Understanding Multiple System Atrophy—Could Genetics Lead the Way?

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Multiple system atrophy (MSA) is a progressive, adult-onset, neurodegenerative disorder characterized by parkinsonism, cerebellar ataxia, autonomic failure, and corticospinal tract dysfunction. It is considered a rare disease, similar in frequency to the more well-known neurodegenerative disease amyotrophic lateral sclerosis or Lou Gehrig's disease. Though MSA has not traditionally been considered a genetic disease, new evidence is emerging supporting some genetic predisposition in many patients. In this short review, we will discuss advances in the knowledge of genetics in MSA and how this has furthered our understanding of the pathophysiology of the disease. There is still much unknown about this disease, but some of the recent advances made in MSA genetics may give important clues to understanding the pathogenesis and treatment of this disease.

Multiple system atrophy (MSA) is a is an adult-onset, sporadic, progressive neurodegenerative disease characterized by a varying combination of parkinsonism, cerebellar ataxia, autonomic failure, and corticospinal dysfunction. Patients either have a predominance of parkinsonian symptoms (MSA-P) such that they are often misdiagnosed with Parkinson's disease, or a predominance of cerebellar ataxia (MSA-C). Onset is usually in the 6th and 7th decades of life. The prevalence of MSA is roughly 3–4 per 100,000 in the US.[1] The disease progression tends to be faster than that of Parkinson's disease, with an average disease duration of 8–10 years from onset of symptoms to demise. MSA is neurologically devastating and quickly leaves patients unable walk, speak, and take care of themselves. Patients suffering from MSA often suffer from orthostatic hypotension that can be debilitating, urinary retention requiring catheterization, and various breathing problems. The cause of death in MSA is usually related to dysphagia, respiratory problems, or cardiovascular complications of dysautonomia. There is a very limited arsenal of medications that can be used to treat this disease. Currently available treatments are symptomatic, and include medications to treat parkinsonian symptoms, orthostatic hypotension, urinary symptoms, and sexual dysfunction. Patients typically get brief and modest responses to these medications. There are no treatments available to slow down or stop the progression of MSA.

There are no objective, quantitative tests to reliably make or confirm this diagnosis in living patients. The diagnosis in this disease, as in many movement disorders, is clinical – i.e., it is made based on history, examination, sometimes using supplementary information such as the results of a magnetic resonance image (MRI) of the brain, iodine-123-metaiodobenzylguanidine (MIBG) nuclear medicine scan,[2,3] serum norepinephrine levels, or testing of the autonomic nervous system.[4] The only certain diagnosis is made with brain autopsy, which shows accumulation of the protein α-synuclein within glial cells in the brain and degeneration in the striatum and substantia nigra, and/or degeneration in the olivo-ponto-cerebellar regions of the brain. The lack of highly sensitive and specific confirmatory tests for the diagnosis of MSA, in addition to the rarity of the disease, have been major factors that have made research in MSA difficult.

More recently there have been some advances in laboratory and translational research in MSA. In particular, genetics of MSA has been a recent topic of interest, and is opening new doors in the understanding of the pathogenesis of MSA. In this short review, we will discuss several past and recent advances in the knowledge of genetics in MSA and how this has furthered our understanding of the pathophysiology of the disease and paved the way for novel therapeutic options.

Genetics of multiple system atrophy

Traditionally, most adult-onset neurodegenerative diseases have been considered sporadic rather than genetic in origin. However, more evidence is emerging that many neurodegenerative diseases may have not only a Mendelian pattern of inheritance, but also genes that strongly predispose to the condition. Examples of this include the *ApoE* gene for Alzheimer's disease and *GBA* in Parkinson disease. There have been several multiplex families with MSA in the scientific literature,[5–7] though a candidate gene has only been identified in two of these families. A large genome-wide association study is currently underway; however, few studies have attempted such modern approaches to analyzing genetic predispositions in MSA. Genetics research in MSA is clearly lagging behind that of other α-synucleinopathies (Parkinson's disease and dementia with Lewy bodies [DLB]), though recently a few candidate genes have given researchers clues as to the etiology of MSA.

Alpha-synuclein gene

Mutations and duplications in the α-synuclein (*SNCA*) gene have been clearly linked with α-synucleinopathies. The clinical syndromes and pathologic findings in several patients with known mutations or duplications have shown significant overlap with MSA,[8] including the finding of frequent glial cytoplasmic inclusions on pathologic examination. Some of the families described with *SNCA* mutations had members with a clinical picture consistent with a diagnosis of MSA. A few studies found significant associations between variants in the *SNCA* gene and sporadic cases of clinical MSA[9,10] though there is some controversy about the generalizability of this finding in Asian populations.[11,12] These findings were supported by the discovery of α-synuclein mRNA overexpression in the brains of patients with MSA.[13] This supports a hypothesis that the toxicity of α-synuclein plays an important role in the pathogenesis of this disease, and may help to pave the way for therapeutic options.

Glucocerebrosidase gene

Glucocerebrosidase (GCase), encoded by the *Glucocerebrosidase* gene (*GBA*), is an enzyme involved in the lysosomal degradation of sphingolipids.[14] Homozygous mutations of this gene result in Gaucher's disease (GD), a rare lysosomal storage disease that is particularly prevalent in certain populations, such as the Ashkenazi Jewish population. Parkinson's disease and DLB patients are roughly 5–10-fold[15] and 8 fold[16] (respectively) more likely to carry *GBA* mutations than the general population. These genetic findings have been followed up with findings of reduced GCase activity in the brains[17] and peripheral blood18 of patients with Parkinson's disease. The prevalence of *GBA* mutations among patients with MSA has been studied by a few groups in recent years, and has yielded varied results.[19–25]

Six studies have found no association between *GBA* mutations and MSA. The most recent and largest study included 969 clinically diagnosed MSA patients and 1,509 controls from Japan, several sites in Europe, and several sites in North America.[21] They found a significantly increased odds ratio for *GBA* variants in MSA patients compared to controls. In fact, two patients with MSA had homozygous mutations in the *GBA* gene without a known clinical diagnosis of GD, while none of the controls had homozygous or compound heterozygous mutations. This study certainly indicates that further study of the relationship between *GBA* and MSA is required. It implies that genetic testing for GD may be indicated in certain populations with MSA, and introduces another area for research into therapeutic options for MSA.

Coenzyme Q2 gene

Recently, four multiplex MSA families were studied with whole exome and subsequent linkage analysis in the attempt at identifying a candidate genetic locus for MSA.[26] In two of four Japanese families, the researchers detected mutations in the *coenzyme Q2 (CoQ2)* gene, which plays a role in the synthetic pathway for CoQ10. They followed this with genetic analysis of 726 Japanese patients with sporadic MSA and 1040 Japanese controls, which revealed 35 *CoQ2* mutations among MSA patients and 17 among controls (OR=3.05, p=0.00015). An association between sporadic MSA and *CoQ2* variants was found in Japanese, Taiwanese and Chinese populations, but these results were not replicated in other cohorts.[26–31] Further studies have revealed reduction in CoQ10 levels in the cerebellum and serum of patients with MSA.[32,33] These findings may be particularly important in implicating CoQ10 supplementation as a therapeutic option in MSA, though this has not yet been systematically studied.

Other implicated genes

A hexanucleotide expansion in the *C9orf72* gene located on chromosome 9 has been found to be present in patients with familial forms of frontotemporal dementia and amyotrophic lateral sclerosis (ALS). There is also a report of clinically diagnosed MSA with *C9orf72* expansion in a family with ALS.[34] Though *C9orf72* expansions are associated with parkinsonian symptoms and syndromes, this is the only report of suspected MSA with *C9orf72*. Subsequent studies, including a series of 100 pathologically confirmed MSA cases,[35] have failed to produce a link between this expansion and MSA.

Microtubule-associated protein tau (MAPT) gene has been associated with frontotemporal dementia and ALS phenotypes as well as parkinsonism. There does not appear to be an association between mutations in this gene and MSA, however this has not been extensively studied.[36]

Mutations in the *Leucine-rich repeat kinase 2 (LRRK2)* have been investigated for a causal link with MSA. Most studies have not found an association between *LRRK2* mutations and MSA.[37,38] However one large series from the US and UK found a protective effect of *LRRK2* variants on MSA.[39]

Genetic mutations in the spinocerebellar ataxia family (SCA) are associated with varying degrees of ataxia, parkinsonism, dystonia, and even autonomic dysfunction. Given the clinical overlap with symptoms seen in MSA, it can be difficult to distinguish SCA from MSA. Patients with SCA syndromes typically present earlier in life than MSA, are usually slower in progression, and will have a family history. In clinical practice, it is often advisable to test for SCA mutations when evaluating patients presenting with adult-onset cerebellar ataxia, with or without a known family history.[40] Most studies looking at the association between clinically diagnosed MSA and mutations in the SCA genes have focused on the utility of SCA genetic testing in patients presenting clinically with MSA. There are no large pathologic series, to our knowledge, of MSA that have been tested for mutations in SCA genes. However, there is one case report of a patient with adult-onset cerebellar ataxia with dysautonomia and parkinsonism who was clinically diagnosed with MSA, who subsequently underwent testing for SCA mutations and was found to have an SCA-3 mutation. On autopsy, this patient had findings typical of MSA. This finding indicates that further studies are required to fully analyze this association.

Conclusion

MSA is not generally considered a genetic disease, and in fact only rarely has been described in families. More recent efforts in the field of MSA genetics have revealed several candidate genes that may be involved in the pathogenesis of the disease. The pathogenesis of MSA remains an enigma, though it is becoming clear that genetic associations exist. Many mechanisms for the development and propagation of MSA have been postulated, including impaired elimination of α-synuclein within the cell,[41–44] mitochondrial dysfunction,[32,33,45,46] direct toxicity of α-synuclein,[47] oxidative stress,[48] and neuroinflammation.[49,50] More recently, there are also data that implicate a prion-like propagation of MSA.[51] We are hopeful that genetic associations may give us further clues into the pathogenesis of MSA, as well as targets for therapeutic interventions. For example, if *GBA* mutations confer a higher risk of developing MSA, it follows that treatment with enzyme replacement therapy may offer some benefit to patients who have MSA, with or without *GBA* mutations. It is clear that none of the genetic associations discussed above confer a high penetrance for development of MSA; rather they likely create a pre-disposition for this rare and devastating disease. With advances in the knowledge of genetic contributions to MSA we may find clues to the understanding and treatment of this disease. ❏

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