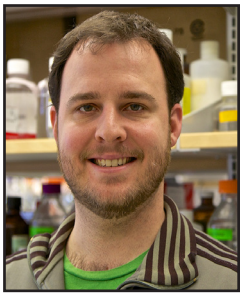
Gene-environment Interactions in Parkinson's Disease

Paul Barrett, Ph.D. and J. Timothy Greenamyre, M.D, Ph.D.
Department of Neurology and Pittsburgh Institute for Neurodegenerative Diseases
University of Pittsburgh, School of Medicine

The movement disorder, Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's, affects more than 1 percent of the worldwide population over 65. Advancing age is the biggest risk factor for developing PD. As the population ages, it is imperative that we gain a deeper fundamental understanding of how the disease initiates and progresses so that we can develop successful therapies and preventives. In this article, we discuss genetic causes of PD and the impact environmental toxins may have on development of the disease.

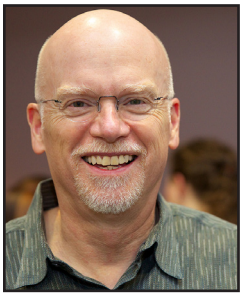


Paul Barrett, Ph.D.

PD is characterized, in part, by progressive loss of dopamine neurons from a region of the brain known as the substantia nigra (SN). The loss of these neurons results in a decrease in levels of the neurotransmitter dopamine, specifically in the striatum. Another characteristic of PD is the formation of clumps of proteins inside neurons, called Lewy bodies. People affected by PD typically experience bradykinesa (slowing of movement), tremors at rest, rigidity, postural instability, and gait disturbances, although the order of symptom appearance and their relative severity varies from person to person. Many of these so-called motor symptoms result from the loss of dopamine; other 'non-motor' symptoms, such as depression, dementia, pain, and gastrointestinal problems are less well understood.

In recent years, a number of genes and chromosomal loci have been linked to the development of PD; however, together, the monogenic (single gene) causes of the disease probably account for less than 10 percent of all cases. Despite the relatively low number of purely genetic cases of PD, these genetic discoveries have been extremely enlightening in terms of identifying new cellular mechanisms that cause neurodegeneration.

The first cases of autosomal dominantly inherited PD were discovered by studying a group of Italian and Greek families in which mutations in a protein called alpha-synuclein were linked to PD. Subsequently, it was found that alpha-synuclein need not be mutated to cause the disease; people who simply make too much of the normal (unmutated) protein by having too many copies of the gene will also develop PD. The normal function of alpha-synuclein is still unknown, but evidence suggests it helps recycle neurotransmitters. Alpha-synuclein is prone to aggregation, and is a major component of the Lewy bodies found in PD brains. Recent work suggests that such protein aggregates, both small (oligomers) and large, may overwhelm the cell's protein disposal machinery and/or interact with and disrupt cellular organelles, such as the mitochondria, leading to neurodegeneration. Mitochondria are intracellular organelles that are responsible for generating the cell's energy supply, ATP, and as a by-product reactive oxygen species.



Timothy Greenamyre, M.D., Ph.D.

Another dominantly inherited gene associated with PD encodes for the leucine rich repeat kinase 2 (LRRK2) protein. As with alpha-synuclein, the normal function of LRRK2 is unclear, but it is a large, multi-functional protein that acts as a kinase (it adds phosphate groups to other proteins) whose substrates are unknown. Stem cell derived human neurons from people with LRRK2 mutations show consistent mitochondrial dysfunction. Of the many defined mutations in LRRK2, the most common mutation increases kinase activity. This has generated interest in the pharmaceutical industry to develop kinase inhibitors. The importance of this gene cannot be understated, as mutations of LRRK2 are very common in certain populations, such as Ashkenazi

Jews and North African Arabs, and it accounts for approximately 15-30,000 current cases of PD in the United States alone.

PD may also be inherited in an autosomal recessive manner. Interestingly, three genes associated with recessive forms of the disease, Parkin, Pink1, and DJ-1, all appear to be critical to mitochondrial quality control or responses to oxidative stress. Discovery of these genes and their roles in PD has led to the critical insight that mitochondrial dysfunction is central to the development of PD.

While the discovery of PD-associated genes has taught us much about disease pathogenesis, the fact remains that single-gene forms of the disease are relatively uncommon. This may indicate minor variations (e.g., single nucleotide polymorphisms rather than mutations) in a large number of genes cumulatively influence risk of disease. It also raises the possibility that environmental exposures affect risk of developing PD. In this regard, toxins such as certain pesticides, fungicides, and solvents have been associated with increased risk of PD. We hypothesize that a person's composite genetic makeup, together with a lifetime of environmental exposures that may not cause symptoms at the time, are major determinants of disease risk.

The potential impact of environmental factors on development of PD was first documented in 1983 when intravenous drug users in the San Francisco Bay Area developed an acute, severe, permanent parkinsonian syndrome. Unfortunately, the drug they injected contained a contaminant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which easily crossed the blood brain barrier where it was converted into a potent toxin, MPP^+, which accumulated in dopaminergic neurons and caused severe mitochondrial dysfunction, ultimately leading to cell death. This unlikely sequence of events provided proof-of-concept that an 'environmental' exposure could produce a syndrome very similar to PD and led to the hypothesis that other compounds might act in a similar manner.

Paraquat is a commonly used herbicide that is structurally similar to MPP^+ but which has a distinct mechanism of toxicity. Recent epidemiological studies have indicated that chronic occupational exposure to paraquat increased the risk of developing PD. This risk was further increased when paraquat exposure was coupled with exposure to the fungicide maneb. When tested in mice, paraquat exposure led to pathological changes and loss of dopamine neurons similar to PD. Scientists working for the manufacturer of paraquat have disputed these findings.

Another toxin associated with PD is the natural product rotenone, most often used to control fish populations in lakes and reservoirs. (It was previously sometimes used in the organic gardening industry.) Rotenone is a potent, membrane-permeable compound; and chronic exposure to it can reproduce many features of PD, including selective dopamine neuron degeneration, Lewy body formation and oxidative damage. Like MPP^+, rotenone disrupts mitochondrial function and causes cell death. Exposure to rotenone is probably a very rare cause of PD, but genetic variation among people could influence who is more susceptible to the pesticide.

Another class of toxins potentially linked to PD is the organochlorines, specifically the compound dieldrin. This toxin has a long half-life and has a strong tendency to accumulate in body tissue over time. Dieldrin was second-most used agricultural pesticide in the US; its use peaked in the 1960's, when approximately 20 million pounds were used each year. Studies in dopaminergic cell lines have demonstrated that dieldrin can create oxidative stress, promote alpha-synuclein aggregation, deplete dopamine levels, and alter mitochondrial function. Dieldrin was also studied in animals, though, and researchers saw no loss of dopaminergic neurons; in addition, the dose of dieldrin required to see any effects, such as oxidative stress, was much higher than that expected to be found in human tissue.

Investigation of the interactions between genetic susceptibilities (or resistances) and environmental toxins as modifiers of PD risk is difficult but important, and at least one unifying theme is beginning to emerge. To date, five leading genetic risk factors for PD (alpha-synuclein, LRRK2, Parkin, Pink1, and DJ-1) have been implicated in mitochondrial dysfunction. Additionally, several of the environmental toxins associated epidemiologically and experimentally with PD disrupt mitochondrial function. Not only do mitochondria help maintain cellular energy levels, they also act to generate damaging free radicals and regulate cell death pathways. As such, impairment of mitochondrial function may represent a critical choke point in the cascade of events that lead to PD. When people with a genetic predisposition toward imperfect mitochondria are exposed to certain toxins—whether natural or man-made— bad things may ensue, and this may result in PD.

Further Reading

Cannon JR, Greenamyre JT. Gene-environment interactions in Parkinson's disease: specific evidence in humans and mammalian models. Neurobiol Dis. 2013;57:38-46.

Hatcher JM, Pennell KD, Miller GW. Parkinson's disease and pesticides: a toxicological perspective. Trends Pharmacol Sci. 2008;29:322-9.

Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, Marras C, Bhudhikanok GS, Kasten M, Chade AR, Comyns K, Richards MB, Meng C, Priestley B, Fernandez HH, Cambi F, Umbach DM, Blair A, Sandler DP, Langston JW. Rotenone, paraquat, and Parkinson's disease. Environmental Health Perspectives. 2011;119:866-72.

Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. Movement Disord. 2013;28:14-23.