# Evidence for a common pathway linking neurodegenerative diseases

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**In the largest Parkinson's disease genome-wide association studies to date, common variants in three familiar genes—*SNCA*, *MAPT* and *LRRK2*—and two new loci are found to increase disease susceptibility. The studies suggest genetic heterogeneity for Parkinson's disease risk in different human populations and lend support to the idea of a common pathway for Parkinson's and Alzheimer's diseases.**

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Parkinson's disease is an insidious and progressive neurodegenerative disorder causing slowed movement, tremors, rigidity and gait impairment. It is the second most common neurodegenerative syndrome after Alzheimer's disease, with a median age of onset of 60 and a risk that increases with age[1]. Parkinson's disease is characterized by neuronal loss in the substantia nigra and other brain regions, and is associated with the formation of intracellular protein inclusions known as Lewy bodies. A major constituent of Lewy bodies is α-synuclein, a synaptic protein of uncertain function. Over the last decade, theories about the etiology of Parkinson's disease have shifted from a focus on a predominantly sporadic disease triggered by unknown environmental exposures to models of a complex genetic disorder reflecting the aggregate impact of environmental risk factors and numerous genes, each with modest effect on susceptibility[1]. This change began with linkage analyses of familial Parkinson's disease, in which rare autosomal-dominant mutations were discovered in the gene encoding α-synuclein (*SNCA*). Loss-of-function mutations in four additional genes have been found to cause autosomal-recessive, juvenile-onset parkinsonism. More recently, dominant mutations in the genes encoding leucine-rich repeat kinase 2 (*LRRK2*) and glucocerebrosidase (*GBA*) have been identified as Parkinson's disease susceptibility alleles in both familial and sporadic cases; however, these variants remain rare in most human populations. Despite great success in dissecting the genetics of familial disease, attempts to identify common genetic variation underlying Parkinson's disease in the general population have yielded mixed results. On pages 1303 and 1308 of this issue, two groups report successful genome-wide association (GWA) studies that substantially expand our understanding of the genetic architecture of sporadic Parkinson's disease[2,3].

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## Familial versus sporadic disease

Compared to prior Parkinson's disease GWA studies[4–6], the new investigations leverage larger sample sizes and benefit from enhanced statistical power. In autopsy series, the frequency of incidental Lewy bodies (in the absence of clinical Parkinson's disease) is as high as 17%, suggesting that there is a substantial burden of subclinical disease in the aging population[7]. Large study cohorts are therefore essential in order to overcome confounding due to the presence of latent cases in the control group. In addition, the new studies analyzed distinct populations (of Japanese[2] and European[3] descent), and data were exchanged in order to replicate each other's findings. Both studies discovered strong association signals within the *SNCA* and *LRRK2* loci previously implicated in familial Parkinson's disease, demonstrating that common variants (with frequencies of >5% in the general population) within these genes also influence susceptibility for sporadic Parkinson's disease. For *SNCA*, these results far surpass the threshold for genome-wide significance ($P < 5 \times 10^{-8}$). A SNP near *LRRK2* also showed genome-wide significant association with Parkinson's disease in the Japanese subjects (rs1994090, OR = 1.39, $P = 2.72 \times 10^{-8}$), whereas the association in subjects of European ancestry was more modest (rs14919123, OR = 1.14, $P = 2.10 \times 10^{-5}$) but is likely to be validated in future studies. Similarly, association at a new locus, *PARK16*, was discovered in the Japanese cohort (rs947211, OR = 1.3, $P = 1.52 \times 10^{-12}$) and replicated in subjects of European ancestry (rs823128, OR = 0.66, $P = 1.32 \times 10^{-7}$), but further investigation will be required to refine the association signal because the locus encompasses five genes. Validation across distinct human populations is a strength of these two studies; these comparisons also uncovered notable differences between individuals of European and Japanese ancestry. The data support a role for a new locus, *BST1*, only in the Japanese population (rs4538475, OR = 1.24, $P = 3.94 \times 10^{-9}$), whereas multiple polymorphisms within and near the microtubule-associated protein tau (*MAPT*) are associated with Parkinson's disease exclusively in subjects of European ancestry (rs17563986, OR = 0.78, $P = 1.67 \times 10^{-14}$). In both cases, low allele frequencies in one population limit the statistical power to address whether a variant is associated with Parkinson's disease in both European and Japanese subjects; therefore, further exploration of a broader range of variants at these loci in each population is clearly warranted.

Given the large sample sizes, robust statistical associations, inclusion of two different human populations and consistent findings at three loci, these GWA studies represent a milestone for Parkinson's disease genetics. The strong association at *SNCA* validates prior reports that common variation at this locus increases Parkinson's disease susceptibility[6,8]. In addition to mutations that promote α-synuclein

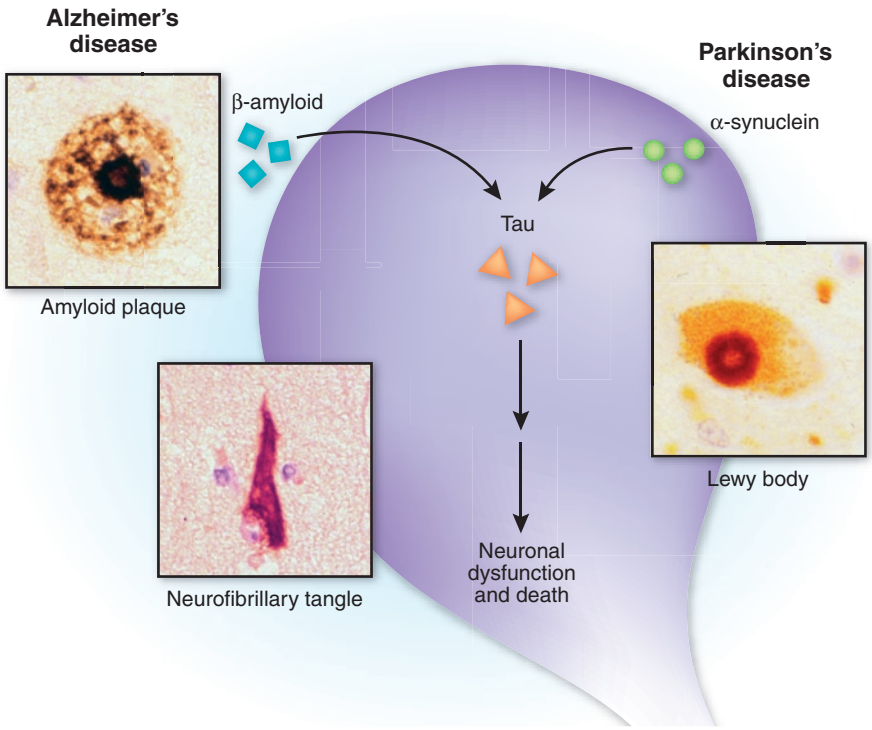


**Figure 1** Proposed link between Parkinson's disease and Alzheimer's disease. In Alzheimer's disease, β-amyloid aggregates to form plaques, and neurotoxicity is mediated in part by tau, which also aggregates to form neurofibrillary tangles. Polymorphisms in the gene encoding tau (*MAPT*) increase susceptibility for Parkinson's disease, which is characterized pathologically by aggregation of α-synuclein into Lewy bodies. Additional clinical and pathological overlap suggests that these pathways may potentiate each other, perhaps through direct promotion of aggregation or by an indirect mechanism. Immunostaining for β-amyloid, tau and α-synuclein reveals an amyloid plaque, neurofibrillary tangle and Lewy body, respectively. (Images provided by Mel Feany.)

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aggregation, rare *SNCA* gene multiplication has been found in familial Parkinson's disease[9], and a repeat polymorphism within the *SNCA* promoter augments both gene expression and risk of sporadic disease[8], suggesting that enhanced levels of the normal protein increase disease susceptibility. The functional consequences of the common susceptibility alleles within *SNCA* identified by these new GWA studies may also be mediated by effects on gene expression, but a definitive evaluation of this hypothesis awaits further investigation. Nonetheless, the discovery that common *SNCA* polymorphisms influence sporadic Parkinson's disease susceptibility is a high point in the saga of discovery that began with the description of Lewy bodies in 1912.

## Alzheimer's disease connection

Like α-synuclein and Lewy bodies, the tau protein aggregates to form pathological neuronal inclusions called neurofibrillary tangles; however, the presence of tangles is most characteristic of another neurodegenerative disorder, Alzheimer's disease[10]. Is the association of *MAPT* with Parkinson's disease susceptibility therefore unexpected? On the contrary, prior association studies suggested that the *MAPT* locus harbored susceptibility alleles[6,11], and the results of Simon-Sanchez *et al.*[3] should settle any remaining debate about the involvement of this gene in Parkinson's disease. Several additional clues suggest a mechanistic link between Parkinson's disease and neurodegenerative disorders with tau pathology. Mutations in *MAPT* cause familial frontotemporal dementia, characterized clinically by dementia and prominent parkinsonian features, and characterized pathologically by neurofibrillary tangles[12]. In addition, common *MAPT* haplotypes have been consistently shown to increase susceptibility for progressive supranuclear palsy and corticobasal degeneration, two tauopathies that share considerable clinical overlap with both frontotemporal dementia and Parkinson's disease[13]. Clinically, dementia often accompanies advanced Parkinson's disease, and reciprocally, parkinsonian signs can be seen in Alzheimer's disease. Neuropathologically, Lewy bodies frequently occur in tandem with typical Alzheimer's disease lesions, amyloid plaques and neurofibrillary tangles[7]. Several reports suggest that, in addition to the usual association of *LRKK2* with Lewy bodies, *LRRK2* mutations cause primary tau pathology in some individuals with clinical Parkinson's disease[14]. Though *MAPT* polymorphisms have not been consistently found to increase risk of Alzheimer's disease, tau is believed to be a key mediator of neurotoxicity in the prevailing amyloid-cascade hypothesis[10,15]. Simon-Sanchez *et al.*[3] do not report the proportion of their Parkinson's disease cohort with cognitive impairment, and it would be interesting to account for co-morbid dementia in modeling the relation of *MAPT* polymorphisms to Parkinson's disease diagnosis. Ultimately, a joint GWA study of a pooled population of individuals with Alzheimer's disease and Parkinson's disease might be a powerful approach to identify common genetic susceptibility factors for these diseases. One speculative model is that tau acts as a downstream mediator of both β-amyloid and α-synuclein toxicity, with neurofibrillary tangles only forming in the presence of amyloid (**Fig. 1**). Therefore, β-amyloid and α-synuclein might potentiate each other's effect on neurodegeneration in the aging population, and the relative proportions of each pathology could correlate with the extent of dementia or parkinsonism, respectively.

A vigorous discussion continues in the genetics community over the relative contributions of common and rare variants to the architecture of complex genetic diseases. In Parkinson's disease, we now know of three genes (*SNCA*, *LRRK2* and *MAPT*) in which rare and highly penetrant dominant mutations cause familial parkinsonian syndromes, and we know that common variants at these same loci increase susceptibility for Parkinson's disease in the general population. These results will inform next-generation sequencing strategies designed to discover and validate the role of less common and rare alleles in neurodegenerative diseases. We anticipate that continued growth in our understanding of Parkinson's disease genetics and of the functional consequences of associated variants will be rapidly translated into tools for risk prediction and new targets for drug development.

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