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The genetics of Parkinson's disease: progress and therapeutic implications

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Abstract

The past 15 years has witnessed tremendous progress in our understanding of the genetic basis for Parkinson's disease (PD). Notably, while most mutations, such as those in *SNCA, PINK1*, *PARK2*, *PARK7*, *PLA2G6*, *FBXO7*, and *ATP13A2*, are a rare cause of disease, one particular mutation in *LRRK2*, has been found to be common in certain populations.

There has been considerable progress in finding risk loci. To date approximately 16 such loci exist, notably some of these overlap with the genes known to contain disease-causing mutations. The identification of risk alleles has relied mostly on the application of revolutionary technologies; likewise second generation sequencing methods have facilitated the identification of new mutations in *PD*. These methods will continue to provide novel insights into PD.

The utility of genetics in therapeutics relies primarily on leveraging findings to understand the pathogenesis of PD. Much of the investigation into the biology underlying PD has used these findings to define a pathway, or pathways, to pathogenesis, by trying to fit disparate genetic defects onto the same network. This work has had some success, particularly in the context of monogenic disease and is beginning to provide clues about potential therapeutic targets. Approaches toward therapies are also being provided more directly by genetics; notably via the reduction and clearance of α-synuclein and inhibition of Lrrk2 kinase activity.

We believe this has been an exciting and productive time for PD genetics, and furthermore, that genetics will continue to drive the etiologic understanding and etiology based therapeutic approaches in this disease.

Introduction

The modern genetic understanding of Parkinson's disease (PD) began publicly in 1997. This year saw the identification of α-synuclein mutations as a rare cause of disease and the

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Conflicts of Interest

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realization that this protein was a core component of all PD in the form of Lewy bodies and Lewy neurites. Over the following 15 years considerable progress was made in both the identification of mutations that cause disease, and in the mapping of common variants that alter risk for PD. The drive behind this work centers on understanding the etiology of this complex disorder. The hope being that such an understanding will facilitate the development of therapies that halt or slow the underlying disease process, rather than just ameliorate symptoms.

It is now clearly established that many, if not all, forms of Parkinson's disease (PD) contain a genetic component. In general the previous supposition of an environmental or genetic cause of PD is now regarded as a false dichotomy, with a likely contribution of both to all forms of this disease, albeit in varying degrees. In this review, which resulted from a session within a small conference discussing therapeutic strategies in PD, we aim to discuss the genetic basis of PD, and the implications of this work on designing etiologic treatments for this disease. Within this article we have not included a section discussing a priori proof for a genetic basis of this disease or the role of environmental influences, in part because we wanted to keep a narrow focus in this piece, and also because this has been well covered by us and others in previous articles and in articles within this issue. Likewise our aim is not to provide a comprehensive discussion of every locus associated with PD or parkinsonism, this too has been addressed elsewhere. Our aim therefore, is to set the scene of our current understanding of the genetics of PD using specific examples and to convey our belief that the rapid, and increasing, pace of genetic discovery in PD is laying the groundwork for a more complete understanding of the molecular etiology of this disease, and that ultimately this is the most likely route to a cure or cures. Our intent here is not to discuss particular pathways identified by genetic in detail, as this will be covered elsewhere in this issue.

Monogenic Loci

The autosomal dominant forms

Mutations in two genes cause autosomal dominant forms of PD. Mutations in the alpha-synuclein gene (SNCA) are rare and include point mutations and whole-locus multiplications (duplications or triplications).[1, 2] Duplications are detected in ~1–2% of the PD families compatible with autosomal dominant inheritance.[3] Triplications and point mutations are exceedingly rare: the Ala53Thr mutation has been found in a few families of Greek ancestry; Ala30Pro and Glu46Lys have been detected so far in single families, of German and Spanish origin, respectively.[3–5] The brain pathology is characterized by abundant α-synuclein-positive neuronal inclusions (Lewy bodies and Lewy neurites), but the associated clinical spectrum is broad, ranging from classical PD to more atypical and aggressive phenotypes (including myoclonus, severe autonomic dysfunction and dementia in addition to parkinsonism), and resembling diffuse Lewy body disease or multiple system atrophy. The patients with *SNCA* duplications often display a classical PD phenotype, whereas the more rare cases carrying triplications display more severe phenotypes, in keeping with a direct relationship between *SNCA* gene dosage and disease severity.[3, 6] However, wide clinical variability is observed also within the same family. The *SNCA* mutations are usually higly penetrant, but instances of reduced penetrance have been reported for the *SNCA* duplication.[7]

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) are the most common, known cause of autosomal dominant PD.[8, 9] The *LRRK2* gene has 51 exons, encoding a very large protein, termed lrrk2 (or dardarin), which contains two predicted enzymatic domains (GTPase and kinase) and multiple protein-protein interaction domains.[10]

Many novel variants have been identified in this large gene in PD patients, but only six of these (Asn1437His, Arg1441Cys, Arg1441Gly, Tyr1699Cys, Gly2019Ser, and Ile2020Thr) can be considered as definitely disease-causing, on the basis of co-segregation with disease in families, and absence in controls.[10, 11] In studies on large referral series, the LRRK2 mutations explain for up to ~10% of the patients with familial PD and a clear autosomal dominant pattern of inheritance.[12] Among these mutations, Gly2019Ser is by far the most common (see below); [13, 14] Arg1441Cys is the second most frequent mutation, detected in several populations.[15] Another variant targeting the same codon, Arg1441Gly, is a frequent founder mutation among PD patients from the Basque population, but rare elsewhere.[16] Asn1437His, Tyr1699Cys, and Ile2020Thr have been found rarely.

An incomplete and age-related penetrance (ranging from ~30 to 70% by age of 80 years old in different studies) has been estimated for the commonest Gly2019Ser mutation.[13, 17, 18] As a consequence, the mutation can be detected in patients with familial and sporadic PD, including those with positive family history, but without a clear pattern of autosomal dominant inheritance.[14] This mutation is frequent in some populations from South Europe (such as Portugal, Spain, and Italy) but very common among the Arabs patients from North Africa and among the Ashkenazi Jewish patients.[13] Dopaminergic neuronal loss and gliosis in the substantia nigra are the common pathological features in patients with *LRRK2* mutations, and classical Lewy bodies are found in the majority of them. However, in some cases alpha-synuclein-positive inclusions are not observed, and only tau-positive or ubiquitin-positive inclusions are seen.[9] Overall, the clinical characteristics of patients with *LRRK2* mutations (particularly those with the common Gly2019Ser mutation) are very similar, if not indistinguishable, from those of the classical (idiopathic) PD.[13, 15] The associated range of PD onset age is broad, including patients with early and late disease onset.

The autosomal recessive forms

Homozygous or compound heterozygous mutations in each of the following three genes: *PRKN* (parkin, PARK2), *PINK1* (PARK6), and *DJ-1* (PARK7) cause autosomal recessive forms of PD, usually without atypical clinical features. [19–21] Furthermore, mutations in each of another three genes: *ATP13A2* (PARK9), *PLA2G6* (PARK14), *FBXO7* (PARK15), cause more rare forms of recessive parkinsonism, usually with very early-onset (<30 years) and atypical clinical features (pyramidal, dystonic, ocular movement, and cognitive disturbances). [22–24]

Mutations in parkin are the most common, and explain up to half of the familial PD cases compatible with recessive inheritance and disease onset before the age of 45 years, and also ~15% of the sporadic cases with onset before 45.[21] Mutations in *PINK1* and *PARK7* are less common, accounting for up to 1–8%, and 1–2% of the sporadic cases with early-onset, respectively. [19, 20, 25] The likelihood of presence of mutations in these genes is a function of the onset age: the earlier the onset, the higher the likelihood. A large number of mutations have been identified in these three genes worldwide, including point or small mutations, but also large genomic rearrangements (deletions and multiplications). These last are especially frequent in the parkin gene.[21] Sequencing and dosage assay of all exons is therefore required for an accurate screening of these three genes.

In some patients only a single heterozygous mutation is detected in one of the genes for recessive PD. This finding remains difficult to interpret.[26] A single heterozygous mutation might be coincidental (unrelated to the disease) - the screening of large series of cases and controls support this view. However, a single heterozygous mutation in one of these genes might also act as a risk factor for PD. Last, a second pathogenic mutation might be present but escapes detection by the standard screening methods.

A small number of patients with recessively-inherited PD have come to autopsy: parkin disease-causing mutations (homozygous or compound heterozygous) are usually not associated with Lewy-body pathology, possibly suggesting pathogenetic differences between the autosomal recessive and autosomal dominant forms of PD.[27] However, a first patient with PINK1 mutations was recently reported with Lewy-body pathology,[28] and the pathology in patients with DJ-1 mutations remains unknown. The clinical phenotype associated with parkin mutations is characterized by parkinsonism of early onset, good and prolonged response to levodopa or dopaminergic drugs, and often a benign course.[29] The average onset age is in the 30s in most patients, but late-onset cases have been described. Motor fluctuations and levodopa-induced dyskinesias are frequent, whereas marked cognitive or vegetative disturbances are rare. The phenotype associated with PINK1 and DJ-1 mutations has been studied in smaller number of patients but it is overall indistinguishable from that of parkin.

Recently Identified Gene Mutations

As described above the identification of genetic causes for Mendelian disorders has been based on the collection of multi-incident families, linkage analysis, and sequencing of genes in candidate intervals. The advent of next-generation sequencing technologies promises to expedite future discovery. First applied to a Swiss kindred presenting with autosomal-dominant, late-onset PD, pairwise comparison of the coding exome in first-cousins concordant for disease recently lead to the discovery of mutations in the gene for vacuolar protein sorting 35 (*VPS35* c.1858G>A; p.Asp620Asn).[30, 31] Findings have been validated in many families of multiple ethnicities but the midbrain pathology has yet to be described. VPS35 is a central component of the tripartite retromer cargo-recognition complex, consisting of VPS35, VPS29 and VPS26a or b, that together form the luminal structure for transport of specific membrane-associated proteins. Retromer formation is critical for membrane-protein recycling in a number of cellular systems. These include recycling of membrane-associated proteins from early endosomes to plasma lemma, from the endosome to trans-golgi network and from mitochondria to peroxisomes. Binding of sorting nexins dictates the compartment to which the tripartite VPS complex and associated cargos are directed. While the complex has many types of cargo and is involved in a diverse array of biologic pathways from developmental Wnt signaling, amyloid precursor protein processing, and mitophagy, it is perhaps best characterized for the sorting and transport of acid hydrolase receptor whose cargo is required for lysosomal function. To date, the role of retromer within neurons is poorly described but the linkage of *VPS35* p.D620N to Parkinson's disease is likely to be a catalyst for future research.

Dynactin is a multisubunit protein complex that is required for most, if not all, long distance trafficking of protein complexes and membranous organelles. *DCTN1* encodes the largest subunit of the dynactin complex, p150glued, for which cytoskeleton protein interactions are best described for the N-terminal 1–110 amino acid domain and its microtubule binding CAP-Gly 'GKNDG' motif. The latter serves as a parking brake of the dynein motor, and enhances the fine control of long-range dynein-based movement. A series of mutations in the N-terminal has now been described in age-associated neurodegenerative disorders associated with TDP43 pathology. *DCTN1* G59S was first identified in a family with dominantly-inherited motor neuron disease (distal hereditary motor neuronopathy with a distinct vocal fold paresis (laryngeal dysfunction)) with onset in the fourth decade and with relatively slow symptom progression.[32] Subsequently, a series of dominant mutations, *DCTN1* G71R, G71E, G71A, T72P and Q74P, within or directly adjacent to the CAP-Gly domain were linked to Perry syndrome with onset in the fifth decade with rapid progression, typically 4 years to death. Perry syndrome is characterized by depression and profound weight loss with parkinsonism and central hypoventilation. Rather surprisingly Perry

syndrome has no peripheral motor neuron involvement. Most recently, a Japanese family was identified with *DCTN1* F52L with onset in the sixth decade, with symptoms reminiscent of Perry syndrome but of longer duration, typically 10–20 years, and with subsequent frontotemporal lobe degeneration (unpublished data). It is remarkable that substitutions within the same protein domain, within 20 amino acids, result in such clinically disparate phenotypes. While DCTN1 mutations have been shown to impair the affinity of p150glued to microtubules to a greater or lesser degree, they presumably affect other p150glued interactions such as with EB1 and CLIP-170, themselves microtubule-binding proteins. However, dynactin also contains several other subunits that are organized into an elaborate structure that participates in interactions with a wide range of cellular structures from extension of early endosome retromer tubules for cargo recycling, to the trafficking of large membranous organelles such as mitochondria. Consequently, *DCTN1* mutations provide an elegant opportunity to understand the selective vulnerability of different neuronal population to neurodegenerative disease, one of the most fundamental yet largely unanswered questions in neuroscience. The dysfunction and death of specific neuronal subtypes that gives rise to such disparate and apparently distinct clinical syndromes is presumably a function of the need to effectively traffic specific cargos within these cells. Recently, expansion mutations in C9orf72 were described in individuals and families with either motor neuron disease or frontotemporal dementia with TDP-43 pathology.[33, 34] Thus it may also be worthwhile to test if C9orf72 is a p150glued cargo or involved in dynactin trafficking.

Most recently translation initiator mutations in eIF4G1 were genetically linked to autosomal dominant late-onset Parkinson's disease with brainstem Lewy body pathology.[35] eIF4G1 is a central component of the eIF4F complex that regulates translation of mRNAs with highly structured 5′ sequences. The two most frequent mutations eIF4G1 A502V and R1205H impair multi-subunit complex formation, consistent with a dominant-negative mechanism. The eIF4G1 N-terminus binds eIF4E (the mRNA m7GTP cap binding protein) and PAPB (poly-adenine binding protein which attaches to the mRNA tail) proteins thereby circularizing the mRNA message. The central eIF4G1 domain recruits eIF4A (an ATP dependent helicase that unwinds double stranded RNA to expose the 5′ AUG start codon) and eIF3. The C-terminal of eIF4G1 contains additional binding sites for eIF4A and regulatory factors including Mnk1 (MAP kinase signal-integrating serine/threonine kinase 1). Together eIF3 and eIF4F bind the ribosomal 40S subunit and methionyl tRNA (Met-tRNAiMet, recruited by GTP-bound eIF2). Met-tRNAiMet then scans the mRNA to find the AUG start codon to initiate translation. eIF4G1 depletion impairs nutrient sensing and mitochondrial function; typically the proteins translated control bioenergetics, growth control and stress response, regulated in part through 4E-BP availability and the mammalian target of the rapamycin (mTOR) pathway. *EIF4G1* mutations directly implicate mRNA translation intiation in parkinsonism and might help unify other monogenic forms, toxin, and perhaps virally-induced disease within a convergent pathway. Notably, 4E-BP is a substrate of human Lrrk2 and the Drosophila ortholog (Lrrk). Lrrk2 pathogenic mutations cause hyperphosphorylation of 4E-BP leading to reduced oxidative stress resistance and dopaminergic neurodegeneration. Conversely, inhibition of mTOR signaling during development or overexpressionof 4E-BP in Drosophila mutants with PINK1 or Parkin loss-of-function suppresses the flies' pathologic phenotypes.

Therapeutic Implications of Monogenic Loci

Parkinson's disease is insidious, age-associated and chronic, and consequently a multitude of factors must come into play not only genetic. Nevertheless, the latter provide an unequivocal foundation to elucidate the molecular and cellular biology going awry. So much neuroscience is based on model systems rather than the human condition. Our continued

ignorance clearly contributes to past failures in clinical trials and our inability to remedy the condition. Genetic discoveries through linkage, reveal profound insights into the mechanisms of cellular dysfunction and death in parkinsonism, and conversely in the mechanisms required for healthy aging of the basal ganglia. Although these findings are not immediately obvious or intrinsically connected within a pathway or temporal sequence of cellular events, the hope of many is that investigating the molecular consequences of these variants will provide clues as to the commonalities and/or differences in the etiology of these forms of disease. Leading on from this, it is clearly hoped that such an understanding will be directly relevant to the more common, apparently sporadic forms of disease.

We do not provide here a detailed discussion of pathways and mechanisms implicated by genetics, as this is covered by others in this issue; however by way of illustration, perhaps the most elegant example of the power of mutation identification came with the discovery of a mechanistic link between pink1 and parkin proteins.[36] Subsequent work has suggested a role for parkin and pink1 in the autophagic clearance of mitochondria (mitophagy).[37–41] (reviewed in [42 and 43]). This effort supports the notion that mitochondrial quality control may be an important factor in PD pathogenesis, consistent with the observation of high levels of mutant mitochondrial DNA accumulating in the brains of PD patients.[44] While this is just the beginning of a coherent network, this work highlights the importance of identifying myriad genetic causes of this and related diseases in understanding the biologic basis of this complex disorder.

In addition to this work, there are preclinical therapeutic efforts aimed at apparent dysfunction directly caused by mutations. The primary examples of this are efforts underway that aim to tackle α-synuclein or Lrrk2. The identification of *SNCA* locus multiplication mutations clearly suggests that overproduction of α-synuclein is sufficient to cause PD; thus there are several efforts aimed at reducing α-synuclein production as a potential therapeutic approach[45]. Likewise, the fact that Lrrk2 is a kinase makes this an attractive and druggable target; this, coupled with the observation that the G2019S mutation consistently results in increased kinase activity means that the majority of large pharmaceutical companies have an active program aimed at targeting Lrrk2 kinase activity.

Risk Loci for Parkinson's disease

Identifying the genetic lesions that cause monogenic forms of disease has been enormously important in our efforts to understand the molecular basis of this complex disorder. In addition to this work, there has long been an attempt to find genetic variability that alters risk for, rather than causes, disease. In this section we will discuss the route to identifying risk loci in this complex disease.

Candidate Gene Association Studies

The majority of efforts in the 1990's through to 2006 centered on simple, and generally small, case control candidate gene analyses. In this design a cohort of cases and controls, usually ~100–200 subjects in size was typed for a single polymorphism in a candidate gene to determine if a variant was more common in cases than controls. The genes selected were usually functional candidates, and the variant selected for typing was most often one that altered an amino acid. This effort was largely unsuccessful, with the some notable exceptions.

The first indication that *SNCA* contained risk variants came from this type of work, with the publication of a nominal association between alleles of the *REP1* polymorphism in the promoter region of *SNCA* and risk for disease.[46] While this initial work was intriguing, a large number of follow up studies failed to produce a clear picture of whether this was a

genuine risk locus, providing both support for and against this association. Clarity only came to this issue with the publication of a large collaborative analysis of ~5000 samples, which showed a clear association between increased risk and the long *REP1* alleles.[47] This work suggests that the disease-linked alleles are associated with a 1.4 fold increase in risk for PD. As is discussed later, this story became more complicated with the advent of genome wide association (GWA) studies.

The identification of *GBA* mutations as risk alleles for PD can possibly be thought of as the result of a candidate gene association study, although it is more appropriate to describe this as an association that was borne of careful and astute clinical observation. The autosomal recessive disorder Gaucher disease is a lysosomal storage disorder that is caused by mutation of the gene encoding glucocerebrosidase, *GBA.* An initial report indicated that Gaucher disease patients may also display signs and symptoms of parkinsonism, albeit infrequently.[48] This was followed by the observation that carriers of a single *GBA* mutation appeared to be at a much higher risk for PD.[49] Despite the strong initial association, it took many years to build a convincing argument for single *GBA* mutations as a risk factor for typical PD. This was eventually achieved with a large meta-analysis of sequencing studies that showed clearly that a single *GBA* mutation increases risk for PD ~5 fold.[50]

As with *SNCA*, the identification of *LRRK2* mutations as a cause of PD created intense activity around assessing the range of genetic variability in this gene, and the role of these variants in disease.[8, 9] Early in this process an apparent mutation, p.G2385R, was described to segregate with PD in a small Taiwanese family.[51] As sequence and genotype data began to accumulate it became clear that this variant was relatively common in the general Asian population, and that this was strongly associated with a ~2 fold increase in risk for PD.[14]

A meta analysis of these studies, performed in a wide variety of Asian cohorts, has shown this mutation to be present in ~4% of controls, and ~9% of cases.[52] While a similar magnitude risk effect has been reported for an additional variant, p.R1628P, again in Asia, the supportive evidence for this is less clear than with p.G2385R.[53, 54]

Genome Wide Association Studies

A large number of GWA studies have now been performed in PD.[55–66] In contrast to candidate gene association studies, GWA attempts an unbiased and comprehensive survey of the genome to identify loci that contain common genetic variability conferring risk for disease. As GWA data have accumulated so too have the number of loci implicated in risk for PD. The most recent analysis includes data on more than 12,000 cases and 20,000 controls, and provides evidence for 16 independent risk loci.[57, 67] Individually, alleles at each of the loci represent small risk or protective factors, conferring 1.1 to 1.4 fold increases and 0.95 to 0.7 fold decreases in risk respectively. The basis for GWA studies is the common disease common variant hypothesis, which posits that for common diseases, risk is likely to be conferred by a collection of common variants that individually increase risk only a small amount. Because of this it is perhaps informative to view the risk conferred by the identified loci collectively, i.e. as a risk profile. In this context, when ordering a population based on the collective burden of genetic risk that each individual carries (and using only these 16 loci), the individuals in the highest quintile of genetic risk are 3 times as likely to have PD as those in the lowest quintile of genetic risk.[67] Interestingly when using deciles of risk burden, this differential increases to 4 fold (data not shown).

We will not describe each of the loci identified here, but rather show a summary (table 1), and comment on a few loci that are of particular interest.

The earliest signals to show up convincingly with GWA were at *SNCA*, *MAPT*, and *LRRK2* loci.[62, 63] Notably these are loci that contain genes linked to autosomal dominant forms of PD. While we cannot be sure that the biological mediator of the risk alleles at these loci are indeed *SNCA*, *MAPT*, and *LRRK2*, because GWA identifies loci, not genes, it does seem likely. The initial association at *SNCA*, described above, centers on the *REP1* allele about 10kb 5′ to the translational start site of the gene. Interestingly, the initial compelling GWA signals at *SNCA* were not in this area of the gene, but rather over the 3′ end of the gene, from intron 4 through till after the 3′ untranslated region. Current data seems to suggest that these signals are distinct, i.e. that there are at least two (and probably more) distinct regions of the *SNCA* locus that contain common variants that alter risk for disease.[68] This implies that the OR estimate of 1.4 for risk conferred by alleles at *SNCA* is an underestimate. Similarly, there appear to be distinct risk effects within the *HLA* locus and evidence that there exists more than one risk haplotype across the *MAPT* locus.[68, 69] These observations are consistent with the notion of graded haplotype risk, and suggest that the initial association observed at individual risk loci can represent only the dominant signal, and that substantive additional risk is likely to occur at many previously identified risk loci.[2, 70] Also of note is that the *MAPT* association with PD has only been observed in Caucasian populations, the GWA published to date in Asian cohorts fails to identify a signal at this locus. It is not yet clear whether this represents the substantial divergence of genetic diversity at this locus between populations (i.e. a true lack of association in Asian populations), or a relative lack of informative markers for the Asian population at this locus in current genotyping arrays.[71]

The association signal at *LRRK2* is complex. As discussed above there is at least one established, common, protein-coding risk allele in the Asian population.[52] GWA in Asian subject shows a clear and strong association close to *LRRK2* but it is not clear whether this represents tagging of the p.G2385R allele or a distinct signal.[62] There also exists a clear association close to *LRRK2* in the Caucasian population and it is clear that this signal is not being driven by the common p.G2019S mutation.[63] A recent report provides evidence of association between a *LRRK2* haplotype that contains protein-coding polymorphisms and risk for disease; it is certainly plausible that this is the effect being tagged by GWA signals but this requires more work.[54] Certainly it is reasonable to suppose that disease may be associated with both non-coding and coding changes in the same transcript, and this forms the basis of the Pleomorphic Risk Locus hypothesis.[2]

Therapeutic Implications of Risk Loci

In the early stages of GWA much was made of the rather small effect sizes identified by GWA; and this has been used to suggest that these loci are not important in the pathogenesis or etiology of disease. This is a logical fallacy, much like the old argument that *SNCA* mutations will tell us little about the disease because they are rare. GWA results provide data on the size of effects of risk alleles, but this tells us nothing about how critical the affected gene is within the molecular process that is PD. Clearly understanding the potential mechanistic implications of these genes is important; particularly whether individual genes are exerting an effect by increasing the likelihood of a disease initiating event or whether they are related to molecular or cellular response to the disease process.

The majority of risk loci identified by GWA cannot be explained by non-synonymous (protein coding) polymorphisms.[72] This suggests that such loci must alter risk by altering the biologically relevant transcript in some other way, either by affecting transcript expression levels, altering splicing, or changing sub cellular localization. There already exists data that has attempted to look at this for PD loci, and while these are quite blunt tools some significant correlations have been detected that suggest risk alleles alter expression of proximal transcripts.[63, 67, 73]

This immediately suggests a potential point of therapeutic intervention lies in modulating expression and that excellent targets in this regard are genes implicated by GWA studies. This is an approach that is already being investigated for *SNCA*, although in this case driven by the finding of *SNCA* multiplication as a cause of PD.[74] What is known about the age-related biology of this protein suggests this is a good target.[75] Notably, the risk alleles identified at *SNCA* are associated with increased *SNCA* expression and this immediately supports the notion that such a therapy may be effective in typical PD as well as rare familial forms.[73]

There are several considerations that need to be addressed before attempting to convert GWA findings such as those described here to expression-based therapies. The first is to identity the pathobiologically relevant transcript within any single risk locus, and in concert with this, to understand quite how the transcript is affected. One can imagine that this might be through several mechanisms; basal expression levels, expression in response to a stimulus (i.e. induced expression), exon splicing, and sub cellular localization of a transcript. Perhaps a more complex endeavor will be to understand quite how modulating this transcript will manifest in downstream effects. Gene therapy is already being tested for PD and other neurodegenerative diseases, in Phase 1 and 2 clinical trials.[76, 77] This is likely to be a hard fought effort, however, the applicability of such an approach to myriad diseases, would suggest that overcoming the practical obstacles to this therapy will be an effort spread across many research fields.

Aside from mechanistic implications, genetics is likely to impact other aspects of therapeutics application in PD. It is conceivable that genetic profiling of individuals could ultimately be used to both predict who is at a high risk for disease and their long term prognosis, in addition to indicating which therapies, and what dosing regimen, is most likely to be effective. Given the relationship between genetic variability and gene expression in the brain,[78] a working understanding of how a patients genetic profile will predict response to modulating gene expression, and how this may be used as a covariate in assessing biomarkers of disease progression, are both likely to be important in designing and monitoring personalized, or boutique therapies.

Where are the cures?

A question that is frequently raised, particularly to the enthusiastic geneticist, is “its been a long time since the first mutation was discovered, where are the cures?”. In truth, this is a question borne partly out of hyperbole surrounding many genetic findings, but mostly out of a lack of understanding regarding the process of drug production coupled with a naïve belief that understanding biology is easy. Inherent in the type of etiologic based therapy discussed here, is to identify a process or target for intervention. For the most part this relies on understanding at least part of the pathobiological effect of a mutant protein. This mechanism is usually not self evident – for example, the identification of α-synuclein mutations led quickly to an understanding that α-synuclein accumulated in Lewy Bodies, but the toxic species, and the nature of toxicity is still not apparent. Understanding the pathobiology is clearly very difficult; this is not only illustrated by the enormous amount of ongoing work in this regard in PD, but similar efforts in other complex diseases. Even when a pathobiological mechanism is revealed (or even hinted at), the route to therapy is a long one. The preclinical stage, of identifying efficient and specific drugs or small molecules that appropriately target the pathobiological process, takes many years. Even when this is achieved, the clinical and approval stage takes close to a decade. Perhaps as important as understanding these time limitations, is acknowledging that the vast majority of therapies that transition from preclinical to clinical stages fail to make it to market.

So, given these hurdles, why are we pursuing genetics? Despite these limitations, we truly believe that the best possible route to treating this complex disease is to understand what goes wrong at the molecular level, and to use this knowledge to reverse, halt, or slow this process. Although the first genetic finding was made in PD more than 15 years ago, we still consider this early days in terms of therapeutic design. While there is a long way to go, we are clearly a lot further along the road to a cure than when we started, and the continued addition of new genetic findings can only take us further down this path.

Conclusions

Continued success in identifying the genetic causes and contributors for PD risk is providing the basic research community with increasing insight into the genetic and molecular basis of this complex disease. We believe that using these findings is the fields best hope in revealing the molecular pathogenesis of PD and identifying a therapy bases on etiology. As history has shown, translation of these genetics findings is extremely difficult and time consuming; however, we predict that this course will become easier with time and the benefit of more gene targets to place into the paradigm.

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Authors Role

Drs. Singleton, Bonifati and Farrer each contributed to initial drafting and critical revision of this manuscript.

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References

1. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997; 276(5321):2045–2047. [PubMed: 9197268]
2. Singleton A, Hardy J. A generalizable hypothesis for the genetic architecture of disease: pleomorphic risk loci. Hum Mol Genet. 2011; 20(R2):R158–162. [PubMed: 21875901]
3. Ibanez P, Lesage S, Janin S, et al. Alpha-synuclein gene rearrangements in dominantly inherited parkinsonism: frequency, phenotype, and mechanisms. Arch Neurol. 2009; 66(1):102–108. [PubMed: 19139307]
4. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004; 55(2):164–173. [PubMed: 14755719]
5. Seidel K, Schols L, Nuber S, et al. First appraisal of brain pathology owing to A30P mutant alpha-synuclein. Ann Neurol. 2010; 67(5):684–689. [PubMed: 20437567]
6. Ross OA, Braithwaite AT, Skipper LM, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. Ann Neurol. 2008; 63(6):743–750. [PubMed: 18571778]
7. Ahn TB, Kim SY, Kim JY, et al. alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008; 70(1):43–49. [PubMed: 17625105]
8. Paisan-Ruiz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron. 2004; 44(4):595–600. [PubMed: 15541308]
9. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron. 2004; 44(4):601–607. [PubMed: 15541309]
10. Gasser T. Molecular pathogenesis of Parkinson disease: insights from genetic studies. Expert Rev Mol Med. 2009; 11:e22. [PubMed: 19631006]

11. Aasly JO, Vilarino-Guell C, Dachsel JC, et al. Novel pathogenic LRRK2 p. Asn1437His substitution in familial Parkinson's disease. Mov Disord. 2010; 25(13):2156–2163. [PubMed: 20669305]
12. Di Fonzo A, Tassorelli C, De Mari M, et al. Comprehensive analysis of the LRRK2 gene in sixty families with Parkinson's disease. Eur J Hum Genet. 2006; 14(3):322–331. [PubMed: 16333314]
13. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008; 7(7):583–590. [PubMed: 18539534]
14. Bonifati V. LRRK2 low-penetrance mutations (Gly2019Ser) and risk alleles (Gly2385Arg)-linking familial and sporadic Parkinson's disease. Neurochem Res. 2007; 32(10):1700–1708. [PubMed: 17440812]
15. Haugarvoll K, Rademakers R, Kachergus JM, et al. Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease. Neurology. 2008; 70(16 Pt 2):1456–1460. [PubMed: 18337586]
16. Simon-Sanchez J, Marti-Masso JF, Sanchez-Mut JV, et al. Parkinson's disease due to the R1441G mutation in Dardarin: a founder effect in the Basques. Mov Disord. 2006; 21(11):1954–1959. [PubMed: 16991141]
17. Goldwurm S, Zini M, Mariani L, et al. Evaluation of LRRK2 G2019S penetrance: relevance for genetic counseling in Parkinson disease. Neurology. 2007; 68(14):1141–1143. [PubMed: 17215492]
18. Latourelle JC, Sun M, Lew MF, et al. The Gly2019Ser mutation in LRRK2 is not fully penetrant in familial Parkinson's disease: the GenePD study. BMC Med. 2008; 6:32. [PubMed: 18986508]
19. Bonifati V, Rohe CF, Breedveld GJ, et al. Early-onset parkinsonism associated with PINK1 mutations: frequency, genotypes, and phenotypes. Neurology. 2005; 65(1):87–95. [PubMed: 16009891]
20. Djarmati A, Hedrich K, Svetel M, et al. Detection of Parkin (PARK2) and DJ1 (PARK7) mutations in early-onset Parkinson disease: Parkin mutation frequency depends on ethnic origin of patients. Hum Mutat. 2004; 23(5):525. [PubMed: 15108293]
21. Lucking CB, Durr A, Bonifati V, et al. Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med. 2000; 342(21):1560–1567. [PubMed: 10824074]
22. Di Fonzo A, Dekker MC, Montagna P, et al. FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology. 2009; 72(3):240–245. [PubMed: 19038853]
23. Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol. 2009; 65(1):19–23. [PubMed: 18570303]
24. Ramirez A, Heimbach A, Grundemann J, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006; 38(10): 1184–1191. [PubMed: 16964263]
25. Kumazawa R, Tomiyama H, Li Y, et al. Mutation analysis of the PINK1 gene in 391 patients with Parkinson disease. Arch Neurol. 2008; 65(6):802–808. [PubMed: 18541801]
26. Klein C, Lohmann-Hedrich K, Rogaeva E, Schlossmacher MG, Lang AE. Deciphering the role of heterozygous mutations in genes associated with parkinsonism. Lancet Neurol. 2007; 6(7):652–662. [PubMed: 17582365]
27. Hattori N, Shimura H, Kubo S, et al. Autosomal recessive juvenile parkinsonism: a key to understanding nigral degeneration in sporadic Parkinson's disease. Neuropathology. 2000; 20 (Suppl):S85–90. [PubMed: 11037196]
28. Samaranch L, Lorenzo-Betancor O, Arbelo JM, et al. PINK1-linked parkinsonism is associated with Lewy body pathology. Brain. 2010; 133(Pt 4):1128–1142. [PubMed: 20356854]
29. Lohmann E, Periquet M, Bonifati V, et al. How much phenotypic variation can be attributed to parkin genotype? Ann Neurol. 2003; 54(2):176–185. [PubMed: 12891670]
30. Zimprich A, Benet-Pages A, Struhal W, et al. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet. 2011; 89(1):168–175. [PubMed: 21763483]
31. Vilarino-Guell C, Wider C, Ross OA, et al. VPS35 mutations in Parkinson disease. Am J Hum Genet. 2011; 89(1):162–167. [PubMed: 21763482]

32. Farrer MJ, Hulihan MM, Kachergus JM, et al. DCTN1 mutations in Perry syndrome. Nat Genet. 2009; 41(2):163–165. [PubMed: 19136952]
33. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011; 72(2):257–268. [PubMed: 21944779]
34. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72(2):245–256. [PubMed: 21944778]
35. Chartier-Harlin MC, Dachsel JC, Vilarino-Guell C, et al. Translation initiator EIF4G1 mutations in familial Parkinson disease. Am J Hum Genet. 2011; 89(3):398–406. [PubMed: 21907011]
36. Yang Y, Gehrke S, Imai Y, et al. Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of Drosophila Pink1 is rescued by Parkin. Proc Natl Acad Sci U S A. 2006; 103(28):10793–10798. [PubMed: 16818890]
37. Narendra DP, Jin SM, Tanaka A, et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 2010; 8(1):e1000298. [PubMed: 20126261]
38. Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol. 2008; 183(5):795–803. [PubMed: 19029340]
39. Geisler S, Holmstrom KM, Skujat D, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol. 2010; 12(2):119–131. [PubMed: 20098416]
40. Matsuda N, Sato S, Shiba K, et al. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. J Cell Biol. 2010; 189(2):211–221. [PubMed: 20404107]
41. Vives-Bauza C, Zhou C, Huang Y, et al. PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. Proc Natl Acad Sci U S A. 2010; 107(1):378–383. [PubMed: 19966284]
42. Jin SM, Youle RJ. PINK1- and Parkin-mediated mitophagy at a glance. J Cell Sci. 2012; 125(Pt 4): 795–799. [PubMed: 22448035]
43. Deas E, Wood NW, Plun-Favreau H. Mitophagy and Parkinson's disease: the PINK1-parkin link. Biochim Biophys Acta. 2011; 1813(4):623–633. [PubMed: 20736035]
44. Bender A, Krishnan KJ, Morris CM, et al. High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat Genet. 2006; 38(5):515–517. [PubMed: 16604074]
45. McCormack AL, Mak SK, Henderson JM, Bumcrot D, Farrer MJ, Di Monte DA. Alpha-synuclein suppression by targeted small interfering RNA in the primate substantia nigra. PLoS One. 2010; 5(8):e12122. [PubMed: 20711464]
46. Kruger R, Vieira-Saecker AM, Kuhn W, et al. Increased susceptibility to sporadic Parkinson's disease by a certain combined alpha-synuclein/apolipoprotein E genotype. Ann Neurol. 1999; 45(5):611–617. [PubMed: 10319883]
47. Maraganore DM, de Andrade M, Elbaz A, et al. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. JAMA. 2006; 296(6):661–670. [PubMed: 16896109]
48. Neudorfer O, Giladi N, Elstein D, et al. Occurrence of Parkinson's syndrome in type I Gaucher disease. QJM. 1996; 89(9):691–694. [PubMed: 8917744]
49. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2004; 351(19):1972–1977. [PubMed: 15525722]
50. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009; 361(17):1651–1661. [PubMed: 19846850]
51. Mata IF, Kachergus JM, Taylor JP, et al. Lrrk2 pathogenic substitutions in Parkinson's disease. Neurogenetics. 2005; 6(4):171–177. [PubMed: 16172858]
52. Tan EK. The role of common genetic risk variants in Parkinson disease. Clin Genet. 2007; 72(5): 387–393. [PubMed: 17868389]
53. Ross OA, Wu YR, Lee MC, et al. Analysis of Lrrk2 R1628P as a risk factor for Parkinson's disease. Ann Neurol. 2008; 64(1):88–92. [PubMed: 18412265]

54. Ross OA, Soto-Ortolaza AI, Heckman MG, et al. Association of LRRK2 exonic variants with susceptibility to Parkinson's disease: a case-control study. Lancet Neurol. 2011; 10(10):898–908. [PubMed: 21885347]
55. Maraganore DM, de Andrade M, Lesnick TG, et al. High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet. 2005; 77(5):685–693. [PubMed: 16252231]
56. Liu X, Cheng R, Verbitsky M, et al. Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. BMC Med Genet. 2011; 12:104. [PubMed: 21812969]
57. Do CB, Tung JY, Dorfman E, et al. Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. PLoS Genet. 2011; 7(6):e1002141. [PubMed: 21738487]
58. Nalls MA, Plagnol V, et al. International Parkinson Disease Genomics C. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011; 377(9766):641–649. [PubMed: 21292315]
59. Simon-Sanchez J, van Hilten JJ, van de Warrenburg B, et al. Genome-wide association study confirms extant PD risk loci among the Dutch. Eur J Hum Genet. 2011; 19(6):655–661. [PubMed: 21248740]
60. Saad M, Lesage S, Saint-Pierre A, et al. Genome-wide association study confirms BST1 and suggests a locus on 12q24 as the risk loci for Parkinson's disease in the European population. Hum Mol Genet. 2011; 20(3):615–627. [PubMed: 21084426]
61. Edwards TL, Scott WK, Almonte C, et al. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. Ann Hum Genet. 2010; 74(2):97–109. [PubMed: 20070850]
62. Satake W, Nakabayashi Y, Mizuta I, et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat Genet. 2009; 41(12):1303–1307. [PubMed: 19915576]
63. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009; 41(12):1308–1312. [PubMed: 19915575]
64. Fung HC, Scholz S, Matarin M, et al. Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. Lancet Neurol. 2006; 5(11):911–916. [PubMed: 17052657]
65. Latourelle JC, Pankratz N, Dumitriu A, et al. Genomewide association study for onset age in Parkinson disease. BMC Med Genet. 2009; 10:98. [PubMed: 19772629]
66. Pankratz N, Wilk JB, Latourelle JC, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet. 2009; 124(6):593–605. [PubMed: 18985386]
67. International Parkinson's Disease Genomics Consortium, Wellcome Trust Case Control Consortium. A two-stage meta-analysis identifies several new loci for Parkinson's disease. PLoS Genet. 2011; 7(6):e1002142. [PubMed: 21738488]
68. Spencer CC, et al. UK Parkinson's Disease Consortium, Wellcome Trust Case Control Consortium. Dissection of the genetics of Parkinson's disease identifies an additional association 5′ of SNCA and multiple associated haplotypes at 17q21. Hum Mol Genet. 2011; 20(2):345–353. [PubMed: 21044948]
69. Hill-Burns EM, Factor SA, Zabetian CP, Thomson G, Payami H. Evidence for More than One Parkinson's Disease-Associated Variant within the HLA Region. PLoS One. 2011; 6(11):e27109. [PubMed: 22096524]
70. Hardy J, Singleton A. Genomewide association studies and human disease. N Engl J Med. 2009; 360(17):1759–1768. [PubMed: 19369657]
71. Evans W, Fung HC, Steele J, et al. The tau H2 haplotype is almost exclusively Caucasian in origin. Neurosci Lett. 2004; 369(3):183–185. [PubMed: 15464261]
72. Hindorff LA, Sethupathy P, Junkins HA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci U S A. 2009; 106(23):9362–9367. [PubMed: 19474294]

73. Nalls MA, Plagnol V, et al. International Parkinson Disease Genomics Consortium. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011; 377(9766):641–649. [PubMed: 21292315]
74. Singleton AB, Farrer M, Johnson J, et al. alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003; 302(5646):841. [PubMed: 14593171]
75. Chu Y, Kordower JH. Age-associated increases of alpha-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: Is this the target for Parkinson's disease? Neurobiol Dis. 2007; 25(1):134–149. [PubMed: 17055279]
76. Nobre RJ, Almeida LP. Gene therapy for Parkinson's and Alzheimer's diseases: from the bench to clinical trials. Curr Pharm Des. 2011; 17(31):3434–3445. [PubMed: 21902665]
77. Ramaswamy S, Kordower JH. Gene therapy for Huntington's disease. Neurobiol Dis. 2011
78. Gibbs JR, van der Brug MP, Hernandez DG, et al. Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. PLoS Genet. 2010; 6(5):e1000952. [PubMed: 20485568]
79. Hamza TH, Zabetian CP, Tenesa A, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet. 2010; 42(9):781–785. [PubMed: 20711177]
80. van der Walt JM, Noureddine MA, Kittappa R, et al. Fibroblast growth factor 20 polymorphisms and haplotypes strongly influence risk of Parkinson disease. Am J Hum Genet. 2004; 74(6):1121–1127. [PubMed: 15122513]
81. Skipper L, Li Y, Bonnard C, et al. Comprehensive evaluation of common genetic variation within LRRK2 reveals evidence for association with sporadic Parkinson's disease. Hum Mol Genet. 2005; 14(23):3549–3556. [PubMed: 16269443]
82. Pastor P, Ezquerra M, Munoz E, et al. Significant association between the tau gene A0/A0 genotype and Parkinson's disease. Ann Neurol. 2000; 47(2):242–245. [PubMed: 10665497]

Table 1

Risk loci for Parkinson's disease, indicating location, minor allele frequency (MAF) and odds ratio (OR), primarily calculated under an additive model. Included are references to papers that initially implicated these loci, and those that proved association (based on genome wide significance).

Chromosome	Gene Names*	MAF	OR	Initially Implicated	Genome Wide Significance**
1q21	*GBA*	0.01	5.43	Neudorfer et al[48]	Sidransky et al[50]
1q21.2	*SYT11*	0.02	1.44	Nalls et al[73]	Nalls et al[73]
1q32	*RAB7L1*	0.44	0.86	Satake et al[62]	Satake et al[62]
2q21.3	*ACMSD*	0.19	1.07	Nalls et al[73]	Nalls et al[73]
2q24.3	*STK39*	0.13	1.12	Nalls et al[73]	Nalls et al[73]
3q27	*MCCC1/LAMP3*	0.14	0.87	Nalls et al[73]	Nalls et al[73]
4p15	*BST1*	0.45	0.87	Satake et al[62]	Satake et al[62]
4p16	*GAK*	0.28	1.14	Pankratz et al[66]	Nalls et al[73]
4q21	*SNCA*	0.39	1.27	Kruger et al[46]	Simon-Sanchez et al; Satake et al[62, 63]
4q21.1	*SCARB2*	0.37	0.90	Do et al[57]	Do et al[57]
4q21.1	*STBD1*	0.36	0.91	IPDGC[67]	IPDGC[67]
6p21.3	*HLA-DRB5*	0.15	0.80	Hamza et al[79]	Hamza et al[79]
7p15	*GPNMB*	0.40	0.89	IPDGC[67]	IPDGC[67]
8p22	*FGF20*	0.27	0.88	Van der Walt et al[80]	IPDGC[67]
12q12	*LRRK2*	0.21	1.30	Skipper et al [81]	Satake et al[62]
12q24	*CCDC62/HIP1R*	0.46	1.13	Nalls et al[73]	Nalls et al [73]
16p11.2	*STX1B*	0.41	1.15	IPDGC[67]	IPDGC[67]
17p11.2	*SREBF1*	0.31	0.95	Do et al[57]	Do et al[57]
17q21.1	*MAPT*	0.22	0.80	Pastor et al[82]	Simon-Sanchez et al[63]

*this does not imply that this gene is the biologically mediator of association, but is used for ease of annotation

**based on $p < 5 \times 10^{-8}$