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Parkinson's Disease and α-synuclein Expression

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Abstract

Genetic studies of Parkinson's disease over the last decade or more have revolutionized our understanding of this condition. α-Synuclein was the first gene to be linked to Parkinson's disease, and is arguably the most important: the protein is the principal constituent of Lewy bodies, and variation at its locus is the major genetic risk factor for sporadic disease. Intriguingly, duplications and triplications of the locus, as well as point mutations, cause familial disease. Therefore, subtle alterations of α-synuclein expression can manifest with a dramatic phenotype. We outline the clinical impact of α-synuclein locus multiplications, and the implications that this has for Parkinson's disease pathogenesis. Finally, we discuss potential strategies for disease-modifying therapies for this currently incurable disorder.

Keywords

Parkinsonism; genetics; α-synuclein

The study of familial forms of Parkinson's disease (PD) has led to the discovery of over a dozen loci linked to the disease and many of these genes have now been cloned.[1] The first was described in 1997: a missense mutation in *SNCA*, encoding α-synuclein, in affected members of a large Italian kindred, and 3 unrelated Greek families, with familial PD.[2] The following year, α-synuclein was found to be the major constituent of Lewy bodies—protein deposits that are the defining neuropathological feature of the disease.[3]

Subsequently, triplication of the *SNCA* locus was reported in a separate kindred with familial PD; branches of this family had been previously reported, but found via genealogical methods to be the same (Iowa, Spellman-Muenter, Waters-Miller kindred).[4–7] This demonstrates that *SNCA* multiplication, as well as point mutations, can lead to PD.[8] The affected individuals from this family, with 4 copies of *SNCA* rather than the normal 2, were found to have a corresponding doubling of *SNCA* messenger RNA and α-synuclein

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protein in postmortem brain tissue.[9] This mechanism parallels that seen in Alzheimer's disease pathogenesis in which either increased dosage or missense mutations of the amyloid precursor protein (*APP*) gene lead to early onset disease.[10]

Two large genomewide association studies have established *SNCA* variation as the most important genetic risk factor for sporadic PD.[11,12] Understanding α-synuclein biology is clearly pivotal to our understanding of PD, and much of the basic research into this disease over the last decade has centered on this protein. Here, we review the phenotypic range of *SNCA* gene dosage alterations, and discuss how this informs our understanding of PD pathogenesis, and therefore how we might be able to treat it.

SNCA Triplication Kindreds

Iowa Kindred

The Iowa kindred is striking because of the spectrum of disease seen in family members, probably the consequence of the large size of the kindred, described since the early 1900s[4–7] (video documentation available in Gwinn et al.[13]). Muenter et al.[6] gave a detailed account of 13 affected individuals from this family over 4 generations with "hereditary parkinsonism with dementia." Clinical and pathological features of most of the affected members were typical for PD except for earlier age of onset (mean age 33 years) and more fulminant course (mean life expectancy 8.1 years after disease onset, in contrast to 18.4 years in sporadic PD with onset before age 50 years[14]).

Many affected individuals in the family have carried the diagnosis of PD, and met published clinical criteria (except for a positive family history).[15] Positron emission tomography scanning with 6-[^{18}F]fluorodopa has revealed severe depletion of striatal dopamine in those family members with typical PD clinically,[6] and the presence of Lewy bodies and neuronal loss in the substantia nigra has been well described.[6,16] However, others have more prominent and early dementia, with parkinsonism, hallucinations, and fluctuations in cognition, consistent with dementia with Lewy bodies (DLB), which has been correlated pathologically with cortical Lewy bodies and Lewy neurites.[17] Another individual in this family had clinical features of parkinsonism, dementia, and dysautonomia, and dramatic α-synuclein immunoreactive glial inclusions were seen at autopsy, neuropathologically consistent with multiple system atrophy (MSA).[16]

PD, DLB, and MSA are collectively known as synucleinopathies, because they feature intracellular α-synuclein deposition neuropathologically, and α-synuclein is believed to be integral to their pathogenesis.[18] Therefore, the clinical phenomenology within this 1 kindred demonstrates that increased dosage of α-synuclein can generate the full spectrum of synucleinopathies.

Additional *SNCA* Triplication Kindreds

Farrer et al.[19] documented the Swedish-American kindred with *SNCA* triplication after screening 42 probands with early-onset autosomal dominant PD. The proband had a similar phenotype to some Iowa kindred affecteds, with a rapidly progressive dopa-responsive parkinsonism starting age 31 years; postural hypotension, visual and auditory hallucinations

arose 14 years later with worsening dementia, severe generalized rigidity, and death at age 52 years. Elevated *SNCA* messenger RNA (mRNA) was found in postmortem brain tissue of affecteds, with doubling of α-synuclein protein, corroborating equivalent findings in the Iowa kindred.[9] Severe neuronal degeneration in the substantia nigra and locus ceruleus, with widespread Lewy body pathology, was seen at autopsy. There was also severe neuronal loss in the CA2/3 area of the hypothalamus—unusual for PD or DLB but similar to that seen in 6 of 7 autopsied cases from the Iowa kindred.[5,6,16]

Ibanez et al.[20] described a kindred with *SNCA* triplication after screening 22 families with atypical autosomal dominant parkinsonism. The 3 affecteds had rapidly evolving symptoms with severe cognitive impairment and short disease duration until death (mean 7 years).

The fourth triplication kindred described is a Japanese family with 3 individuals of consecutive generations who had early-onset parkinsonism with dementia and orthostatic hypotension.[21] Triplication was confirmed in the grandson, with disease onset at 31 years; his father had disease onset aged 31 years (and died at age 40 years). The proband's grandfather's age of onset was 49 years (death at age 57 years).

SNCA Duplication Kindreds

α-synuclein duplication is now recognized as a rare cause of familial parkinsonism, including cases which are phenotypically similar to idiopathic PD, with no atypical features.[22,23] Duplication has also been documented in sporadic PD—these cases are clinically indistinguishable from idiopathic PD.[20,24]

However, more recent reports have described atypical features in duplication cases, with variability within the same family.[24,25] In 4 duplication kindreds, 11 members presented with parkinsonism, 6 of whom developed hallucinations or delusions and 3 developed dementia.[26] All kindreds had asymptomatic carriers, the oldest aged 79 years; the lifetime penetrance was estimated at 43.8%. A recent screen found 2 patients with α-synuclein duplication, parkinsonism developing around the fifth decade, followed by rapid cognitive decline, hallucinations, and orthostatic hypotension.[27] Neither had any family history. The authors retrospectively reviewed 32 duplication patients and found cognitive dysfunction in one-third. Autonomic involvement was seen in one-half, a similar prevalence to that seen in triplication cases. The time course of disease progression was also comparable to triplication cases, but with an onset over 2 decades later. The Swedish-American kindred includes an individual with α-synuclein duplication,[28] presenting with orthostatic hypotension aged 71 years, parkinsonism a year later, with frequent falls and urinary incontinence, although tremor was very mild. Imaging revealed significant reduction of dopamine transporter (DAT) in both striata. The clinical diagnosis was MSA.

Four members of a Japanese duplication kindred developed dopa-responsive parkinsonism, accompanied by dementia and visual hallucinations during the late stages of the disease.[29] A further member developed parkinsonism aged 28 years, dementia aged 35 years, and died aged 48 years: a disease trajectory similar to many triplication cases. He was found to have homozygous duplication of *SNCA*, due to consanguinuity in the family, and therefore had 4 copies of the gene.

Overall, the data from these families demonstrate that gene dosage of α-synuclein, rather than extent of the replicated region, determines initiation of disease and the severity of progression.[20,30]

Sporadic PD

How might increased α-synuclein dosage be relevant to sporadic disease? Postmortem sporadic PD brain tissue has a higher expression of α-synuclein mRNA compared to controls,[31] suggesting that a similar pathogenetic mechanism might be responsible.

Genomewide association studies reveal that variation at the *SNCA* locus is associated with sporadic PD[11,12] and variation at this locus has also been demonstrated in MSA.[32] Polymorphisms in a complex repeat site called Rep1, located ~10 kb upstream of the translational start of *SNCA*, have been linked to sporadic PD and might account for these associations.[33–36] A luciferase-based assay found a surprisingly large 3-fold difference in α-synuclein expression with different Rep1 alleles in SH-SY5Y cells.[37] Moreover, associations have been found between Rep1 and levels of α-synuclein protein in blood samples from PD patients[38] and *SNCA* mRNA in control brain.[39] Furthermore, α-synuclein mRNA varied 1.7-fold in transgenic mice carrying the different Rep1 alleles.[40] It is not yet known whether the higher expressing mice also have a higher incidence of PD-type pathology but nevertheless, these data point to the possibility that sporadic disease is also caused by higher expression of α-synuclein.

Implications for α-synuclein Pathogenesis

These clinical studies point to a clear dosage relationship between α-synuclein and disease. Genetic variation in *SNCA* might increase risk of sporadic PD through increasing expression, whereas 3 copies of the locus rather than the normal 2 can, in around one-half of individuals, lead to parkinsonism identical to idiopathic PD (albeit with atypical features being more common). However, 1 additional copy confers full penetrance of what is in many cases an early-onset condition, with clinical features that can encompass PD, DLB, and MSA. Therefore, subtle alterations in expression level are sufficient to cause a wide spectrum of disease. Degeneration may be confined to the nigrostriatal pathway, but as α-synuclein dosage increases, the likelihood of more widespread pathology (eg, cortical involvement in DLB or glial and cerebellar involvement in MSA) increases in tandem. Table 1 summarizes the clinical features seen in the multiplication kindreds.

Increased accumulation of α-synuclein is also seen with dysfunction of several other PD genes, including LRRK2 and GBA, mutations in which comprise the 2 most common genetic causes of PD.[41,42] Overexpression of mutant LRRK2 increased α-synuclein deposition and neurodegeneration in A53T transgenic mice, possibly explained by the observed impaired microtubule dynamics and Golgi fragmentation that increase local concentrations of α-synuclein in the soma, whereas knockout of LRRK2 was protective.[43] Glucocerebrosidase (GBA) deficiency leads to accumulation of its substrate glucocerebroside, which has recently been shown to stabilize oligomeric α-synuclein intermediates, permitting their conversion into fibrils, meanwhile α-synuclein itself inhibits the normal lysosomal activity of glucocerebrosidase, leading to further accumulation of

glucocerebroside thus forming a pathogenic positive feedback loop.[44] Recessive mutations in Parkin cause young-onset disease.[45] Parkin encodes an E3 ubiquitin ligase that provides specificity for the process of tagging proteins for degradation in the proteasome[46] and PD-associated mutations disrupt this ligase activity.[47] A glycosylated form of α-synuclein has been shown to be a potential target of this ligase activity[48] although it remains unclear whether this form is pathologically relevant. Nevertheless, Parkin mutations may also augment accumulation of α-synuclein via impairing its degradation in the proteasome. Taking this clinical and genetic evidence together (summarized in Fig. 1), what can we infer about the possible mechanisms of α-synuclein-mediated pathogenesis?

Disruption of the Normal Role of α-synuclein

Synucleins are abundant neuronal proteins, enriched in presynaptic termini,[49] but their physiological role is unknown. α-synuclein knockout mice are normal, apart from increased release of dopamine from nigrostriatal neurons under certain conditions, implying that the protein can negatively regulate dopaminergic neurotransmission.[50] Given potential redundancy between synucleins, this work was extended in triple knockout mice lacking α-, β-, and γ-synuclein; here, a clear phenotype emerges of an age-dependent alteration in axonal morphology, neuronal dysfunction, and decreased survival.[51]

Maintenance of protein complexes involved in synaptic release requires chaperone activity mediated by synucleins; these protein complexes are decreased in the αβγ-synuclein knockout mouse.[52] Subtle overexpression of α-synuclein in mice, in a range similar to that seen clinically, impaired neurotransmitter release via defective synaptic vesicle recycling, in the absence of overt toxicity.[53] It remains to be seen whether this functional perturbation can lead to neuronal loss over the time course anticipated in PD.

α-synuclein has been shown to bind to mitochondria, more so when overexpressed, impairing complex I function, decreasing respiration and increasing free radical production.[54,55] In cultured cells and C. elegans, α-synuclein can also cause fragmentation and dysfunction of mitochondria,[56] which is relevant given the importance of mitochondria in maintaining neuronal viability in PD.[57,58] Mice overexpressing the disease-associated A53T α-synuclein mutation develop mitochondrial DNA damage and degeneration,[59] and α-synuclein pathology in this model is exacerbated by exposure to paraquat.[60] In contrast, dopaminergic neurons in α-synuclein knockout mice are resistant to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[61]

Overexpression of α-synuclein has also been shown to impair macroautophagy, a major route for clearance of aggregate-prone intracytoplasmic proteins, whereas α-synuclein depletion enhances this pathway.[62] Overexpressing cells would also clear dysfunctional mitochondria less efficiently, increasing susceptibility to apoptotic stimuli. The combination of these perturbations, persisting over many decades, might be sufficient to cause neuronal death.

Toxicity of α-synuclein

Fibrillogenic monomers of α-synuclein form oligomeric intermediates that assemble into fibrils, and finally deposit in Lewy bodies.[63] α-synuclein has a strong tendency to self-

aggregate in vitro, so increasing its expression would be expected to generate more of these aggregates.[64] However, a pivotal question is which of these species, if any, are toxic to neurons. For example, there is a dissociation between presence of Lewy bodies and cellular loss: Lewy bodies are present in 10% to 15% of individuals over the age of 65 years who die without clinical evidence of neurological illness, despite having an identical pattern of deposition to that seen in PD or DLB.[65] Cytotoxicity in model systems can occur without aggregated α-synuclein.[66] Lentiviral expression of α-synuclein in rat nigrostriatal neurons results in selective dopaminergic toxicity, but without fibrillar inclusions, whereas missense mutations in *SNCA* (for example, A30P) increases oligomerization of α-synuclein, but not fibril formation.[67,68] The hypothetical mechanism of toxicity is not clear but may be through disruption of membranes through the formation of pores.[69] Lewy body formation might, in fact, be an adaptive cellular response, protecting neurons from the damaging effects of oligomeric intermediates.

Permissive Templating of α-synuclein

Transplantation of fetal dopamine neurons began over 20 years ago as a potentially curative treatment for PD.[70] Recently, individuals with these transplants have come to autopsy, with surprising results. Lewy body pathology is observed in surviving neurons of the patient, as expected. But in 8 patients who have received this treatment, Lewy bodies were observed in the transplanted dopaminergic neurons as well.[71–73] These transplants have all been less than 14 years old, which is thought to be too young for Lewy bodies to arise de novo. An alternative explanation is that disease spreads from the host to the grafted cells, reminiscent of a prion-like process. Prion diseases are characterized by spread of prion protein (PrP) from 1 organism to another. Healthy cellular PrP (designated PrP^{C}) is ubiquitously expressed and has the same amino acid sequence as the disease-causing scrapie isoform (PrP^{Sc}) but a different secondary structure, being composed largely of α-helices whereas PrP^{Sc} is predominantly β-sheets. Disease is caused by a change in conformation of PrP^{C} to PrP^{Sc}, which can act as a template for recruitment of PrP^{C}, converting them into PrP^{Sc}. Aggregates of the disease isoform build up, and propagate between cells leading to disease progression. Like PrP, α-synuclein is unstructured in aqueous buffers, while adopting a predominantly α-helical structure when membrane bound, which can become β-sheet when present at high concentration or in mutant form.[74]

α-synuclein is present in cerebrospinal fluid and plasma of healthy subjects and patients with neurodegenerative diseases,[75,76] and can be detected in media of neuronal culture models,[77] suggesting that it can be exocytosed. Recent studies have provided direct evidence of cell-to-cell spread: neurons overexpressing α-synuclein can transmit the protein to neighboring neurons in culture, and to neural precursor cells in a transgenic model of PD-like pathology,[78] and also to postmitotic nigrostriatal neurons, in a direct model of the fetal transplantation clinical studies.[79] Oligomers of α-synuclein can recruit, and aggregate, α-synuclein endogenously expressed by primary cortical neurons, and this effect increases with time and also with concentration of the applied oligomers.[80] In other words, misfolded α-synuclein can operate as a template catalyzing further misfolding events.[81]

Transmission of misfolded α-synuclein between cells provides a mechanistic basis for the findings of Braak et al.[82] where α-synuclein pathology extends sequentially from the dorsal motor nucleus in the lower brainstem, to upper brainstem areas and from there to the cerebral hemispheres. They speculate that PD pathology may arise first in the nose and foregut, which act as portals for entry of an unknown neurotropic pathogen, via inhalation or ingestion, and suggest that this pathogen may trigger misfolding of α-synuclein.[83] An alternative possibility is that an environmental toxin, rather than a pathogen, is responsible. Many potential neurotoxins, including metals, solvents, pesticides, and herbicides have been linked to PD (reviewed in Uversky[64]). Paraquat and rotenone enhance production of α-synuclein in vivo, whereas in vitro, fibrillation of α-synuclein is dramatically accelerated by these and other substances, including heavy metal cations and organic solvents. These can all induce structural perturbations in α-synuclein and stabilize partially folded structures, which are prone to form fibrils.

Increased *SNCA* expression could cause PD by augmenting the likelihood of α-synuclein misfolding, the quantity of exocytosed misfolded proteins, and the speed of nucleation in recipient cells. Age is the major risk factor for sporadic PD, and concentration of α-synuclein increases with age in neuronal cell bodies.[84] Therefore, in both *SNCA* multiplication and sporadic PD, initiation of disease relates to and appears to be dependent on the concentration of the pathogenic protein, perhaps through increasing the chances of a misfolding species to emerge, which could form a scaffold for further proteins to misfold and aggregate.

α-synuclein fibrillization starts in vitro with a lagphase while soluble oligomers form a nucleus, but once the nucleus forms, aggregates grow rapidly.[85] Therefore, the prediction would be that permissive templating is efficient and less dependent on the concentration of the protein than the initial misfolding event, such that the process becomes self-propagating. This would explain the variable age of onset of disease, even in triplication cases, given the stochastic nature of protein misfolding. Recent data suggests that prion propagation in vivo proceeds in 2 phases: an initial exponential phase not dependent upon levels of PrP^{C}, followed by a plateau phase prior to clinical onset, the duration of which is shortened as endogenous PrP^{C} levels are increased.[86] The authors suggest that toxicity is exerted by neither PrP^{C} nor PrP^{Sc} but via a toxic intermediate, generation of which requires conversion to take place and is therefore dependent on local availability of PrP^{C}. If a similar mechanism is at work in the synucleinopathies, the implication of increasing *SNCA* expression becomes clear: time to onset of disease is shorter.

Disease-Modifying Therapies for PD

Neither the physiological nor the pathogenic roles of α-synuclein are understood. Nevertheless, the clinical, genetic, and toxin studies described speak to the importance of α-synuclein concentration, and cell-to-cell spread, in driving disease onset and progression. Therefore, strategies that seek to either deplete or prevent the spread of α-synuclein ought to be clinically beneficial.

A recent report of an inducible α-synuclein transgenic mouse model of DLB showed that reducing α-synuclein expression triggered a reversal in pathological changes and improved behavior and memory.[87] This provides proof of concept data that α-synuclein depletion might not just slow disease progression, but in fact reverse it. However, it is not yet clear how this depletion should be achieved. Several studies have employed RNA interference to successfully reduce α-synuclein expression in cells,[88] rodents,[89,90] and primates,[91] although reversal of pathological changes has not been demonstrated with this approach so far. Moreover, nigral degeneration caused by α-synuclein silencing has been described in rat,[92] precisely the opposite effect of that desired. The reasons for this are not certain but, given that in vivo levels of α-synuclein are likely to be tightly regulated, perhaps the goal should be normalization of α-synuclein levels rather than full suppression. There is also the wider problem of turning such antisense strategies into viable drugs. Problems with degradation of the oligonucleotides, and off-target effects are commonly seen,[93] notwithstanding the considerable difficulties of delivering such an agent into the brain.

Enhancing degradation of α-synuclein protein might be a viable possibility. Pharmacological upregulation of autophagy has been shown to help clear the protein, for example.[94] Antibody-based strategies also look promising. Vaccination of human α-synuclein-expressing mice with human α-synuclein protein led to degradation of aggregates of human α-synuclein, a reduction in formation of new aggregates, and diminished neurodegeneration.[95] Indeed, the presence of autoantibodies directed against α-synuclein has recently been reported in PD patients, and antibody titers reduce with progression of disease, implying that immune-mediated clearance of α-synuclein may be a factor in determining disease onset.[96]

Much current work focuses on α-synuclein depletion as a possible therapeutic strategy. However, when we consider the ascending pathology noted by Braak et al.,[82] the spectrum of pathology seen in the multiplication kindreds, and the presence of Lewy bodies in grafted fetal dopaminergic neurons, then cell-to-cell protein propagation begins to take on a central role in the disease process. The mechanistic basis for this propagation has not yet been fully defined. Nor is it known whether it serves a physiological role. Nevertheless, blocking it is an attractive potential therapeutic target. This strategy may help preserve brain areas not yet affected by the pathological process, if potentially toxic forms of α-synuclein are prevented from reaching them. It might also avoid possible side effects of excessive α-synuclein depletion. However, it remains possible that cellular release of α-synuclein might be a mechanism by which cells can lower concentrations of this protein before they become dangerously high. Therefore, it is conceivable that the combination of α-synuclein depletion with blockade of its propagation will be required to make a clinically measurable impact on disease progression.

Research priorities are now clear. We need strategies that normalize α-synuclein levels rather than fully deplete it, and are deliverable intrathecally. In addition, we need to understand precisely how, and importantly why, α-synuclein propagates from cell to cell, in order to appropriately target this critical pathogenic mechanism.

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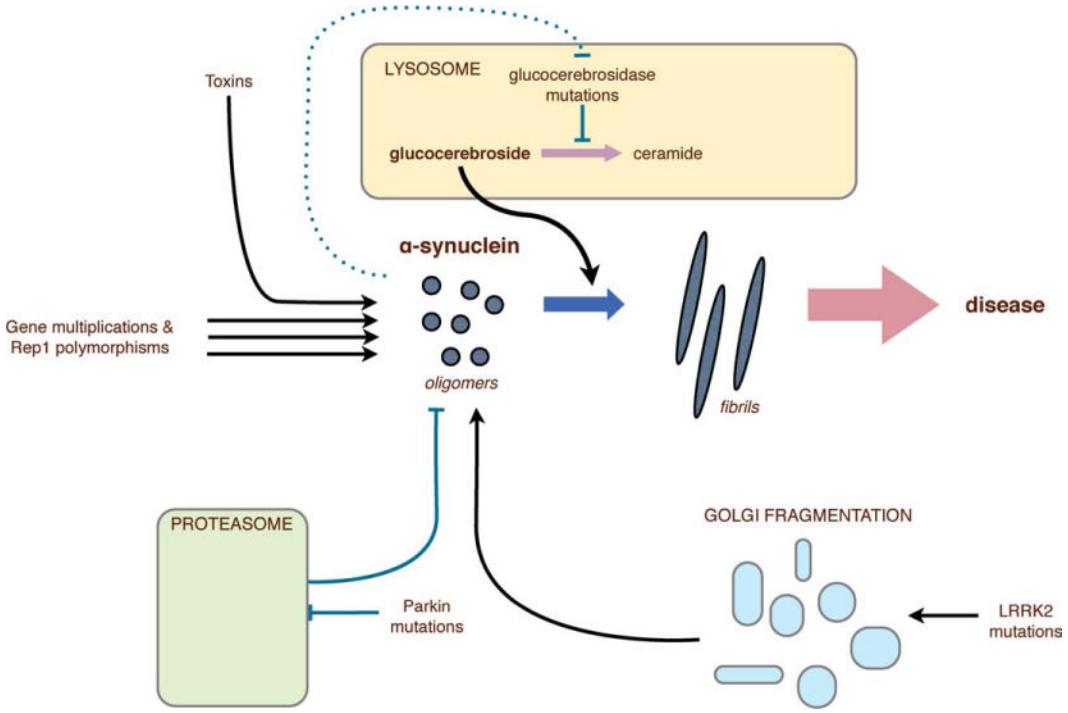

FIG. 1.

Multiple pathways promote accumulation and aggregation of α-synuclein. Gene multiplications and certain Rep1 polymorphisms can increase expression of α-synuclein directly. On the other hand, degradation of α-synuclein in the proteasome may be impaired by Parkin mutations. LRRK2 mutations can fragment Golgi, disrupting vesicular trafficking and thereby increasing α-synuclein in the soma. Mutations in glucocerebrosidase cause accumulation of glucocerebroside, which stabilizes oligomeric α-synuclein, enhancing fibril formation. In turn, α-synuclein impairs physiological glucocerebrosidase function. Multiple environmental toxins, including heavy metal cations, organic solvents and pesticides, can enhance misfolding and aggregation of α-synuclein. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1

Summary of clinical features of *SNCA* multiplication cases

Reference	Kindreds (cases)	Onset (mean, SD)	Duration (mean, SD)	Age at death (mean, SD)	L-Dopa responsive	Rest tremor	Postural hypotension	Other dysautonomia	Sleep dysfunction	Hallucinations	Dementia	Depression	Other remarks
Duplication													
Chartier-Harlin et al.[22]	1 Kindred (5 cases)	48(10); range 39–65	17(7.2); range 9–23	Range 57–84	Yes	4/5	3/5	–	–	–	–	2/5; 1 suicide	Similar clinical course to IPD
Ibanez et al.[23]	2 Kindreds (2 cases)	46, 50	NA	NA	Yes	+; −	−	−	−	−	−	−	Similar clinical course to IPD
Mishioka et al.[25]	2 Kindreds (3 cases)	44 (5.5); range 38–48	NA	NA	Moderate to excellent	− in all cases	1/3	−	NA	Psychosis in 1 case	++1/3	NA	6 Asymptomatic carriers identified; penetrance ratio 33.3% (2/6 in one kindred)
Fuchs et al.[28]	1 Case (Swedish-American kindred)	71	NA	NA	Slight	Mild	Early, requiring drug treatment	Moderate urinary incontinence	NA	Visual, olfactory and auditory	Late	Short episode	Frequent falls; dx MSA
Ahn et al.[24]	1 Kindred and 2 sporadic cases	1: 40 (FHx): 2: 65; 3. 50	1: Short; 2,3: similar to IPD	NA	Excellent in all 3 cases	1: Moderate: 2: NA; 3: NA	1: Moderate: 2: absent: 3: absent	−	NA	NA	1: Moderate: 2: absent: 3: absent	NA	Asymptomatic carriers identified in all 3 families (4 individuals. 1 of whom had alcoholism)
Uchiyama et al.[97]	1 Kindred (2 cases)	1: 47 (proband): 2: 73 (mother)	1: Rapid progression	NA	Yes	1: Moderate: 2: mild	−	−	NA	1: 50; 2: 74	1: 50; 2: 72	NA	Both had fluctuating cognitive deficits; 1: dx PDD; 2: dx DLB.
Ikeuchi et al.[29]	1 Kindred (3 cases)	57(16.4); range 39–71	10.3(4.2); range 7–15	67.3(12.2); range 54–78	NA	3/3	NA	NA	NA	NA	3/3	NA	
Mishioka et al.[26]	4 Kindreds (10 cases). 1 sporadic	48.5(11.2); range 31–69	NA	NA	8/11 (72.7%)	Present but less problematic	NA	NA	RBD in 1/6 examined	6/11 (54.5%)	3/11 (27%)	1 Severe: 3 moderate: 1 mild (Beck)	14 Asymptomatic carriers (oldest 79); penetrance ratio 43.8%.
Ibanez et al.[20]	4 Kindreds (9 cases)	46 (8.7); range 38–65	10.5(7.2); range 1–23	67.7(14.4); range 57–84	Yes	6/9	0/9	0/9	NA	NA	0/9	NA	Similar clinical course to IPD
Shin et al.[27]	2 Sporadic cases	1: 48; 2: 55	Rapid progression in both	NA	Yes	Yes	1:+2: +	NA	NA	1: + 2: +	1: 52; 2: 59	NA	Rapid cognitive decline in both
Sironi et al.[98]	1 Kindred (1 case)	41	Rapid progression	NA	Yes	−	+	−	Periodic leg movements at night	−	−	Yes	Left foot dystonia, depression: Mother had PD age 47. dementia 57, died 63
Triplication/double duplication													
Muenter et al.[6]	Iowa kindred (10 cases)	36 (8.2)	8.4 (3.7)	NA	7/7	Yes	6/7	3/5 Constipation: 3/5 urinary symptoms: 1/5 erectile dysfunction	2/7 Insomnia: 3/7 RBD	NA	7/8	9/9; 2/9 Suicide attempts	
Farrer et al.[19]	Swedish-American kindred (proband)	31	Rapidly progressive	52	Dramatic effect initially	Yes	Moderate to severe early in illness	NA	NA	Visual and auditory hallucinations began age 45	Dementia by age 47	Suicidal late in illness	
Ikeuchi et al.[29]	1 Homozygous duplication case	28	20	48	NA	Yes	Yes	NA	NA	Yes	35; Severe	NA	
Ibanez et al.[20]	1 Kindred (3 cases)	48.3(12.5); range 36–61	7 (2.6); range 5–10	58.7(15.6); range 42–73	Limited at onset or decreased rapidly after onset	2/2	NA	3/3	NA	NA	NA	3/3	
Sekine et al.[21]	1 Kindred (3 cases)	1: 49: 2: 33; 3. 28	1: 8: 2: 7; 3: NA	1: 57: 2: 40; 3: NA	1: Yes: 2: Yes; 3: Yes	1: Yes: 2: Yes; 3: Yes	1: Yes: 2: Yes; 3: Yes	1: Constipation: 2: impotence and constipation: 3: nil	1: NA: 2: NA; 3: nil	1: NA: 2. NA; 3: nil	1: Yes: 2: NA; 3: WAIS-R impaired but	1: Yes; 2. neurosis and suicidal intent	2: Pathological gambling

Reference	Kindreds (cases)	Onset (mean, SD)	Duration (mean, SD)	Age at death (mean, SD)	L-Dopa responsive	Rest tremor	Postural hypotension	Other dysautonomia	Sleep dysfunction	Hallucinations	Dementia	Depression	Other remarks
											MMSE 29/30 MMSE 29/30		

Rigidity and bradykinesia were present in all cases.

SD, standard deviation; IPD, idiopathic Parkinson's disease; NA, not available; dx, diagnosis; MSA, multiple system atrophy; FHx, family history; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; RBD, REM sleep behavior disorder; PD, Parkinson's disease; WAIS-R, Wechsler Adult Intelligence Scale–revised; MMSE, Mini–Mental State Examination.