Genetics of Progressive Supranuclear Palsy

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ABSTRACT

Progressive supranuclear palsy (PSP) is a neurodegenerative syndrome that is clinically characterized by progressive postural instability, supranuclear gaze palsy, parkinsonism and cognitive decline. Pathologically, diagnosis of PSP is based on characteristic features, such as neurofibrillary tangles, neutrophil threads, tau-positive astrocytes and their processes in basal ganglia and brainstem, and the accumulation of 4 repeat tau protein. PSP is generally recognized as a sporadic disorder; however, understanding of genetic background of PSP has been expanding rapidly. Here we review relevant publications to outline the genetics of PSP. Although only small number of familial PSP cases have been reported, the recognition of familial PSP has been increasing. In some familial cases of clinically probable PSP, PSP pathologies were confirmed based on NINDS neuropathological diagnostic criteria. Several mutations in *MAPT*, the gene that causes a form of familial frontotemporal lobar degeneration with tauopathy, have been identified in both sporadic and familial PSP cases. The H1 haplotype of *MAPT* is a risk haplotype for PSP, and within H1, a sub-haplotype (H1c) is associated with PSP. A recent genome-wide association study on autopsy-proven PSP revealed additional PSP risk alleles in *STX6* and *EIF2AK3*. Several heredodegenerative parkinsonian disorders are referred to as PSP-look-alikes because their clinical phenotype, but not their pathology, mimics PSP. Due to the fast development of genomics and bioinformatics, more genetic factors related to PSP are expected to be discovered. Undoubtedly, these studies will provide a better understanding of the pathogenesis of PSP and clues for developing therapeutic strategies.

Key Words
Progressive supranuclear palsy; Genetics; *MAPT*; Microtubule-associated protein tau; Familial progressive supranuclear palsy.

INTRODUCTION

Since the first description of progressive neurodegenerative cases with supranuclear gaze palsy and bulbar palsy, progressive supranuclear palsy (PSP; formerly, Richardson's syndrome) has been established as a neurodegenerative disorder with characteristic clinicopathological features.[1] Clinically PSP is diagnosed according to the NINDS-SPSP criteria,[2] where falls and supranuclear gaze palsy are the most important features. Definitive diagnosis of PSP is based on pathological criteria.[3] Accumulation of 4 repeat tau protein in neurons and glia in basal ganglia and the brainstem is a characteristic feature of PSP.[4] The clinical phenotypic spectrum of PSP has broadened during the last decade.[5-11] After a seminal article published by Williams et al.[5] introduced the concept of PSP-parkinsonism and PSP-Richardson's syndrome, subtypes of PSP have been recognized in pathologically confirmed PSP cases.[12] These include pure akinesia with gait freezing,[13] corticobasal syndrome,[6] progressive non-fluent aphasia,[14] primary lateral sclerosis,[8] and a behavioral variant of frontotemporal dementia.[15] Differential burden and distribution of tau pathologies between cortices, and basal ganglia and brainstem are related to atypical phenotypes.[4] Likewise, although PSP has been generally recognized as a sporadic disorder, understanding of the genetic background of PSP has been expanded.

This review will cover the genetic aspects of PSP, focusing on family history, single gene mutation causes of PSP, common risk alleles or haplotypes and PSP-mimicking disorders with known causative genes.

FAMILIAL PSP

Traditionally, PSP has been considered as a sporadic condition. The prevalence of PSP is reportedly 5−6 cases/100,000.[16-19] The incidence of PSP increases steeply with age, from 1.7 at 50 to 59 years to 14.7 at 80 to 99 years.[20] It was not long ago that family history of PSP and other neurodegenerative conditions was investigated systematically in PSP.[21] Using a structured questionnaire studying family history, Donker Kaat et al.[21] found that 57 (33%) out of 172 patients with PSP had at least one first-degree relative who had dementia or parkinsonism, which is higher compared to those for controls from the Rotterdam study (25%) [odds ratio (OR) 1.5, 95% confidence interval (CI) 1.02−2.13]. In patients with PSP, first-degree relatives with parkinsonism were more commonly observed compared to controls (OR 3.9, 95% CI 1.99−7.61). Seven percent of the patients with PSP fulfilled the criteria for an autosomal dominant mode of transmission.

Recently, Fujioka et al.[32] reviewed 59 cases out of 19 families with familial PSP.[21-31] While not all reported patients with familial PSP fulfilled the NINDS-SPSP criteria for the diagnosis of clinically probable PSP in which supranuclear ophthalmoplegia was observed in 76.3% of the cases and falls were in reported in 44.1% of the cases, there were pathologically confirmed cases.[32] In a retrospective study reviewing autopsy results and medical records of 375 pathologically confirmed PSP cases, excluding those carrying a *MAPT* mutation, family history of PSP was observed in 3% of the cases, whereas family history of PSP, parkinsonism or dementia was observed in 15% of the cases.[33] PSP cases with a family history showed atypical features more often, and the H1 haplotype was overrepresented in familial PSP compared to sporadic PSP.

SINGLE-GENE MUTATION AS A CAUSE OF PSP

Cases of familial or sporadic PSP caused by single-gene mutation, which includes the *MAPT* and *LRRK2* genes, have been reported.

MAPT mutations in PSP

Tau protein, which is encoded by *MAPT*, is a microtubule-binding protein that is believed to be involved in assembly and stabilization of microtubules.[34,35] Neuropathological changes in tau protein accumulation is observed in Alzheimer's disease, PSP, corticobasal degeneration (CBD), Pick's disease and argyrophilic grain disease.[36] There are imperfect amino acid repeats in exons 9, 10, 11, and 12 which constitute the microtubule-binding region in tau protein. Alternative messenger ribonucleic acid splicing of *MAPT* in the human adult brain produces 6 isoforms of the tau protein. They differ from one another by the presence or absence of exons 2 or 3 in the amino-terminal half and inclusion, or not, of exon 10 in the carboxy-terminal half.[35] Exclusion

of exon 10 leads to the production of 3-repeat isoforms, whereas its inclusion leads to 4-repeat isoforms. The expression levels of 3-repeat and 4-repeat isoforms are similar in normal adult human cerebral cortex, whereas those may change in neurodegenerative tauopathies.[35]

Mutation of *MAPT* was identified as a causative gene for familial tauopathies, which have several different clinicopathological diagnoses.[37-39] These familial tauopathies caused by mutations of *MAPT* (FTDP-17T/*MAPT*) are characterized by frontal lobe dysexecutive symptoms, disinhibition, dementia, parkinsonism, amyotrophy or supranuclear gaze palsy[40] and are highly variable within or between families. FTDP-17T/*MAPT* may present with a variety of clinical syndromes such as frontotemporal lobar degeneration with parkinsonism, a behavioral variant of frontotemporal dementia, Pick disease, PSP-like, CBD-like, or neurodegeneration with overlapping features. Biochemical analysis of insoluble tau is also variable, which shows predominance of 3-repeat, or 4-repeat, or 3- and 4-repeat at a similar level.[35]

The first *MAPT* mutation found in PSP was a p.R5L mutation in a sporadic case whose brain showed globose neurofibrillary tangles, neutrophil thread, and tufted astrocytes, which were stained with anti-tau antibodies in basal ganglia and brainstem.[41] Biochemical analysis of insoluble aggregates from subcortical regions showed predominance for four-repeat tau, similar to PSP. Additionally, a functional study revealed that the p.R5L allele of *MAPT* alters the ability of tau to promote microtubule assembly. Although pathological confirmation was not performed in all published cases of familial or sporadic PSP with a *MAPT* mutation, there are cases of PSP with a *MAPT* mutation diagnosed either clinically or pathologically.[21,31] Because the number of PSP cases included are small and studies were not systematically performed,[21,41-43] the prevalence of a *MAPT* mutation in PSP cannot be estimated.

Currently, more than 40 different *MAPT* mutations have been shown to cause FTDP-17T/*MAPT* in individuals from over 100 families, while in PSP, 10 different *MAPT* mutations have been reported (Figure 1).[44-47] Interestingly, except for the R5L mutation, all other variants (p.L284R, p.S285R, p.delN296, p.N296N, p.P301L, p.G303V, p.S305S, IVS10+3, and IVS10+6) are located in exon 10 and its splicing region. Seven mutations are in coding regions and the other two mutations are in the splicing region of exon 10. Patients with p.L284R or p.S285R *MAPT* mutations presented with only the PSP phenotype; however, both PSP and FTDP-17T/*MAPT* phenotypes were recognized in the other
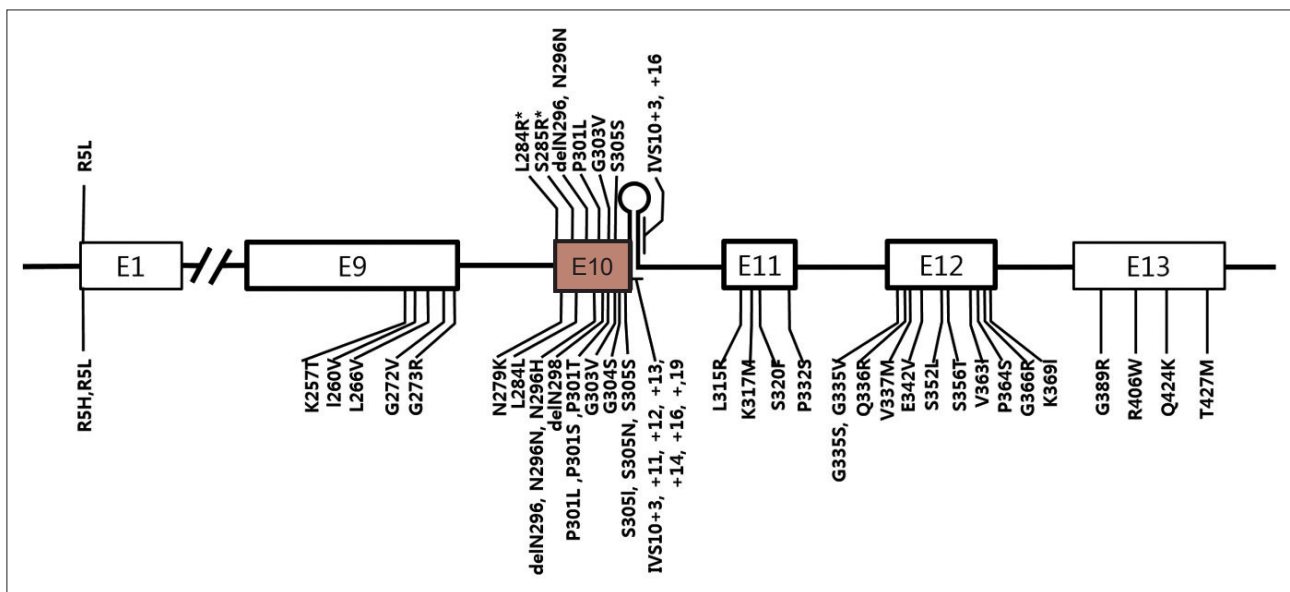

Figure 1. A schematic diagram showing exons of *MAPT* and locations of mutations. Mutations discovered in patients with progressive supranuclear palsy (PSP) or PSP-like phenotypes were marked in the upper half of the diagram and those with frontotemporal lobar degeneration presentation were marked in the lower half. E1 to E13 refer to number of exons. Note all mutations except for p.R5L are located in exon 10 or in stem-loop structure at the boundary between exon 10 and the intron following exon 10. Two mutations (p.L284R and p.S285R; marked with asterisk) were found only in patients with PSP phenotype.

mutations. Given that PSP is 4-repeat tauopathy, mutations in *MAPT* exon 10 or its splicing regions may enhance production of 4 repeat tau isoforms[48,49] or alter conformation of tau protein and affect its degradation process.

LRRK2 mutations and PSP

Patients with levodopa-responsive parkinsonism in western Nebraska kindred in whom a *LRRK2* (PARK8) R1441C mutation was discovered, pleomorphic pathology was reported in the autopsied brain.[50] Within this family, affected members showed Lewy body Parkinson's disease, diffuse Lewy body disease, nigral degeneration without distinctive histopathology, or PSP-like pathology. The affected family members with PSP-like pathology had supranuclear palsy, neuronal loss in the substantia nigra, and tau pathologies (globose neurofibrillary tangles, tufted astrocytes, and oligodendroglial coiled bodies) without Lewy body or Lewy neuritis.

In an analysis of the *LRRK2* mutation in familial or sporadic PD from Crete by Spanaki et al.,[51] two parkinsonian brothers were identified with a R1441H mutation in *LRRK2*. In both siblings, parkinsonism began as typical levodopa-responsive parkinsonism followed by a relatively rapid deterioration after a decade. The brothers later showed postural instability, supranuclear gaze palsy, bulbar dysfunction, dementia and other symptoms/signs, which are typical for PSP. However, neuropathological studies of these cases were not reported.

Contrary to these two families suggesting that mutations in *LRRK2* may be a genetic cause of PSP, other studies failed to detect a *LRRK2* mutation in patients with PSP, although only small number of PSP cases were included for a *LRRK2* mutation screen. Screening for *LRRK2* mutations were negative in clinically diagnosed PSP patients of Caucasian origin[52,53] or of Asian origin.[54] A similar study of definite PSP cases in whom diagnosis was confirmed by neuropathology also reported negative results.[55,56] Taken together, these results suggest that mutations of *LRRK2* in patients with PSP are rare.

Other locus for familial PSP

Currently, only one PSP locus has been identified by linkage analysis. Ros et al.[28] identified a PSP locus from a linkage analysis of a large Spanish family in which PSP was inherited in autosomal dominant fashion.[26-28] Clinical phenotypes were typical of PSP, although a minority of patients showed atypical features. Pathological diagnosis of PSP was confirmed according to the NINDS pathological criteria.[27] Haplotype analysis around a chromosomal region with a maximum multipoint LOD score identified a 3.4 cM candidate disease locus between markers D1S238 and D1S2823 on chromosome 1q31.1.[28] However, no further progress has been published on the gene responsible.[57] Recently, familial PSP with a definite PSP pathology but negative for a *MAPT* mutation has been published, but no locus has been reported.[21,31]

GENETIC RISK FACTORS ASSOCIATED WITH PSP

MAPT haplotypes and sub-haplotypes

Conrad et al.[58] identified an association of an intronic dinucleotide repeat polymorphic marker in *MAPT* with PSP, but not with other tauopathies such as Alzheimer's disease or parkinsonism-dementia complex of Guam. Single nucleotide polymorphisms (SNPs) in an extended haplotype of 1.3 Mbp covering *MAPT* were found to be in complete linkage disequilibrium. Moreover, a common haplotype (H1 or *MAPT* H1-clade) was significantly over-represented in patients with PSP.[59-61] The identification of the H1 haplotype conferring a risk for PSP was consistently replicated in Caucasian populations. Although underlying molecular mechanisms conferred by the H1 haplotype have not been identified, supporting evidence in cell models is that the H1 haplotype enhanced *MAPT* expression.[62] The H2 haplotype that is present exclusively in Caucasians was found to be inversion polymorphism.[63] Using haplotype tagging SNPs spanning *MAPT*, Pittman et al.[64] identified sub-haplotypes within H1. They found that a common sub-haplotype (*MAPT* H1c) on the background of the *MAPT* H1-clade is over-represented in PSP. *MAPT* H1c was also found over-represented in patients with PSP-parkinsonism compared to controls.[9] The *MAPT* H1-clade was also found associated with an increased risk of PD, however, *MAPT* H1c is not involved.[65,66] *MAPT* H1c was associated with increased *MAPT* expression, especially the 4 repeat-containing transcript.[67]

Genome-wide association study in PSP

To find additional PSP risk variants other than the *MAPT* H1 haplotype, a genome-wide association (GWA) study was performed using a pooled-DNA approach in 288 PSP patients from the US or Canada diagnosed based on neuropathology and 344 age- and sex-matched normal controls.[68] By assessing differences in allelic frequency, based on ranking differences in probe intensities for more than 500,000 SNPs between two cohorts, this study confirmed the *MAPT* H1 haplotype as a risk for PSP. A second major locus on chromosome 11p12-p11 showed evidence of association at allelic ($p < 0.001$), genotypic ($p < 0.001$), and haplotypic ($p < 0.0001$) levels. The DNA damage-binding protein-2 and lysosomal acid phosphatase-2 genes located in a single haplotype block of this locus were suggested as candidates for conferring risk of PSP.

Höeglinger et al.[69] carried out a GWA study in two stages. Stage 1, a discovery cohort consists of 1,114 autopsy-confirmed PSP cases and 3,247 controls of European ancestry. SNPs that passed a cutoff ($p \leq 10^{-3}$) in Stage 1 were genotyped in the second stage (an independent set of validation cohort), which consisted of 1,051 PSP cases that were diagnosed clinically and 3,560 controls. Joint analysis of stage 1 and 2 revealed that SNPs in *STX6, MOBP, MAPT*, and *EIF2AK3* were associated with PSP. In the *MAPT* H1 region, after controlling H1/H2, some SNPs remained associated with the maximum falling in *MAPT* (rs242557). *STX6* encodes syntaxin 6, a SNARE class protein that is involved in intracellular membrane trafficking along endocytic and secretory transport pathways.[70] A recent study showed that the GWA SNP rs1411478 in *STX6* is a strong expression quantitative trait locus with significantly lower expression of *STX6* in the white matter of carriers of the risk allele.[71] *EIF2AK3* encodes PERK, a component of the endoplasmic reticulum (ER) unfolded protein response (UPR). When excess unfolded proteins accumulate in the ER, PERK is activated by dimerization and trans-autophosphorylation, which in turn phosphorylates eukaryotic translation-initiation factor 2α (eIF2α). eIF2α inhibits global translation, which allows ER to clear unfolded proteins. In the affected regions in PSP, the UPR was activated.[72] *MOBP* encodes MOBP protein, which is produced by oligodendrocytes and is present in the major dense line of central nervous system myelin. Regions of high MOBP expression overlap with those affected in PSP, suggesting that dysfunction of myelin or oligodendrocytes is involved in the PSP pathogenesis. Genotype-expression correlation analysis showed that SNP alleles across the entire H1/H2 inversion and flanking regions show strong correlation with *MAPT* expression. However, after controlling for H1/H2, all significant genotype-expression correlation for MAPT disappeared.[69] CBD is a neurodegenerative disorder with tauopathy that mimics PSP. Recently, a GWA study for CBD was reported to share common risk variants with PSP, which included rs1768208 at *MOBP* and rs242557 in *MAPT* H1c.[73]

HEREDITARY NEURODEGENERATIVE DISORDERS MIMICKING PSP: PSP-LOOK-ALIKES

The expression of "look-alikes" in neurodegenerative disorders was first coined by Dr. Marsden in describing five cases whose symptoms and signs on clinical grounds were compatible with typical CBD, but who turned out not to have CBD, but rather, other disorders, such as periventricular ischemic lesion with multiple infarction, sudanophilic leurkodystrophy, Pick disease and PSP in postmortem examination.[74] As current understanding of the genetics and molecular pathology of neurodegenerative disorders has been advancing, the complicated relationship of convergence and divergence among clinical manifestation, pathology and causative genes has been recognized.[75,76] Differentiation of a hereditary neurodegenerative disease from a similar phenotypic syndrome may be important with regard to different prognoses and genetic counseling, as well as potential therapeutic and research implications.[77,78] "PSP-look-alikes" refer to hereditary neurodegenerative disorders that clinically mimic PSP, showing parkinsonism and early supranuclear gaze palsy, but that are not compatible with neuropathology of PSP. Recently, PSP-look-alikes were extensively reviewed by Stamelou et al.[79] PSP-look-alike disorders include frontotemporal lobar degeneration caused by mutations in *PGRN, C9orf72, CHMP2B* or *FUS*, Perry syndrome (mutations in *DCTN1*), Kufor-Rakeb disease (mutations in *ATP13A2*), Niemann-Pick type C (mutations in *NPC1*), Gaucher disease

(mutations in *GBA*), mitochondrial disorders, and familial Creutzfeldt-Jakob disease (mutations in *PRNP*).

CONCLUSIONS

Our understanding of the genetic background of PSP has been expanding rapidly. This knowledge will not only help improve accurate diagnosis of PSP and other PSP-look-alike disorders, but will also provide insight into the pathogenesis, toward the eventually development of therapeutic strategies.

Conflicts of Interest

The authors have no financial conflicts of interest.

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