TABLE 449-3 FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM

Symptoms/Signs	Alternative Diagnosis to Consider
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Exam	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired down gaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

HLA as risk factors. It has been proposed that most cases of PD may be due to a "double hit" involving an interaction between a gene mutation that induces susceptibility coupled with exposure to a toxic environmental factor that may induce epigenetic or somatic DNA alterations. In this scenario, both factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease.

Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, mitochondrial dysfunction, and proteolytic stress. Recent studies have demonstrated that with aging dopamine neurons switch from sodium to calcium pacing through calcium channels, potentially making these high-energy neurons vulnerable to calcium-mediated neurotoxicity. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or "suicidal" process.

TABLE 449-4 GENETIC CAUSES OF PARKINSON'S DISEASE

Name	Chromosome	Locus	Gene	Inheritance
Park 1	Chr 4	q21-23	*α-Synuclein*	AD
Park 2	Chr 6	q25-27	*Parkin*	AR
Park 3	Chr 2	p13	Unknown	AD
Park 4	Chr 4	q21-23	*α-Synuclein*	AD
Park 5	Chr 4	p14	*UCHL-1*	AD
Park 6	Chr 1	p35-36	*PINK-1*	AR
Park 7	Chr 1	p36	*DJ-1*	AR
Park 8	Chr 12	p11-q13	*LRRK2*	AR/Sp
Park 9	Chr 1	p36	*ATP13A2*	AR
Park 10	Chr 1	p32	Unknown	Sp
Park 11	Chr 2	q36-37	*GIGYF2*	AD
Park 12	Chr X	q21-25	Unknown	Sp
Park 13	Chr 2	p13	*Omi/HtrA2*	AD
Park 14	Chr 22	q13	*PLA2G6*	AR
Park 15	Chr 22	q12-13	*FBX07*	AR
Park 16	Chr 1	q32	Unknown	Sp

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; Chr, chromosome; Sp, sporadic.

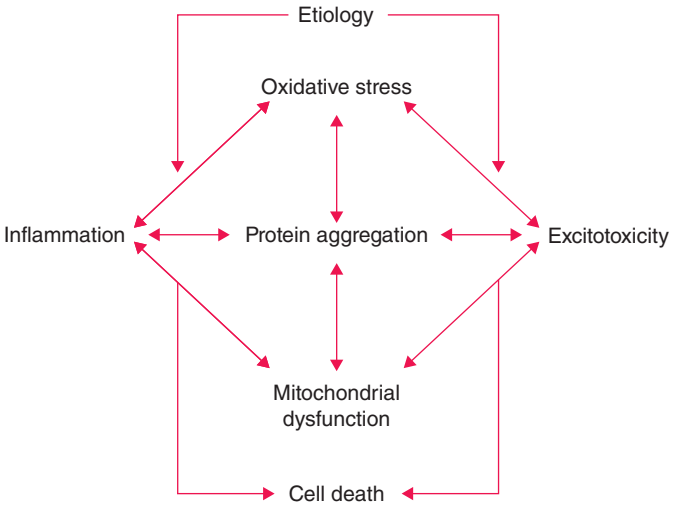

FIGURE 449-4 Schematic representation of how pathogenetic factors implicated in Parkinson's disease interact in a network manner, ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. *(Adapted from CW Olanow: Movement Disorders 22:S-335, 2007.)*

Each of these mechanisms offers a potential target for neuroprotective drugs. However, it is not clear which of these factors is primary, if the mechanism is the same in each individual case, if they act by way of a network such that a cocktail of agents might be required to provide neuroprotection, or if the findings to date merely represent epiphenomena unrelated to the true cause of cell death that remains undiscovered (Fig. 449-4).

Gene mutations may not cause all cases of PD, but may be helpful in pointing to specific pathogenic pathways and mechanisms that are central to a neurodegenerative process that might be relevant to all forms of the disease. To date, most interest has focused on pathways implicated by mutations in *α-synuclein*, *LRRK2*, and *PINK1*/*Parkin*.

Most interest has focused on *α-synuclein*. Mutations in α-synuclein cause rare familial forms of PD, and α-synuclein constitutes the major component of Lewy bodies in patients with sporadic PD (Fig. 449-1). Furthermore, duplication or triplication of the wild-type *α-synuclein* can also cause a form of PD, indicating that increased production of the normal protein alone can cause the disease. More recently, Lewy pathology was discovered to have developed in healthy embryonic dopamine neurons that had been implanted into the striatum of PD patients, suggesting that the abnormal protein had transferred from affected cells to healthy unaffected dopamine neurons. Based on these findings, it has been proposed that α-synuclein is a prion and PD is a prion disorder. Here it is proposed that, like the prion protein PrP^{C}, α-synuclein can misfold to form β-rich sheets, generate toxic oligomers and aggregates, polymerize to form amyloid plaques (i.e., Lewy bodies), cause neurodegeneration, and spread to involve unaffected neurons. Indeed, injection of α-synuclein fibrils into the striatum promotes the development of Lewy pathology in host neurons, neurodegeneration, behavioral abnormalities, and the spread of α-synuclein pathology to anatomically connected sites. Further support for this hypothesis comes from the demonstration that inoculation of α-synuclein derived from human Lewy bodies induces widespread Lewy pathology in mice and primates. Collectively, this evidence supports the possibility that neuroprotective therapies for PD might be developed based on inhibiting accumulation or accelerating removal of α-synuclein aggregates.

Mutations in the glucocerebrosidase (*GBA*) gene associated with Gaucher's disease numerically represent the most important risk factor for the development of PD. While the responsible mechanism is not precisely known, it is noteworthy that *GBA* mutations are associated with altered autophagy and lysosomal function and could impair the clearance of α-synuclein.