment of parkinsonism, while in Asia, with the majority of patients presenting with MSA-C, management of cerebellar dysfunction may be more important.

DO GENETIC RISK VARIANTS FOR MSA DIFFER BETWEEN POPULATIONS?

α-synuclein gene (SNCA)

The neuropathological hallmark of MSA is the GCI associated with neuronal cell loss in brain regions involved in motor and preganglionic autonomic control [30]. The major protein component of the GCI is insoluble, fibrillar α -synuclein hence MSA is recognized as a member of the group of α -synucleinopathies, which also includes PD and dementia with Lewy bodies [31]. Previous studies including sequencing of the *SNCA* coding sequence, gene dosage measurements, and microsatellite testing have failed to identify significant associations of *SNCA* variants with MSA [32–34]. *SNCA* expression studies did not detect altered gene expression levels in MSA brains [35–37]. Furthermore, a haplotype study by Ozawa and colleagues using single nucleotide polymorphism (SNP) failed to demonstrate any association with MSA [38]; this negative finding might be explained by the fact that the SNPs selected for examination were limited and therefore unable to detect *SNCA* risk variants for MSA. Recently, Scholz and colleagues found increased risk for MSA associated with *SNCA* variants in Caucasian MSA patients [6]. They reported that the SNPs rs11931074 and 3857059 in *SNCA*, originally identified in a genome-wide association study of PD, exhibited highly significant associations with increased risk of development of MSA. The finding for SNP rs11931074 was subsequently replicated in an independent set of autopsy-proven cases of MSA from the Mayo Clinic in Jacksonville [39]. However, whether SNPs rs11931074 and 3857059 in *SNCA* contribute to the diversity of clinical subtypes including MSA-P and MSA-C remains to be elucidated. Al-Chalabi and colleagues found another two positive associations in the *SNCA* gene with Caucasian patients with MSA, one with rs3822086 and the other with rs3775444 [7]. Interestingly, the association between MSA-C and these two SNPs was strong despite the small number of MSA-C cases in their cohort [7]. It would be of interest to examine whether these two SNPs of *SNCA* are also associated with increased risk of MSA in Asian cohorts, which feature a high prevalence of MSA-C patients.

Although genetic variants of *SNCA* have been found in Caucasian patients to be associated with MSA, this finding has not been replicated in Asian patients with MSA. Yun and colleagues, seeking an association between SNP rs11931074 and possible or probable

MSA in Korean patients ($n = 100$), could not replicate the results previously reported in Caucasian patients [40]. They observed that the inconsistent results regarding the association between SNP rs11931074 and risk for MSA could be related to the fact that the frequency of risk allele T of rs11931074 is low (2 to 10%) in European populations but very high (51 to 58%) in Asian populations [40]. It is tempting to speculate that the *SNCA* risk variants for MSA contribute to the disequilibrium in MSA phenotype distribution between populations. If this is the case, the broad range of variation in risk-allele frequencies in different populations should be carefully reviewed.

Duplication or triplication of *SNCA* has been identified in families with parkinsonism [41–43]. Gwinn-Hardy and colleagues performed neuropathological investigation on an individual from the family with parkinsonism, in which the *SNCA* triplication was subsequently identified [44]. This patient had striking alpha-synuclein pathology characterized by numerous Lewy bodies in the brainstem and cerebral cortices, but also widespread GCIs in the cerebral and cerebellar white matter [44]. In cases of *SNCA* duplication, alpha-synuclein positive GCIs have also been found in substantia nigra and other CNS regions [45]. These observations emphasise that further investigations are required to determine whether altered expression of *SNCA* contributes to the pathogenesis of MSA.

Genes responsible for spinocerebellar ataxia

Patients with dominantly inherited spinocerebellar ataxia (SCA) have been reported to occasionally exhibit parkinsonism [46–49], autonomic failure [50, 51], and other non-motor symptoms [52, 53], clinical features similar to those seen in MSA. Furthermore, neuropathological examination demonstrated that a few cases of SCA1 [54], SCA2 [55, 56] and SCA3 [57] had inclusions resembling GCIs. The nature of the glial inclusion in the patient with SCA1 remains uncertain as immunohistochemical profile for α -synuclein was not available [54]. The two cases of SCA2 were reported to have ubiquitin-positive, α -synuclein-negative glial inclusions indicating that although there is some morphological resemblance, these inclusions should be considered as different from the GCIs of MSA [55, 56]. In the reported case of SCA 3 the pathological changes were found to be typical of MSA including α -synuclein immunoreactive GCIs and it was considered likely that this was a case of MSA with concomitant SCA3 expansion, although it does raise the possibility that SCA3

expansion may be a risk factor for MSA [57]. Considering the phenotypic diversity of MSA, it should be noted that the relative prevalence of SCA genotypes also differs between Caucasian and Japanese patients; SCA1 and SCA2 are more prevalent in Caucasians, whereas SCA3, SCA6, and dentatorubral pallidolusian atrophy (DRPLA) are more prevalent in the Japanese population [58]. Interestingly, the frequency of normal alleles with relatively large numbers of CAG repeats is also associated with the prevalence of these SCA genotypes [58]. In this regard, further study is needed to determine whether normal alleles with a relatively large number of CAG repeats in SCA genes have any relationship to the pathogenesis or phenotype of MSA.

Other genes related to neurodegeneration or inflammation

Previous studies have failed to identify significant associations between MSA and other genes implicated in neurodegenerative diseases such as those for apolipoprotein E [33, 59, 60], dopamine beta-hydroxylase [61, 62], ubiquitin C-terminal hydrolase-1 (UCHL1) [63], fragile X mental retardation 1 [64–67], and leucine-rich kinase 2 (LRKK2) [68, 69]. Mutations in the glucocerebrosidase gene coding for lysosomal beta-glucocerebrosidase have recently been found to be a risk factor for PD and dementia with Lewy bodies [70–76]; however, these mutations have not been found in patients with MSA [77, 78]. Recently, a mutational screening study of *parkin* and *PINK1* has been performed in 87 pathologically proven MSA cases, but the frequencies of the possibly pathogenic variants were not significantly different from control data [79]. Thus any relationship between the genes mentioned above and MSA phenotypic diversity appears to be unlikely. Regarding the tau gene (*MAPT*) and MSA, haplotype analyses had failed to identify any association between *MAPT* and MSA [33, 60]; however, a recent study involving 61 cases of pathologically confirmed MSA demonstrated that the frequency of SNP rs 1052553 in *MAPT*, which corresponded to H1 haplotype, was significantly increased in MSA cases [80]. In this regard, it is important to determine whether this finding is replicated in Asian patients with MSA, because the frequency of A0 allele in H1 haplotype in Japanese population was reported to be very high (98.5% in control subjects) [81]. Whether *MAPT* H1 haplotype contributes MSA phenotypic diversity remains to be elucidated.

Several studies of the genes responsible for inflammatory processes indicated that polymorphisms of interleukin-1A [82], interleukin-1B [83], interleukin-8 [84], and intercellular adhesion molecule-1 genes [84] were associated with increased risk of MSA. Another study demonstrated an association between polymorphism of the alpha-1-antichymotrypsin gene and risk of MSA [85]. Promoter region polymorphism in the tumor necrosis factor gene has also been reported to be associated with increased risk of MSA [86]. However, whether variants of these genes may contribute to phenotypic diversity in MSA has not been investigated.

ARE ENVIRONMENTAL FACTORS RESPONSIBLE FOR THE DIVERSITY OF MSA PHENOTYPE?

Environmental toxins associated with parkinsonism or cerebellar dysfunction

Accumulating evidence indicates that the prevalence of PD in Asian countries is slightly lower than that in Western countries [87, 88]. Professional exposure to some pesticides (e.g., organochlorine insecticides) has been reported to be associated with PD [89, 90]. In this regard, it is tempting to speculate that agricultural use of pesticides might also differ between Asian and Western countries. Further studies are needed to determine differences in the pattern of pesticide use between Asian and Western countries. For patients with MSA, the relationship between exposure to pesticides and increased risk of MSA has been controversial [16, 91–93], and whether exposure to pesticides modifies the MSA phenotype is unclear.

Given the finding that MSA-C is more frequent than MSA-P in Asian populations, environmental exposures related to cerebellar dysfunction should be carefully reviewed. Recently, beta-fluoroethyl acetate (ethyl fluoroacetate, FEA), a highly potent toxic chemical that has been used against rats and wild animals, was reported to cause selective cerebellar dysfunction [94]. This is a unique finding reported from South Korea. In South Korea, FEA had been available to the general public as an effective pest control agent with less than optimal regulation until 2005 [94]. In Japan, FEA has been designated as a Type II Monitoring Chemical Substance, indicating that the use of this compound is under government surveillance. On the whole, FEA is banned or severely restricted in most countries, and so cases of FEA poisoning are very

rare [94]. Whether FEA is likely to be an environmental toxin in South Korea and Japan warrants further investigation.

Perspective on the interaction between environmental toxins and genetic risk variants

Brighina and colleagues tested possible joint effects of pesticide exposures and *SNCA* variants (REP1 genotypes) on risk of PD, and found that both *SNCA* REP1 score and pesticide exposure were significantly associated with PD in younger subjects, though no pairwise interactions were detected [95]. The synergistic interaction between genetic risk variants and environmental toxins may be important when considering the reasons for the differences in emphasis on StrN or OPC involvement in MSA. Further study is needed to determine epigenetic factors in the phenotypic diversity of MSA.

CONCLUSION

Comparative study of MSA pathology with an identical methodological approach in two large patient cohorts (one British, one Japanese) demonstrated a difference in the distribution of phenotypes between the two populations. The frequent observation of OPC-predominant pathology in Japanese cases of MSA is in keeping with previous findings that the majority of Asian patients exhibit MSA-C. These observations raise the possibility that different populations may have different disease susceptibility factors for MSA. Although genetic variants of *SNCA* have been found to be associated with MSA in Caucasian patients, this finding has not been replicated in Korean patients with MSA. It is tempting to speculate that *SNCA* risk variants for MSA may contribute to the difference in MSA phenotype distribution among populations; thus, the broad range of risk-allele frequencies in different populations should be carefully reviewed. In the case of environmental factors, the relationship between exposure to pesticides and increase in risk of MSA has been controversial, and whether exposure to pesticides modifies MSA phenotype remains unclear. Nevertheless, the synergistic interaction between *SNCA* variants and some environmental toxins could play a role in the pathogenesis and phenotypic diversity of MSA. Further investigation is needed to determine the environmental, genetic and epigenetic factors that account for the differences demonstrated in the

clinicopathological phenotype of MSA in different populations.

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