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Invited Review Article

INVITED REVIEW ARTICLE

Progress in the genetic analysis of Parkinson's disease

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Abstract

The pace of genetic discovery in complex disease has accelerated exponentially over the last decade. Our fund of knowledge of the foundational genetics in disease has never been as great. There is a clear path forward to the resolution of the genetic architecture toward a point at which we will saturate the biological understanding of disease through genetics. This understanding continues to provide fundamental insights into disease biology and, with the advent of new data and methodologies, the path from gene to function is becoming clearer and cleaner. In this opinion piece, we discuss progress in the genetics of Parkinson disease. We explore what genetics has revealed thus far in the context of disease biology. We highlight mitophagy/autophagy, dopamine metabolism and the adaptive immune system. We try and link these findings together to give a holistic view of pathogenesis with the underlying theme that disease pathogenesis relates to a failure of damage response pathways. In the 1990s, Parkinson's disease was regarded a non-genetic disorder. Since that time, however, a huge number of Mendelian loci and risk loci have been identified by positional cloning and by genome-wide association studies. In this review, it is not our intent to list each gene and locus and review their identification [Hernandez, D.G., Reed, X. and Singleton, A.B. (2016) Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. J. Neurochem., 139 Suppl 1, 59–74] but rather to outline the pathogenetic mechanisms that these analyses are revealing and then, given the large number of loci already identified, to lay out what we hope future analyses may help us understand, both in terms of disease mechanisms and for risk prediction for the syndrome.

Mendelian Genes

The Mendelian genes for Parkinson's (PD) disease point to two closely related pathways and overlapping pathways: mitophagy and autophagy.

Mitophagy

Parkin is the prototypic mitophagy gene (Table 1). The Mendelian loci linked to mitophagy are recessive and lead to early onset disease, and in general, their clinical features are restricted to those associated with nigral and raphe loss (parkinsonism and depression). In general, their clinical features do not progress far beyond the results of these brain stem lesions. In this regard, it is worth noting that MPTP, the toxin which caused parkinsonism in humans and which is widely used in modeling the movement features of PD, is a mitochondrial toxin which selectively targets the nigra (2). This, perhaps, is a clue as to the selective vulnerability in this form of the disease: perhaps, these mitophagy pathway genes lead to selective loss of the nigra and parkinsonism because catecholamine metabolism leads to more mitochondrial damage and thus a greater susceptibility to defects in mitophagy (*vide infra*). It is worth noting at this point that these mitophagy loci involve genes in mitochondrial metabolism which prepare damaged mitochondria for autophagy (i.e. they are upstream of the general autophagy processes discussed in the following section).

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Table 1. Mendelian loci for Parkinson's disease

Locus	Inheritance	Onset	Gene	Function
PARL1/4	Dominant	30–70	SNCA	Vesicle fusion
PARK2	Recessive	Teens	PKRN	Mitophagy
PARK6	Recessive	Teens	PINK1	Mitophagy
PARK7	Recessive	Teens	DJ1	Mitophagy
PARK8	Dominant	50–70	LRRK2	Autophagy control?
PARK9	Recessive	Teens	ATP13A2	Lysosomes
PARK14	Recessive	Teens	PLA2G6	Not clear
PARK15	Recessive	Teens	FBX07	Mitophagy
PARK17	Dominant	50–70	VPS35	Endosomes
PARK19	Recessive	Young	DNAJC6	Endosomes
PARK20	Recessive	Teens	SYNJ1	Endosomes
PARK21	Dominant	30–70	DNAJC13	Endosomes
Unassigned	X-linked	30–50	RAB39B	Not clear
Unassigned	High risk	30–70	GBA	Lysosomes

Autophagy

Those Mendelian (both dominant and recessive) genes for PD whose functions are understood have a role in autophagy. Of these, the prototypic example is LRRK2 (3). Autophagy is one of the processes by which excess and damaged proteins and organelles are removed. In this regard, it makes teleologic sense that general problems in the removal of damaged proteins should lead to a late-onset disease. Synuclein is a very abundant protein, is the major component of Lewy bodies and is largely degraded via autophagy (4). Its deposition in the disorder is thus consistent with the hypothesis propounded by Dobson and colleagues that deposited proteins are those closest to their solubility threshold (5).

Risk Genes

Risk genes for PD have been identified through genome-wide association studies (GWAS) and through sequencing. For convenience, we divide them into lysosome storage disease (LSD) genes and others, largely identified through GWAS.

LSD genes and other lysosomal genes.

The prototypic lysosomal Parkinson risk gene is the glucocerebrosidase 1 (GBA) gene. This was identified because of the clustering of PD cases in the families of Gaucher's disease (6). However, more recent data shows that this LSD association is not unique to GBA but is more general to other (though perhaps not all) LSD genes (7). The relationship between synuclein metabolism and partial GBA deficiency has been extensively investigated and indicates that synuclein is cleared through the lysosome and that a high expression of synuclein inhibits the flux through this autophagic pathway (8,9).

Other GWAS loci

Other pathways identified through genetic analysis of PD include mitochondrial genes. These data are consistent with earlier pathologic work showing evidence for damage, especially to mitochondrial complex 1 in the PD nigra (10). These data, of course, complement the data concerning the role of mitophagy genes in PD referred to in the preceding section. Dopamine metabolism genes, COMT and GCH1, are also associated with disease, possibly consistent with the view that dopamine metabolism can contribute to mitochondrial damage (11,12). However, the other major pathway highlighted by GWAS analysis is the adaptive immune system, first identified through a human leukocyte antigen association but increasingly recognized as a major determinant of risk across the genome (13,14).

Interpretation of Genetic Data

These disparate data implicating mitophagy/autophagy, dopamine metabolism and the adaptive immune system with the etiology of the disease may appear difficult to reconcile with a holistic view of Parkinson's pathogenesis. However, we believe that we can offer a broad outline of these pathogenic processes based on the notion that as we age, we accrue damage and as this happens, the biological systems dealing with damage repair which were sufficient in early life become overwhelmed.

In the case of mitochondria, the nigra accrues mitochondrial damage, we would suggest, because dopamine metabolism generates oxidative damage (15). This damage overwhelms mitophagic processes if these are already genetically compromised. Alternatively, these systems can be overwhelmed if there is excessive mitochondrial damage caused by environmental exposures as occurs in cases of MPTP toxicity.

In the case of a more general insufficiency in autophagic processes, as damage accrues during aging, it will eventually overwhelm the clearance mechanisms. This would manifest with the deposition of those cellular components which are most dependent on autophagy, among which is synuclein. Secondary damage response in the CNS is largely dependent on microglial response, and the involvement of the adaptive immune system largely reflects the microglial damage response (16). It is worth noting at this stage that other late-onset diseases can also be largely envisaged as failures of damage response: Alzheimer's disease as a failure in the microglial response to membrane damage, and motor neuron disease as a failure of stress granules (17,18). Thus, this view is consistent with a general view that late-onset neurodegenerative disease can be viewed, in part, as a failure in damage repair.

Going beyond Case Control Association Studies

All the studies discussed above have dealt with the genetics of risk of disease. However, it is clear that genetics also has effects on the age at onset of disease, on the clinical phenotypes of

disease and on the rate of decline of disease, and neither of these outcomes have had been as comprehensively examined as the genetics of risk because more complete data is required.

Genetics of age at onset

One might expect that in general, individuals who had a higher genetic load would have an earlier-onset age and that, therefore, a GWAS of age at onset would simply resemble the GWAS for risk, but that does not seem to be the case (19). The SNCA locus has a large effect on age at onset, as one might have expected, but TMEM175, a minor risk locus, has an unexpectedly large effect on age at onset whereas, surprisingly, the MAPT locus has no discernible effect on age at onset. These data indicate the relationship between the genetics of risk, and those of age at onset are complicated and are likely to be giving us clues as to the pathogenesis of the disease that, because of the limited nature of the analyses, we do not yet understand.

Genetics of phenotypes

From the description of the phenotypes of the Mendelian genes summarized about (and see (20)), it is clear that different genetic mutations give widely different clinical outcomes. The extent to which different genetic risk profiles give rise to different clinical outcomes in the cases without Mendelian mutations has been less well studied, but there are clear indications that they do. For example, GBA mutations appear to be associated with rapid decline progressing to dementia consistent with the association of GBA mutations with dementia with Lewy bodies and the MAPT haplotype has been reported to influence cognition in Parkinson patients (21–23). Unsupervised machine learning algorithms have suggested that Parkinson disease features map onto three phenotypic clusters: whether these clusters represent different genetic architectures of disease is not yet clear, but two related hypotheses we would like to suggest is that in any individual case, the more important mitophagy is in the etiology, the more benign is the disease progression: the more important autophagy is, the more aggressive the disease course and that Lewy body pathology is a general marker of autophagy, rather than mitophagy, failure.

Genetics of progression

Idiopathic Parkinson's shows clear evidence for anatomic progression almost certainly reflecting neuron-to-neuron transmission ('Braak staging') (24–26). How this clear evidence of spread of disease relates to the genetics of the disorder is not clear; however, accumulating evidence suggests that lysosome insufficiency may contribute to this neuron spread (27,28) and this may provide the link between this anatomical spread and the genetics of the disease.

Using Genetics to Predict Disease

Our current estimate of the heritable component of disease that is due to relatively common genetic variability is about 35%. Thus, we will never be able to accurately predict PD in all individuals using genetic analysis based on the hypothesis that each locus acts independently. Because genetics is indeed a substantive contributor to lifetime risk, it can now be used as a contributor in what will likely be a multi-modal predictor of PD. Our previous work has shown that genetics, anosmic status, age, sex and family history can be used as an accurate predictor of disease (29) but of course anosmia (and other phenotypic measures such as REM sleep disorder) is really evidence of an ongoing disease process and not a predictor of it. If this is a substantive missing heritability for PD, one possibility is that there is epistasis between loci for which some modest evidence has been presented (30,31). It should be noted, however, that the now strong evidence that Lewy body pathology can spread from cell to cell (32,33) suggests that the disease could be initiated by a stochastic event in a single cell and may not be predictable.

A Speculative Synthesis

We suggest that the primary problem in PD is an age-related failure in the autophagic clearance of damaged proteins and organelles. The predominant subjects of this failure are either damaged mitochondria or damaged and misfolded proteins of which synuclein is the most highly expressed. Mitochondrial damage is a particular problem in the nigra because of the oxidative stress induced by catecholamine metabolism, and so the greater the failure in mitophagy, the purer the dopaminergic nature of the resultant phenotype. If the problem is more generally a problem with lysosomal failure, then the resultant pathology will be more widespread, the clinical features of the disease will be more generalized and the resultant pathology will include prominent synuclein deposits. Most cases of disease will involve some elements of both mitophagic failure and more general lysosomal failure, but parkin disease represents the mitophagy of the spectrum and synuclein duplications or GBA insufficiency the other.

What does this speculative synthesis suggest for treatment approaches? Clearly reducing damage—mitochondrial damage through antioxidative strategies or through substrate reduction in terms of alpha synuclein (e.g. antisense therapies)—is a therapeutic approach which has a face validity.

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