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Association Studies of Sporadic Parkinson's Disease in the Genomic Era

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Abstract: Parkinson's disease is a common age-related progressive neurodegenerative disorder. Over the last 10 years, advances have been made in our understanding of the etiology of the disease with the greatest insights perhaps coming from genetic studies, including genome-wide association approaches. These large scale studies allow the identification of genomic regions harboring common variants associated to disease risk. Since the first genome-wide association study on sporadic Parkinson's disease performed in 2005, improvements in study design, including the advent of meta-analyses, have allowed the identification of ~21 susceptibility loci. The first loci to be nominated were previously associated to familial PD (*SNCA*, *MAPT*, *LRRK2*) and these have been extensively replicated. For other more recently identified loci (*SREBF1, SCARB2, RIT2*) independent replication is still warranted. Cumulative risk estimates of associated variants suggest that more loci are still to be discovered. Additional association studies combined with deep re-sequencing of known genome-wide association study loci are necessary to identify the functional variants that drive disease risk. As each of these associated genes and variants are identified they will give insight into the biological pathways involved the etiology of Parkinson's disease. This will ultimately lead to the identification of molecules that can be used as biomarkers for diagnosis and as targets for the development of better, personalized treatment.

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INTRODUCTION

Parkinson's disease (PD) is an age-related multisystem disorder that manifests with motor and non-motor symptoms, significantly impacting a patient's quality of life. It is one of the most common neurological disorders affecting approximately 1% of people over 60 years of age [1]. The defining pathologic features of PD are aggregations of the α-synuclein protein that form cytoplasmic inclusions in neurons called Lewy bodies and loss of dopaminergic neurons in the *substantia nigra* of the brain [2]. Genetic studies have shown that PD is in fact a heterogeneous group of diseases with a range of clinical presentations. Approximately 10 to 20% of patients report a positive family history of PD, and of those, a minority (about 5-10% overall) have a known monogenic form of disease with dominant or recessive inheritance [3, 4]. The vast majority of patients suffer from sporadic PD which is often described as a complex disorder triggered by the interaction of genetic and environmental risk factors. One hypothesis is that sporadic PD is caused by the combined effects of common genetic variants with low penetrance; the common disease-common variant hypothesis. Over the last decade population-based genetic association studies that compare the frequencies of variants between groups of unrelated patients and controls have been focussed on the detection of these common risk variants.

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The publication of the complete sequence of the human genome [5, 6], the creation of the HapMap project [7], as well as technical advances such as the development of microarrays, provided the foundation for the development of large-scale population based genotyping studies that were designated as genome-wide association studies (GWAS). GWA approaches revolutionized the study of complex disorders by shifting the methodology away from candidate gene or hypothesis driven association studies to unbiased discovery driven studies. GWAS allowed for the genotyping of a limited number of variants - tagging the common variability of the entire genome - in one single microarray experiment. In principle, this approach would lead to the identification of new disease causing genes, new biological pathways to explain disease origin or progression, and potential therapeutic targets.

Although the results of the initial GWAS in PD were disappointing with studies which had low power to detect association signals, as technology improved and sample size increased, more genomic loci were found to alter disease risk. The first common variants associated to PD in the GWAS were located in genes previously recognized through linkage studies to harbor rare penetrant mutations causing familial forms of parkinsonism. Recent meta-analyses have been even more successful in identifying risk loci. To date, ~21 loci have been identified to affect the individual risk of PD but estimations of phenotypic variance suggest that many more are still to be discovered.

FIRST GWAS HAD LOW POWER OF DETECTION

The early GWAS to be published were plagued by several problems: the SNP genome coverage of the first chips

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was low, the sample size of the studies was often too small (a few hundred patients) and patient-control series were sometimes mismatched. These characteristics contributed to a low power of detecting the association signals of modest impact risk factors to complex diseases (predicted to increase risk by a factor of 1.1 to 1.5 per associated allele) [8].

The first PD GWAS study was published in 2005 by Maraganore *et al.* [9] The US team genotyped ~200,000 SNPs in 413 sib pairs discordant for PD. No association signal reached genome-wide significance. Soon after, a team from the National Institute of Health published the result of their GWAS performed in 267 PD patients and 270 controls [10]. None of the 408,000 SNPs genotyped showed a statistically significant association signal. In 2009, Pankratz and colleagues published the result of their study performed in 857 patients with familial PD and 867 controls [11]. Although several suggestive association signals were detected (some of which would later be replicated with genome-wide significance), none reached genome-wide significance in this specific study. The same group published another paper describing a GWAS that combined data from their first familial PD GWAS and an additional 440 patients with idiopathic PD [12]. The analysis of this GWA data was focused on identifying the genetic contribution to age at onset, however as with the case-control approaches no signal reached genome-wide significance.

FAMILIAL GENES AND NEW PD GENES

These first discoveries can be attributed to improved study design as the next wave of GWAS had generally larger sample sizes (from a couple of hundred samples to over a thousand). This increase improved the capacity to detect modest signal and discoveries of genes associated to sporadic PD were made with this approach. The first variants associated to PD detected by GWAS are located in genes previously identified to cause familial forms of parkinsonism: *SNCA*, *MAPT* and *LRRK2*. In fact, the association between PD and genetic variation in the *SNCA* and *MAPT* regions were already well established through linkage and targeted association studies. This observation supports common risk genes for familial and sporadic PD. Following a GWAS, Simón-Sánchez *et al.* [13] identified a variant in the *SNCA* gene (rs2736990, OR = 1.23, $P = 2.24 \times 10^{-16}$) encoding α-synuclein (the major protein component of Lewy bodies) and another near the *MAPT* gene (rs393152, OR = 0.77, $P = 1.95 \times 10^{-16}$) encoding the tau protein. Of note, aggregation of hyperphosphorylated tau protein is observed in the brain of patients suffering from tauopathy disorders including Alzheimer's disease and progressive supranuclear palsy [14]. Simón-Sánchez *et al.* screened 1713 patients with PD and 3978 controls of European ancestry and replicated their findings in 3361 patients and 4573 controls. Published back-to-back with Simón-Sánchez *et al.*, the study of Satake *et al.* [15] reported a GWAS in a discovery cohort consisting of 988 PD patients and 2521 controls from Japan. The authors identified a variant in *LRRK2*, another gene which had been previously linked with Mendelian forms of PD [16]. Several other groups have also shown association to the known autosomal dominant familial genes (*LRRK2*, *SNCA*, and *MAPT*) [17-20].

Satake *et al.* also identified variants on chromosome 1q32 (designated as *PARK16*) and around the gene bone marrow stromal cell antigen (*BST1*) on chromosome 4p15. Simón-Sánchez *et al.* and Satake *et al.* attempted the replication of each other's findings in their respective series. *PARK16* and *LRRK2* were found to be associated in both populations, *BST1* was not replicated in Europeans at this time whereas *MAPT* was not replicated in the Japanese study. Lack of power in the studies could possibly explain that these loci were not replicated at this point; however the authors propose that inter-population heterogeneity at the *MAPT* locus is the reason why it was not nominated in Asians. Two major *MAPT* haplotype exist, H1 and H2, but H2 is not generally present in East Asians. This observation helps demonstrate the possible effects of population heterogeneity in characterizing the genetic etiology of PD.

In 2010, Hamza *et al.* performed a GWAS in 2000 PD patients and 1986 controls from the US, genotyping a total of 811,597 SNPs [21]. Their main novel finding was an association with the human leukocyte antigen (HLA) region, which supported a link between the immune system and the pathophysiology of PD. This link has since then been reinforced by an *in silico* pathway-based analysis of the findings from PD GWAS [22]. More specifically, Holmans *et al.* used an algorithm to analyze the associated SNPs (even those that did not reach genome-wide significance) from two GWAS for enrichment in functionally related genes. They observed that these SNPs were, more often than could be expected by chance, located in genes involved in 'regulation of leucocyte/lymphocyte activity' and 'cytokine-mediated signaling'. In addition, expression of immune modulators has been shown to be up-regulated in PD patients but it is unclear if the immune reaction is a cause or consequence of the neuronal damage [23, 24]. Nevertheless, the association to the HLA region and the additional functional studies support a role for the immune response in the etiology of PD.

Hamza *et al.* also supported suggestive associations from previous GWAS and identified *GAK* encoding cyclin G–associated kinase that was previously proposed as a risk gene in Pankratz *et al.* [11]. GAK is involved in the regulation of the cell cycle and interestingly a gene expression profiling study has reported that *GAK* is differentially expressed in patients with PD compared to controls [25].

23andMe, a biotechnology company offering personal genome tests to assess inherited traits, disease risk, and genealogy, performed a PD GWAS with a cohort of patients recruited through email solicitation [17]. Interested individuals were invited to fill out a form indicating personal information such as the name of their doctor and their year of diagnosis, and were offered the 23andMe genome services for a nominal fee. The main strength of this approach is that 23andMe was able to recruit a large sample, collecting 3426 patient and 29624 control samples over an 18 month period of time; on the other hand, the main weakness is that the accuracy of the clinical information, derived from surveys, is questionable. However, the analysis confirmed association to many genes identified in previous GWAS, (including *MAPT*, *LRRK2*, *SNCA*, *GAK*, and the HLA locus) which seems to validate their approach. They also nominated *GBA*, a gene which encodes enzyme glucocerebrosidase. Specific reces-

sive *GBA* mutations cause Gaucher's disease, a rare lysosomal storage disorder. *GBA* was first recognized in PD when it was observed that a subset of Gaucher's disease patients suffered from parkinsonian symptoms and that about 25% of them had a first or second degree relative with PD. Family members affected with PD were found to be heterozygous carriers of the *GBA* mutations [26]. To assess the importance of the *GBA* mutations in PD, several PD series have since then been screened; carriers represent 10.7% to 31.3% of Ashkenazi Jewish (AJ) patients and 2.3% to 9.4% of patients of other ethnicity [27]. A study performed on AJ patients identified a *GBA* risk haplotype carrying the N370S substitution which is suggested to be due to a common founder [28]. Of note, *GBA* is located on chromosome 1q21 near a pseudogene with 96% sequence identity and as such, is not detectable by usual GWA approaches. Rare variants located on different haplotypes need to be specifically typed. In the case of the 23andMe GWAS, specific *GBA* SNPs were added on the array. 23andMe also nominated two new loci: 4q21.1 near *SCARB2* and 17p11 near *SREBF1* and *RAI1*, however associations to these new loci have yet to be replicated independently.

The GWA approaches described previously have mostly been performed on patients with late onset PD or were not discriminating between patients with late and early onset PD. Since the disease develops earlier, early onset diseases are thought to be influenced by genetic variants with stronger effect sizes than late onset disease genes. Some groups have undertaken GWAS on early onset PD patients in order to find monogenic or recessive risk factors with varying degrees of success. Hernandez *et al.* performed a GWAS on 387 Finnish early onset PD patients (less than 55 years old) and 496 controls; no significant associations were observed [29]. Simón-Sánchez *et al.* looked at region of excessive homozygosity (which would pinpoint to risk genes) in 1445 early onset PD patients and 6987 controls [30]. They found increased homozygosity in the 19p13.3 chromosomal region in patients compared to controls but were unable to identify a specific gene after sequencing the locus.

TRANSITION TO META-ANALYSES

Following the first round of success at identifying risk genes in GWAS performed in larger cohorts, research groups began to pool their data together in order to achieve a greater power to identify genes with modest impact on disease risk. Three meta-analyses were published in a matter of months by collaborating groups, while these studies are not independent - a lot of genotyping data overlap from the earlier independent GWAS studies (see Fig. **1**) – each identified at least one novel association signal. The first of these meta-analyses published in 2011 [31] by the International Parkinson Disease Genomics Consortium (IPDGC) pooled data from five PD GWAS from the USA and Europe [10, 11, 13, 18, 19, 32]. The discovery phase consisted of 5333 patient samples and 12019 control samples and the follow-up consisted of 7053 case and 9007 control samples (the samples were pooled from the replication phase of the five GWAS and from the discovery phase of [32]). Eleven loci reached genome-wide significance, six were previously nominated (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2*) and five were novel (*ACMSD*, *STK39*, *MCCC1*/*LAMP3*, *SYT11*, and *CCDC62*/*HIP1R*). The cumulated population attributable risk for these loci was calculated to be ~60% [31]. In an attempt to capture the missing loci, the IPDGC followed up on loci that had not quite reach genome-wide significance in the first meta-analysis ($10^{-8}>p>10^{-3}$) [33]. To reach power to detect these association signals with genome-wide significance, they combined data from their discovery and follow-up stages, and attempted to replicate their findings in the independent study sample of 23andMe [17]. In this combined analysis, four new loci reached genome-wide significance the strongest candidate at these loci are *STX1B*, *FGF20* (which was previously reported in a candidate-gene study performed in a large family [34]), *STBD1*, and *GPNMB*. They also were the first to report a genome-wide significant association to the *PARK16* locus in Europeans.

In order to follow-up all the suggestive genetic associations to PD that were not included in replication phases because they did not reach genome-wide significance, Lill *et al.* catalogued and meta-analyzed association study data from ~27,000 published articles on the PD gene website (http://www.pdgene.org) [35]. For the Lill *et al.* publication, data was pooled from both candidate gene studies and all previously published GWAS on Caucasians. SNP data was imputed which yielded a total of 7 million SNP from up to 16,452 PD patients and 48,810 controls. Eleven loci were replicated and a new locus was identified: *ITGA8*. The gene, *ITGA8*, encodes integrin α 8, a cell-cell interaction protein expressed in several different tissue and cell types (BioGPS.org). Interestingly, two loci that showed association with PD in previous GWAS, the HLA and *ACMSD* did not reach genome-wide significance in Lill *et al.*

The most recent meta-analysis was published by Pankratz *et al.* and included data from five GWAS for a total of 4230 patients with PD and 4239 controls in the discovery set [10, 11, 13, 20, 21]. The authors replicated associations to *SNCA*, *MAPT*, *GAK* and the HLA region. Following a combined analysis of their discovery and replication sets (~8000 patients with PD); a novel gene, *RIT2*, reached genome-wide significance. Interestingly, protein interaction assays suggest that the RIT2 protein interacts with tau and α-synuclein via the protein calmodulin [36-38]. However this genetic association has not yet been replicated independently.

NEED FOR INDEPENDENT REPLICATION

Genetic association studies are mainly a game of numbers. Significance thresholds are nominated but studies are not protected against spurious associations (false positives). Additionally, no GWA study yet has had perfect power to identify every association and each time some loci are missed (false negatives). In this context, and considering most recent meta-analyses have overlapping samples (see Fig. **1**), it is particularly important to perform independent replication studies to confirm loci. To date, two published studies attempted to do this in PD. Sharma *et al.* performed a replication study using a case-control series of 8750 cases and 8955 controls from 21 sites in 19 countries collected by members of the Genetic Epidemiology of PD (GEO-PD) consortium [39]. Of those, 1625 samples overlap with previous GWAS but the authors declare that removing them of the analysis has no consequence on risk estimates. One SNP for

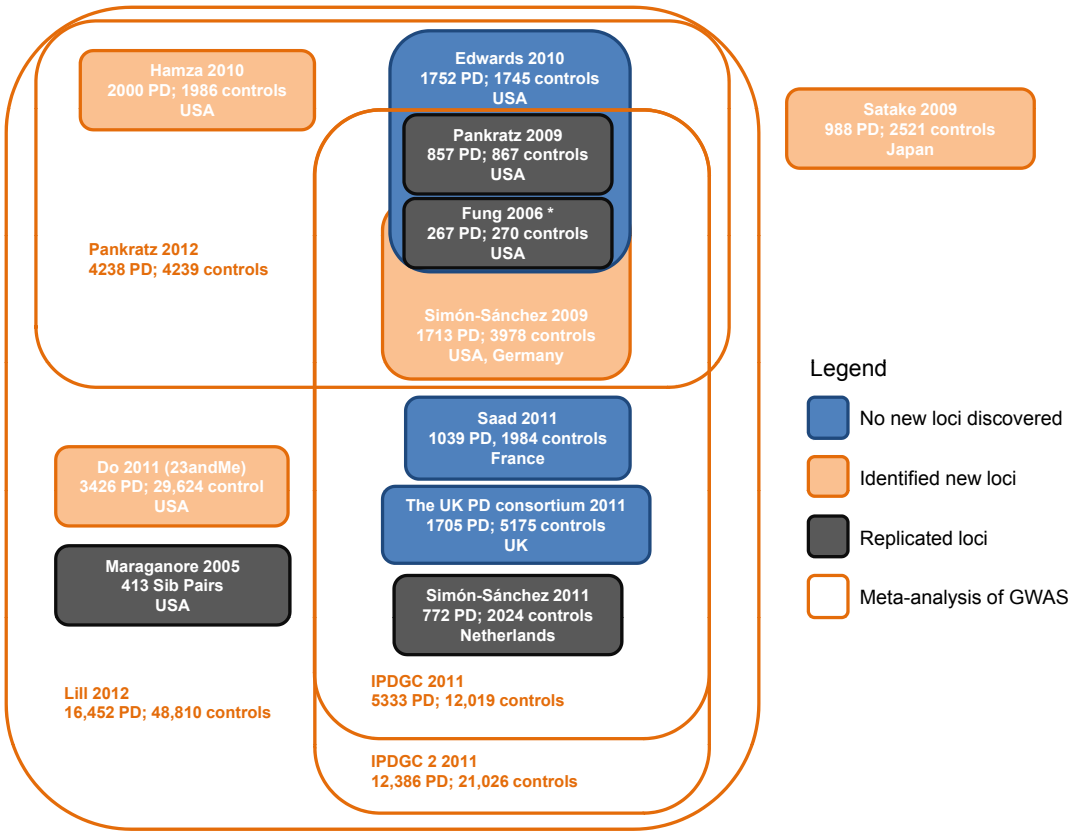

Fig. (1). Overlap in discovery samples of published PD GWAS and meta-analyses.

Each rounded rectangle represents a GWAS in PD or a meta-analysis of GWAS. The reference, the number of samples in the discovery phase, and the country of origin of the samples used are included in the rectangles. The color of the rectangle reflects the findings of the study: no new identified loci, identified loci with genome-wide significance, and replication of previously identified loci (see legend for color chart). Differences between sample size of a meta-analysis and individual GWAS are due to quality control differences. The discovery sample of IPDGC2 includes both the discovery and the replication samples of IPDGC. * The Fung *et al.* sample set is part of the replication phase of IPDGC 2011.

each of the eleven locus nominated by the IPDGC study was tested [33]. Association to nine loci was replicated (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, *HIP1R*, *LAMP3*, *BST1*, and *MAPT*); two loci were not confirmed *ACMSD* and *HLA-DRB5*. The authors suggest that association to *ACMSD* in the IPDGC study was a false positive. On the other hand, they suggests that lack of association to *HLA-DRB5* in their replication study is due to population-specific variation in allele frequencies (and only SNP rs3129882 was tested) within the European population and should not be interpreted as meaning that this association is false.

A second replication study was published by Pihlstrøm *et al.* [40] The study was performed on 1345 PD patients and 1225 controls from Norway and Sweden. The authors genotyped 18 loci previously associated with genome-wide significance in GWAS as well as three additional suggestive loci (*USP25*, *NMD3*, *MMP16*). Associations to *SNCA*, *STK39*, *MAPT*, and *GPNMB* were replicated with Bonferroni-corrected significance (here $p < 0.0023$) and associations to *CCDC62*/*HIP1R*, *SYT11*, *GAK*, *STX1B*, *MCCC1*/*LAMP3*, *ACMSD*, and *FGF20* were replicated at nominal significance ($p < 0.05$). Given the homogenous nature of the series from Norway and Sweden, genetic heterogeneity across other Caucasian populations might explain why some loci were not found to be associated in this study.

In addition, there have been a few smaller studies focusing on single loci such as *RAB7L1* in the *PARK16* region [41] and *SCARB2* in chromosomal region 4q21 [42, 43] which confirmed association to the locus tested.

LESSONS FROM GWAS IN PD

Sporadic PD was not traditionally recognized as a genetic disease but the described population-based association studies have since challenged this view. Studies calculate PD heritability to be around 25% [17]. To date, GWAS and meta-analyses have identified at least 21 loci associated with genome-wide significance to the susceptibility to PD (see Table **1**). Meta-analyses have improved their power to detect association signals but no single study has identified all known genes with genome-wide significance. This observation implies that improvement in study design is possible and needed (larger sample size, cohorts with more homogenous phenotypes). Associations to *LRRK2*, *SNCA*, *MAPT*, and a handful of other loci have been confirmed in several studies

Table 1. PD Loci Identified in GWAS and Meta-analyses.

Locus	Gene(s) of Interest	Reference
GBA (1q22)	*GBA*	Do *et al.* [17]
1q21-22	*SYT11, RAB*	IPDGC [31]
1q32 (*PARK16*)	*RAB7L1*	Satake *et al.* [15]
2q21.3	*ACMSD*	IPDGC [31]
2q24.3	*STK39, B3GALT1, CERS6*	IPDGC [31]
3q26-27	*MCCC1, LAMP3*	IPDGC [31]
4p15	*BST1*	Satake *et al.* [15]
4p16	*DGKQ, GAK*	Hamza *et al.* [21]
4q21	*SNCA*	Simón-Sánchez *et al.* [13]
	SCARB2	Do *et al.* [17]
	STBD1	IPDGC2 [33]
6p21.3	*HLA* class II region	Hamza *et al.* [21]
7p15	*GPNMB*	IPDGC2 [33]
8p22	*FGF20*	IPDGC2 [33]
10p13	*ITGA8*	Lill *et al.* [35]
12q12	*LRRK2*	Satake *et al.* [15]
12q24	*CCDC62, HIP1R*	IPDGC [31]
16p11	*STX1B*	IPDGC2 [33]
17p11	*SREBF1, RAI1*	Do *et al.* [17]
17q21	*MAPT, STH*	Simón-Sánchez *et al.* [13]
18q12.3	*RIT2*	Pankratz *et al.* [53]

but independent replication of others (e.g. *SCARB2*, *SREBF1*, *RIT2*) is still warranted. Furthermore, current estimations of the proportion of PD heritability that can be explained by SNPs tested directly or indirectly by GWAS (whether they were found to be associated or not) suggest that most of the heritability has yet to be identified. In a meta-analysis of GWAS, Keller *et al.* calculated that 27% of the phenotypic variance is explained for PD in general, 15% for early-onset PD and 24% for late-onset PD [44]. The missing heritability is expected to be to be hidden in common modest effect variants located in loci still unknown but also in rare variants such as the *GBA* mutations located in both known and unknown loci and in variants that are not traditionally well captured by current genotyping and sequencing platforms. Little work has been done on copy number variants (CNVs) but evidence from monogenic PD forms indicates that this should be looked at more closely. For example, triplications of the *SNCA* gene have been shown to cause an aggressive form of PD and deletions of *PINK1*, *PRKN*, and *DJ-1* are also known to cause recessive forms of PD [45-48]. Pankratz *et al.* used the genotypes from their previous GWAS [11] and two CNV calling algorithms to detect large regions of duplications or deletions [49]. CNVs within the *PARK2* locus were found to be associated with risk of disease, although the true impact of CNVs in PD remains to be resolved.

NEXT STEPS

GWAS typically identify a genomic region of association but they do not necessarily identify specific variants or even genes related to disease susceptibility. More often than not, an associated region will be large and include several genes or on the contrary be a gene desert. This is because SNPs tested by commercial array are typically common and used to tag the variability of a relatively large genomic region. The actual causal variant driving the disease risk may be located hundreds of kilobases away in an exon and modify a protein structure, or in an intronic or intergenic regulatory region and modulates gene expression. The next step to follow-up on PD GWAS discoveries is deep-sequencing of every locus to identify potential causal variants [50]. Next generation sequencing approaches will help in this endeavor as they allow to capture specific genomic regions both coding and non-coding. Sequencing approaches aim to identify the variants that have the potential to be functional (carry the disease risk).

Another important issue is to understand how susceptibility loci interact. Given the number of risk loci found to be associated with sporadic PD, it has been hypothesize that interaction between genes exist so that the risk to a patient who carries two susceptibility variants is significantly more than a simple combination of the independent effect of each one. Considering that tau and α-synuclein protein aggregation is regulated by similar mechanisms [51], members of the GEO-PD consortium have also looked into the interactions between variants in *SNCA* and *MAPT* [52]. No significant interaction was detected but additional studies are necessary to fully assess the network of interactions between PD genes.

Finally, functional assays are essential complements of the GWAS approach. Targeted functional assays are aimed at authenticating causal variants and identifying their effects on biological pathways and disease development are crucial. The overall goal is to identify the specific molecules whose function or expression is modulated by PD associated genetic variants and use these molecules for drug development. Functional studies are the link between genetic studies and application in the clinic. These clinical applications of GWAS will come in two stages: first, when we can use specific genetic variations as diagnostic tools to test for biological changes that are typical of PD subtypes and second, when PD subtype-specific molecules can be targeted for therapy. It is likely that no universal solution to cure PD will come out of GWAS discoveries but the hope is that better treatment tailored to each patient's genome can be developed.

GWAS have shaped the field of common genetic factors in susceptibility to sporadic PD. Several PD loci have been identified and researchers are now starting to group genes in biological pathways. A clearer picture of the underlying molecular mechanisms behind PD development is starting to emerge and hope of effective and personalized treatments for this devastating neurodegenerative disease is on the horizon.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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