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Update on novel familial forms of Parkinson's disease and multiple system atrophy

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SUMMARY

Parkinson's disease (PD) and multiple system atrophy (MSA) are progressive neurodegenerative disorders classified as synucleinopathies, which are defined by the presence of α-synuclein protein pathology. Genetic studies have identified a total of 18 PARK loci that are associated with PD. The *SNCA* gene encodes the α-synuclein protein. The first pathogenic α-synuclein p.A53T substitution was discovered in 1997; this was followed by the identification of p.A30P and p.E46K pathogenic substitutions in 1998 and 2004, respectively. In the last year, two possible α-synuclein pathogenic substitutions, p.A18T and p.A29S, and two probable pathogenic substitutions, p.H50Q and p.G51D have been nominated. Next-generation sequencing approaches in familial PD have identified mutations in the *VPS35* gene. A VPS35 p.D620N substitution remains the only confirmed pathogenic substitution. A second synucleinopathy, MSA, originally was considered a sporadic condition with little or no familial aggregation. However, recessive *COQ2* mutations recently were nominated to be the genetic cause in a subset of familial and sporadic MSA cases. Further studies on the clinicogenetics and pathology of parkinsonian disorders will facilitate clarification of the molecular characteristics and pathomechanisms underlying these disorders.

1. Introduction

The synucleinopathies are a group of disorders characterized by the presence of α-synuclein protein aggregation at autopsy [1]. Parkinson's disease (PD) is the major synucleinopathy and the most common neurodegenerative movement disorder. Patients with PD typically present with bradykinesia, muscle rigidity, resting tremor, and postural instability; they respond well to L-dopa therapy. PD is characterized pathologically by Lewy bodies and Lewy neurites in which the α-synuclein protein accumulates. Although approximately 15% of PD patients report a family history of PD [2], large families with Mendelian inheritance are rare. To date, various genetic methods have been applied to familial forms of PD, revealing a total of 18 genomic loci, which now includes seven known genes. Among these seven genes, four (*SNCA*, *LRRK2*, *VPS35*, and *EIF4G1*) are associated with autosomal dominant PD [3].

Multiple system atrophy (MSA) is a rare neurodegenerative movement disorder. Patients with MSA typically present with dysautonomia accompanied by a combination of parkinsonism, cerebellar ataxia, and pyramidal signs. MSA is characterized pathologically by glial cytoplasmic inclusions composed of α-synuclein protein [4]. MSA originally was considered a sporadic condition; however, an international collaborative group recently nominated a potential gene for this condition [5].

This paper focuses on the recent genetic research on PD with regard to novel *SNCA* and *VPS35* mutations; in addition, we also introduce our series of clinically diagnosed familial MSA cases.

2. Familial Parkinsonism related to α-synuclein pathology

PD and MSA are major neurodegenerative parkinsonian disorders related to α-synuclein pathology [4]. In this section, we discuss the current status of clinical and genetic research on PD with *SNCA* gene mutations and on MSA.

2.1. Parkinson's disease with SNCA mutations

The first point mutation in the *SNCA* gene, resulting in α-synuclein p.A53T substitution, was identified in an American–Italian family (Contursi kindred) and in three apparently unrelated small families of Greek origin in 1997 [6]; thereafter, two additional mutations in the *SNCA* gene, resulting in α-synuclein p.A30P and p.E46K substitutions, were reported in German and Spanish families, respectively [7,8]. In addition to these point mutations, genomic multiplications of the entire *SNCA* gene also cause PD [9,10]. Although α-synuclein protein appears to play a central role in the pathogenesis of PD, mutations in the *SNCA* gene have been identified very rarely. However, recently four additional α-synuclein substitutions (p.A18T, p.A29S, p.H50Q, and p.G51D) have been identified. In this subsection, we review these newly discovered mutations.

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2.1.1. α-Synuclein p.A18T and p.A29S

Hoffman-Zacharska et al. screened the *SNCA* gene for 629 Polish PD patients, including 169 with early-onset PD and 460 with late-onset PD [11]. Thirteen percent of the patients had a familial form of PD. They identified p.A18T and p.A29S substitutions in the α-synuclein protein. These two substitutions were absent in 630 healthy controls and in the Exome Variant Database (http://evs.gs.washingon.edu/EVS/). One patient carrying the α-synuclein p.A18T substitution presented with a typical PD phenotype at age 60, later developing mild dysautonomia and cognitive impairment. The patient did not have a family history of neurodegenerative disorders. His parents were not available for genetic sequencing; however, one of the unaffected siblings did not carry the substitution. The other patient carrying an α-synuclein p.A29S substitution experienced rapidly progressive PD beginning at age 60 years, which was followed by the appearance of restless legs syndrome and psychiatric symptoms, including anxiety and depression. The patient did not have a family history of neurodegenerative disorders. The brain of the patient with the α-synuclein p.A29S substitution showed characteristic pathological findings of PD. The parents of the patient were not available for genetic sequencing.

Overall, the clinical phenotype of patients with α-synuclein p.A18T and p.A29S substitutions is characterized by a relatively typical PD phenotype. The pathogenicity of these two substitutions still remains unclear; therefore, further genetic and functional analyses on other patients with the mutation are warranted.

2.1.2. α-Synuclein p.H50Q

Appel-Cresswell et al. performed Sanger sequencing on the coding region of the *SNCA* gene for 110 PD patients [12]. Sixty-six percent of patients had a familial form of PD. The α-synuclein p.H50Q substitution was identified in a single PD patient. The mutation was absent in an additional 1,105 PD patients, 875 healthy controls, and a publicly available next-generation sequencing database (http://main.genome-browser.bx.psu.edu/). The patient developed L-dopa responsive familial PD at age 60 years, which was followed by cognitive impairment, including apathy and dementia. His mother had parkinsonism, and his aunt, as well as a sibling, had dementia. Proukakis et al. [13] performed genetic sequencing on the coding region of the *SNCA* gene for five cases from the Queen Square PD Brain Bank. They identified the α-synuclein p.H50Q substitution in a single sporadic PD patient. The mutation was absent in the database of single nucleotide polymorphisms and in 450 healthy controls. The patient developed L-dopa-responsive PD at age 71, which was followed by forgetfulness. His brain showed characteristic pathological findings of PD, which was accompanied by mild Alzheimer's pathology. Overall, the clinical phenotype of patients with the α-synuclein p.H50Q substitution is characterized by a PD phenotype accompanied by cognitive impairment. Of note, the patients described by the two groups shared a common ancestral founder [12].

2.1.3. α-Synuclein p.G51D

Lesage et al. [14] performed whole-exome sequencing on three PD patients from a three-generation French family. They identified the α-synuclein p.G51D substitution in the patients. The mutation was absent in 236 neurologically normal controls and 200 additional index patients with autosomal dominant PD. The clinical features of the patients are characterized by early-onset and rapidly progressive PD with mild-to-moderate responsiveness to L-dopa therapy. All of the patients had pyramidal signs, and two had severe psychiatric symptoms, such as anxiety and depression. The brain of one of the patients showed a wide distribution of α-synuclein Lewy body pathology, similar to that of patients with *SNCA* multiplications. Cytoplasmic inclusions in the cortex were p62 and ubiquitin positive but Aβ and TDP-43 negative. Kiely et al. [15] performed Sanger sequencing on three family members from a two-generation British family. They identified the α-synuclein p.G51D heterozygous substitution in all of the affected patients. The mutation was absent in 4,500 normal controls. The proband developed PD at age 19; progressive cognitive impairment, visual hallucinations, dysautonomia, limb myoclonus, and pyramidal signs subsequently appeared. He eventually had seizures and died following a disease duration of 29 years. His father had a similar illness and his sibling developed L-dopa-responsive PD with occasional visual hallucinations. At autopsy, the patient's brain showed extensive α-synuclein pathology, accompanied by mild Alzheimer's pathology. The Lewy-body pathology included neuronal α-synuclein positive inclusions as well as glial cytoplasmic inclusions, which more typically are seen in cases of MSA. Cytoplasmic inclusions were p62 positive. TDP-43 positive neurocytoplasmic inclusions were present in moderate intensity in the basal ganglia. Overall, the clinical phenotype of patients with the α-synuclein p.G51D substitution is characterized by early-onset, rapidly progressive PD accompanied by pyramidal signs and psychiatric symptoms, with the absence of cognitive impairment in the early stage of illness. These features are distinguishable from those of patients with the other *SNCA* mutations. Characteristic clinical and pathological features of patients with *SNCA* mutations are summarized in Table 1.

2.1.4. Structure of α-synuclein and substitutions

The structure of the α-synuclein protein can be divided into three major domains: the N-terminal amphipathic region, the central NAC domain (non-amyloid β-component) and the C-terminal, highly acidic region containing several phosphorylation sites [16]. All six *SNCA* point mutations have been identified in the N-terminal amphipathic region of α-synuclein protein. The structure of the N-terminal amphipathic region can be subdivided into two α-helix stretches (positions 3–30 and 45–92), which are divided by Helix–Turn–Helix in the secondary structure (Fig. 1A) [12,13,16]. α-Synuclein p.A18T, p.A29S and p.A30P substitutions are in the first helical fragment; p.E46K, p.G50Q, p.G51D and p.A53T substitutions are in the second helical fragment. The clinical phenotype of newly identified p.A18T and p.A29S carriers resembles the phenotype observed in patients with the previously reported pathogenic p.A30P substitution [8]. These three mutations are associated with a typical late-onset form of PD [11]. However, the phenotypes exhibited by α-synuclein p.E46K, p.G50Q, p.G51D and A53T substitutions show severe and rather rapidly progressive parkinsonism, cognitive decline and sometimes visual hallucinations, suggesting a clinical presentation for these substitutions more reminiscent of dementia with Lewy bodies [7,12–15]. Patients with α-synuclein p.G51D and p.A53T substitutions have earlier disease onset than patients with the other five substitutions [12–15].

2.2. Multiple system atrophy

MSA is a rare neurodegenerative disorder characterized clinically by dysautonomia with various combinations of poorly L-dopa-responsive parkinsonism, cerebellar ataxia, and pyramidal signs [17]. MSA originally was considered a sporadic condition. However, several small familial aggregations of MSA have been reported and, more commonly, familial aggregates of α-synucleinopathy, (i.e. PD and MSA) in the same kindreds. Wüllner et al. [18,19] first reported a German family in which two members were diagnosed with MSA. Subsequently, seven families with MSA with detailed clinical information have been reported from two independent Japanese groups [20,21]. Within these eight families,