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Genetics of Parkinson disease: an introspection of its journey towards precision medicine

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Abstract

A substantial proportion of risk for Parkinson disease (PD) is driven by genetics. Progress in understanding the genetic basis of PD has been significant. So far, highly-penetrant rare genetic alterations in *SNCA, LRRK2, VPS35, PRKN, PINK1, DJ-1* and *GBA* have been linked with typical familial PD and common genetic variability at 90 loci have been linked to risk for PD. In this review, we outline the journey thus far of PD genetics, highlighting how significant advances have improved our knowledge of the genetic basis of PD risk, onset and progression. Despite remarkable progress, our field has yet to unravel how genetic risk variants disrupt biological pathways and molecular networks underlying the pathobiology of the disease. We highlight that currently identified genetic risk factors only represent a fraction of the likely genetic risk for PD. Identifying the remaining genetic risk will require us to diversify our efforts, performing genetic studies across different ancestral groups. This work will inform us on the varied genetic basis of disease across populations and also aid in fine mapping discovered loci. If we are able to take this course, we foresee that genetic discoveries in PD will directly influence our ability to predict disease and aid in defining etiological subtypes, critical steps for the implementation of precision medicine for PD.

Keywords

Genetics; Parkinson disease; risk; Post-GWAS era

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Introduction

Parkinson Disease (PD) is a neurodegenerative disease characterized by the presence of Lewy bodies in the midbrain and the loss of activity of dopaminergic neurons, particularly in the substantia nigra. First clinically described by James Parkinson in 1817, PD exhibits symptoms that include muscle tremors and rigidity, bradykinesia and loss of balance, among others (Poewe et al. 2017). Years before distinct neuromotor symptoms are manifest, PD initially begins in a long prodromal period. Patients with prodromal PD present non-motor symptoms such as constipation and REM sleep disorder (Heinzel et al. 2019). PD currently has no cure and treatments are only symptomatic.

PD exerts a significant burden on the global economy and society, and this is expected to worsen; as of 2016, there are estimated to be more than 6 million PD cases. As the fastest growing neurological disorder in disability-adjusted life years, deaths, and prevalence (GBD 2016 Neurology Collaborators 2019), the number of PD cases is expected to grow to over 12 million by 2040 (GBD 2016 Neurology Collaborators 2019; Dorsey et al. 2018).

Age is the biggest risk factor to PD, and sex is a contributing factor with men being disproportionately affected (Wright Willis et al. 2010; Van Den Eeden 2003). A wide number of studies have shown that known and unknown environmental factors can contribute to PD risk. Environmental factors such as pesticide exposure, well water consumption, and head injury, as well as premotor symptoms including constipation and depression among others (Noyce et al. 2012), have been associated with increased risk for PD (van der Mark et al. 2012), while other factors such as tobacco, coffee, and alcohol usage have controversially shown possible protective associations with PD (Li et al. 2015; R. Liu et al. 2012; D. Zhang, Jiang, and Xie 2014).

The genetics of Parkinson disease in the pre-GWAS and GWAS era

Monogenic Parkinson disease

Historically, PD was considered a sporadic disorder in which environmental factors and age were the main risk factors. Indeed, before the 1990s, there was significant doubt that PD had any heritability (Duvoisin 1984). However, family history of PD (first degree relative definition) is found in approximately 15% of the patients and 5–10% of PD patients follow a classical Mendelian inheritance pattern (Lesage and Brice 2009).

Since the discovery of disease causing mutations in *SNCA* in a large Italian kindred and three unrelated Greek families in the late nineties (Polymeropoulos 1997), several genes have been linked to both autosomal dominant and recessive familial PD. However, only *SNCA, LRRK2, VPS35, PRKN, PINK1, GBA* and *DJ-1* have been convincingly associated with typical PD (Figure 1). It is noteworthy that additional genes harbor rare mutations that lack replication and functional validation, and thus should be considered putative. Despite the high disease penetrance of familial cases, known monogenic loci only explain a small fraction of the observed familial aggregation of PD, suggesting that much remains to be found, likely in both genetic and non-genetic domains.

Apart from the widely reviewed genes involved in Mendelian PD, recent findings have nominated *TMEM230*, *LRP10*, *NUS1* and *ARSA* as putative disease-causing candidates. In 2016, Deng and colleagues identified *TMEM230* as the disease-causing gene in the same Canadian family where mutations in *DNAJC13* had been previously found to be causative (Deng et al. 2016; Vilariño-Güell et al. 2014). Three other PD-associated *TMEM230* variants were detected in 7 additional Chinese families (Deng et al. 2016). However, many other studies, including large series of PD patients, have failed to replicate this association (Yan et al. 2017; Giri et al. 2017; He et al. 2017; Baumann et al. 2017; Wu et al. 2017; Quadri et al. 2017; Buongarzone et al. 2017; X. Yang et al. 2017; Shi et al. 2017; Wei et al. 2018; Ibanez et al. 2017; Ma et al. 2017; Fan et al. 2017; Conedera et al. 2018; Tejera-Parrado et al. 2018); thus, casting doubt on its implication in PD etiology (Iqbal and Toft 2019; Deng, Pericak-Vance, and Siddique 2019; Farrer 2019).

Genome-wide linkage analysis of a large Italian family with 13 members affected by autosomal-dominant PD and one affected by dementia with Lewy bodies (DLB) led to the identification of heterozygous variants in *LRP10* associated with PD, PD dementia (PDD), and DLB (Quadri et al. 2018). Further screening of *LRP10* in an international cohort of 660 probands revealed 8 additional rare and potentially-pathogenic *LRP10* variants (Quadri et al. 2018). Therefore, *LRP10* together with *SNCA, LRRK2*, and *GBA*, would support the idea that PD, PDD and DLB are parts of a continuum of Lewy body disease (Langston et al. 2015; Jellinger and Korczyn 2018). However, replication of this association in different populations remains inconsistent (Kia, Sabir, et al. 2018; Guerreiro et al. 2018; Pihlstrøm et al. 2018; Tesson et al. 2018; Shi et al. 2018; Y. Chen et al. 2019; Vergouw et al. 2019), and further studies are needed to determine the involvement of *LRP10* in PD pathogenesis.

NUS1 has been nominated as a possible candidate gene for PD in the Han Chinese population (Guo et al. 2018). Guo *et al.* performed whole-exome sequencing of 39 EOPD patients, their parents and 20 unaffected siblings in order to investigate the effects of *de novo* mutations in PD. They identified 12 genes with plausible functional relevance to PD pathogenesis. Further analyses in two independent case-control cohorts found a significant association between *NUS1* and PD (p-value combined = 1.01×10^{-5}). Subsequent functional studies on *Drosophila* demonstrated that the loss of *NUS1* affects climbing ability, dopamine level and the number of dopaminergic neurons; thus, supporting a potential link between *NUS1* and PD pathogenesis (Guo et al. 2018). *NUS1* encodes the Nogo-B receptor (NgBR) that is a type I single transmembrane domain specific receptor for the neural and cardiovascular regulator Nogo-B. Mutations in *NUS1* have been previously associated with a congenital disorder of glycosylation (E. J. Park et al. 2014) and epileptic encephalopathies (Hamdan et al. 2017). It is also involved in intracellular cholesterol trafficking by interacting and stabilizing Niemann-Pick type C2 protein (NPC2) (Harrison et al. 2009). Although a recent study does not support a role for *NPC1/2* mutations in the pathogenesis of PD (Zech et al. 2013), the association between cholesterol and PD risk has been suggested in multiple studies (Klemann et al. 2017; Arenas, Garcia-Ruiz, and Fernandez-Checa 2017; García-Sanz et al. 2017; Huang et al. 2019).

More recently, pathogenic and protective mutations in the arylsulfatase A gene (*ARSA*) have been linked to PD (J. S. Lee et al. 2019). The authors analyzed *ARSA* mutations in a family

with a history of PD and identified two compound heterozygous missense mutations. *ARSA* encodes a lysosomal hydrolase and its complete deficiency causes metachromatic leukodystrophy, an autosomal recessive lysosomal storage disease. Therefore, these data provide additional support for the lysosomal system in PD pathogenesis (Klein and Mazzulli 2018; Robak et al. 2017). Further screening in 92 familial and 92 sporadic PD cases did not detect additional pathogenic *ARSA* variants, but identified a non-synonymous variant that was proposed to be protective (J. S. Lee et al. 2019). Interestingly, the authors found that ARSA acts as a cytosolic molecular chaperone regulating α-synuclein accumulation and propagation. However, large international consortiums have failed to replicate the association between *ARSA* and PD (Makarious et al. 2019).

The number of familial and early onset cases with no known genetic cause remains high, and as demonstrated above, the validation of novel genes associated with PD remains extremely challenging. Families harbouring rare genetic variants are uncommon and globally dispersed, thus making replication of segregating mutations or mutations in the same gene difficult. Further, modern genetic approaches such as whole genome sequencing remain expensive and are not always readily available. A logical path to solving this challenge is the creation of a global resource for mutation discovery, which democratizes the analysis of rare, but highly valuable families.

Sporadic Parkinson disease

Only a small percentage of sporadic PD cases harbor mutations in known PD genes. Over the past decade, many studies have pursued the '*common disease-common variant*' (CDCV) hypothesis, which postulates that the genetic component of most common and complex disorders, such as PD, is due to a large number of common low-risk alleles (Lohmueller et al. 2003). Genome-wide association (GWA) studies are the gold-standard tool for testing the CDCV hypothesis. The first GWAS in PD to identify genome wide significant associations were reported in 2009. The first consisted of 5,074 cases and 8,551 controls of European origin (Simón-Sánchez et al. 2009). The authors identified two strong association signals, one in *SNCA* and the other in *MAPT* locus, as major risk factors for PD (Simón-Sánchez et al. 2009). The second, a GWA in an ancestral Asian population, replicated association at *SNCA* and identified 3 additional PD susceptibility loci, including *PARK16*, *LRRK2* and *BST1* (Satake et al. 2009). Since then, numerous GWA studies with increasing number of participants have been performed across populations (Kara et al. 2014; Siitonen et al. 2017; Bandres-Ciga, Ahmed, et al. 2019). The last and largest PD GWAS to date including around 37,700 cases, 18,600 'proxy' cases and 1.4 million controls has robustly identified 90 independent risk signals associated with sporadic PD (Nalls et al. 2019).

In spite of the success of GWA at expanding our understanding of the genetic basis of human complex diseases, for most traits, including PD, the associated loci do not account for all the genetic variance underlying the disease (Manolio et al. 2009). Analysis of common genetic variability suggests that only ~22% of the liability for PD is driven by these variants and the known associated GWAS SNPs only represent a fraction of this detected heritability (Nalls et al., 2019). Different explanations for the 'missing heritability problem' have been proposed (Young 2019; Génin 2019). First, GWA analyses are not currently

powered to capture all of the common genetic variability contributing to disease susceptibility, particularly those that may be rare and / or have small effect sizes. Increasing sample sizes of GWA allows researchers to identify new susceptibility loci in situations where statistical power is low and therefore may improve the proportion of explained heritability. It is also worth noting that rare variants of both large and small effect, and some structural variation, are not well-captured by GWA chips and imputation. There is increasing evidence that these may indeed play a major role in common diseases (Gibson 2012; Bomba, Walter, and Soranzo 2017; J. Yang et al. 2015; Weissbrod et al. 2019). In addition, gene-gene and gene-environment interactions could also be contributing to common disease susceptibility (Zuk et al. 2012; Cordell 2009; Ritchie and Van Steen 2018; Cannon and Greenamyre 2013). In PD, there is scant evidence for epistatic interactions, although this is a common theme in disease genetics because of the extreme sample sizes required to reliably detect such associations (Fernández-Santiago et al. 2019; Pecanka et al. 2017; Kuwahara et al. 2016; Beilina et al. 2014; Göbel et al. 2012). It is noteworthy however, that the explanation of epistasis as a piece of the missing heritability puzzle is controversial since dominance variance (due to genetic interactions) appears to have a minimal effect on heritability estimates and does not explain the missing heritability for some complex diseases (Zhu et al. 2015; Guerreiro et al. 2019; Diez-Fairen et al. 2019). Lastly, epigenetic factors can be transmitted through generations and thus may also contribute to disease risk (Bourrat, Lu, and Jablonka 2017; Trerotola et al. 2015; Cortijo et al. 2014; Bell and Spector 2011).

Linking familial and sporadic forms of the disease

Besides identifying several risk loci for sporadic PD, large population-based GWAS and meta-analyses have also established that disease linked common variability exists at loci known to contain rare causal mutations. These include *SNCA, LRRK2, GBA* and *VPS13C*, previously associated with Mendelian forms of PD (Satake et al. 2009; Chang et al. 2017; Nalls et al. 2014; Simón-Sánchez et al. 2009); thus, suggesting a link between familial and sporadic forms of disease. These loci harboring both rare large effect and common smaller effect variants are known as pleomorphic risk loci (A. Singleton and Hardy 2011). Therefore, both the CDCV hypothesis and the multiple rare variant hypothesis are not mutually exclusive. Instead, various disease-related genetic mechanisms may coexist at the same locus, each influencing disease through different biological effects on a single gene. For example, *SNCA* locus has been linked to PD etiology through: (i) duplications and triplications with a clear gene-dose effect (A. B. Singleton et al. 2003; Ibáñez et al. 2004; Chartier-Harlin et al. 2004); (ii) coding mutations causing early-onset PD familial cases (Krüger et al. 1998; Zarranz et al. 2004; Polymeropoulos 1997; Lesage et al. 2013; Kiely et al. 2013; Pasanen et al. 2014); (iii) different association signals in GWAS illustrating the presence of low-effect common variability in this locus (Satake et al. 2009; Chang et al. 2017; Nalls et al. 2014; Simón-Sánchez et al. 2009); and (iv) non-coding risk/protective variants (Trotta et al. 2012).

Understanding the biological consequences of genetic risk

Many of the PD-related genes are involved in common biological pathways, which suggests that several critical cellular routes contribute to the disease risk. Mitochondrial dysfunction was one of the first biological processes to be associated with PD pathogenesis through the analysis of the recessive Mendelian genes. *PINK1*, a mitochondrial kinase, and *PRKN*, an E3 ubiquitin ligase, converge in the mitophagy pathway where *PINK1* phosphorylates *PRKN* to eliminate damaged mitochondria (Kane et al. 2014; J. Park et al. 2006; I. E. Clark et al. 2006). *DJ-1*, another ubiquitin ligase, promotes *PINK1* transcriptional activity and is also involved in mitochondrial physiology (Requejo-Aguilar et al. 2015; Cookson 2010). Other genes previously linked to classical and atypical PD risk such as *FBXO7*, *PLA2G6*, *VPS13C* and *CHCHD2*, have also been linked to the mitochondrial quality control system (Burchell et al. 2013; Lesage et al. 2016; Funayama et al. 2015; R. G. Lee et al. 2018; Cieri, Brini, and Calì 2017). A recent study estimated that common variation within the mitochondria function associated genes can contribute around 7% of the overall heritability (22%) of PD and that mitochondrial processes are involved in both monogenic and sporadic PD pathogenesis and contribute to later age at onset (Kimberley J. Billingsley et al. 2019).

Pathway-based analyses have started to be implemented in PD research in order to identify biological processes that contribute to the disease. Recent studies have pointed out a high genetic risk burden for PD in the lysosomal and endocytic membrane trafficking pathways (Robak et al. 2017; Bandres-Ciga, Saez-Atienzar, et al. 2019). The immune response is another pathway that has been strongly associated with PD susceptibility (M. Zhang et al. 2017; Holmans et al. 2013), through both inflammation and autoimmune response. In fact, major histocompatibility complex (MHC) proteins are displayed on dopamine neurons of the substantia nigra, suggesting that antigenic epitopes could activate T cells involved in autoimmune responses and cell death (Garretti et al. 2019). Previous PD GWAS have identified risk loci spanning key immune associated genes such as *BST1* (bone marrow stromal cell antigen 1) and *HLA* (human leukocyte antigen) (Satake et al. 2009; Nalls et al. 2014). *BST1* has been proposed to play a role in neutrophil adhesion and migration, and it has been reported that it could be a cause of selective vulnerability of dopaminergic neurons in PD (K. J. Billingsley et al. 2018). Additionally, the *HLA* locus which encodes the MHC-II has been associated with PD (Nalls et al., 2019). GWAS have identified an association of PD with two MHC genes, including *HLA-DRB1* and *HLA-DRB5 (Hamza et al. 2010; Nalls et al. 2019)*. Indeed, it has been reported that α-synuclein-derived fragments act as antigenic epitopes displayed by *HLA* receptors, where both helper and cytotoxic T-cell responses are present in a high percentage of patients when tested (Bandres-Ciga and Cookson 2017; Sulzer et al. 2017). Further investigation of these pathways can provide novel insights into PD pathogenesis and uncover novel therapeutic targets.

Predicting risk, progression and defining etiological subtypes of disease

Individually GWA identified loci confer relatively small amounts of disease risk; however, the use of polygenic risk scores (PRS) affords the ability to attribute a total known genetic risk score to an individual by summing their collective genetic risk. To date, the PRS reveals that, collectively, the 90 susceptibility loci confer considerable risk for disease, with those in

the top decile of genetic risk being 6-fold more likely to have PD than those in the lowest decile of genetic risk (Nalls et al. 2019). Additionally, by creating a composite risk score for PD diagnosis that combines the cumulative effect of genetic risk variants as well as the presence or absence of anosmia, age, sex, and family history, the ability to predict individuals at high risk for PD is remarkable, showing an AUC sensitivity of ~ 83.4% and specificity of ~ 90% (Nalls, McLean, et al. 2015).

Research focused on age at onset disease modifiers is one area where consistent effort has been seen. The largest PD age at onset GWAS to date (Blauwendraat et al. 2019) included data from > 25K cases and identified two GWAS significant signals; one at *SNCA* and the other was a protein-coding variant in *TMEM175*, both of which are known PD risk loci. Notably, these results showed that not all PD risk loci influence age at onset and therefore suggest the idea that risk and onset might operate through mechanisms that do not completely overlap.

Despite the progress made in dissecting risk and understanding onset due to the availability of large sets of samples for genome-wide assessment, for the most part, these cohorts lack substantial clinical data, making it difficult to investigate progression in a well-powered manner. Collecting comprehensive longitudinal data is costly, and harmonizing and combining individually small sample sets is time consuming and challenges. Despite these difficulties, the latest PD progression GWAS to date (Iwaki et al. 2019), managed to identify two GWAS signals in loci not previously linked to PD risk (*SLC44A1* associated with a faster rate of progression via Hohn and Yar score, and an intergenic variant related to *ADRA2A* expression associated with insomnia) (https://pdgenetics.shinyapps.io/pdprogmetagwasbrowser/).

Although laborious, accurate models of disease progression will enable the next generation of clinical trials. In recent years, several initiatives such as the Parkinson's Progression Markers Initiative (PPMI) (https://www.ppmi-info.org/), the Parkinson's Disease Biomarkers Program (PDBP) (https://pdbp-demo.cit.nih.gov/), Predict PD (Noyce, R'Bibo, et al. 2017), and the Accelerating Medicines Partnership for Parkinson Disease (AMP-PD) (https://www.nih.gov/research-training/accelerating-medicines-partnership-amp) have emerged as valuable resources to aggregate and harmonize efforts in PD.

Predicting the precise clinical, molecular, and pathological subtypes in such a complex and heterogeneous disorder, will prove invaluable and will likely have an impact on drug development, therapeutic testing, and ultimately treatment (Leonard et al. 2019).

Inferring causal relationships across phenotypic traits and exploring shared polygenic risk

A corollary of abundant GWA data is the ability to test other traits that can predispose or protect individuals to disease. Access to large amounts of GWA data affords the opportunity to explore causal inferences between myriad traits and PD through Mendelian Randomization (MR), the gold standard approach for causality in genetic studies that sits at the interface between observational epidemiology and interventional trials (Lawlor et al.,

n.d.). MR has emerged as a statistical approach that uses genetic data in the form of SNPs to study whether an exposure exerts a causal effect in an outcome. This addresses the question of whether an observational association between a risk or protective factor and a disease of interest is consistent with a causal effect by focusing usually only on genome-wide significant SNPs. Put simply, genetic variants that explain variation in a certain exposure can be used as proxies to determine how a change in that exposure might influence a disease outcome. One of the key strengths of this method is that it relies on genetic variants that remain constant over the lifespan of an individual, are randomized during gametogenesis and fixed at conception, which means that genetic variants are not associated with all the confounder factors that affect an observational study.

In the PD field, two-sample MR has been applied considering both targeted (hypothesis-driven) exploration of causal associations, as well as hypothesis-generating approaches in a large-scale, high-throughput, unbiased manner.

For the former, an inverse causal association between body mass index (BMI) and risk of PD has been reported. A genetically-estimated 5kg/m^2 higher BMI was associated with a reduced risk of PD (Noyce, Kia, et al. 2017). Negative causal associations have also been necessary to refute spurious associations. For instance, observational studies have reported that modulating plasma urate could be a potential preventive avenue for PD (Noyce et al. 2012; Bellou et al. 2016). However, MR did not find evidence for a causal protective effect of urate levels on PD risk (Kia, Noyce, et al. 2018), corroborating the results from the Phase III of the SURE-PD3 clinical trial. The randomized, placebo-controlled, double-blinded trial conducted nationwide at 57 clinical sites of the Parkinson Study Group (PSG), failed at demonstrating that a treatment with Inosine raised blood levels of the natural antioxidant urate and therefore these molecular changes could slow the rate of progression in PD.

For the latter, a useful interactive resource for the PD community has been made publicly available (https://pdgenetics.shinyapps.io/pdgenetics) (Noyce et al. 2019). By using the PD MR Research Portal, users can search for evidence of causality on a broad range of exposures from 5,839 different GWASes. This resource can be used to provide evidence to support, and over time, evidence against, causality when undertaking observational studies or pursuing interventions aimed at reducing the risk of PD.

To date, the main limitations of applying MR, is that many studies are underpowered, either as a consequence of relatively low samples sizes in the exposure GWAS data or the small amount of variation (heritability) in an exposure trait that is explained by the reported common genetic variation.

Another approach that has recently taken importance is applying Linkage disequilibrium score regression (LDSC) to investigate the extent to which genetic etiologies are shared across different diseases. In the PD genetics field, it has been successfully implemented to test whether polygenic risk contributing to a phenotype of interest might also contribute to the risk of PD. Cross-trait genetic correlations between the latest PD GWAS (Nalls et al. 2019) summary statistics and 757 other GWAS available datasets revealed four significant genetic correlations, including positive correlations with intracranial volume and putamen

volume (suggesting that both may prove to be valuable PD biomarkers) and negative correlations with current tobacco use and “academic qualifications: National Vocational Qualifications (NVQ) or Higher National Diploma (HND) or Higher National Certificate (HNC) or equivalent”. Interestingly, the negative association with one’s academic qualifications indicates that those individuals without a college education may have a lower likelihood of developing PD than individuals with higher levels of education, but again, correlation does not imply causation. Although there remains a lot to be done, the current work represents a novel approach towards the foundation to pursue PD research in the Post-GWAS era.

Translating Genetics into Precision Medicine

Pharmacogenetics

The decrease in genetic testing cost has positioned precision medicine, medical practice specifically attuned to genetics of the individual patient, as the focus of clinical genetics research and the US health care policy (Collins and Varmus 2015). Genetics-informed personalized therapeutics, also called pharmacogenetics, are the future of healthcare, and already an indication for drug usage and dosing. Currently, there are clinical trials that take into account crucial genes associated with PD such as *GBA* (Silveira et al. 2019) and *LRRK2* (J. Chen, Chen, and Pu 2018; Whiffin et al., n.d.).

As one of the most well understood PD risk genes, *GBA* is frequently seen as a treatment target. In general, *GBA* carrier PD cases present worse disease symptoms and mutation severity has been associated with differences in age-at-onset (Brockmann et al. 2015; Gan-Or, Liong, and Alcalay 2018). For instance, *GBA* p.N370S variant is known to increase PD risk and when homozygous cause Gaucher Disease (GD) (L. N. Clark et al. 2005). In the largest PD age at onset GWAS to date, significant hits within the *GBA* region were variants p.N370S, p.E326K, and p.T369M with effect sizes between 2.6 to 0.9 year reduction in ageat-onset (Blauwendraat et al. 2019). In a longitudinal study, PD patients with *GBA* variants that cause neuropathic GD have shown to have accelerated cognitive decline over time compared to other PD patients (G. Liu et al. 2016). Despite these findings, the role and the mechanism of *GBA* and its product Glucocerebrosidase (GCase) remains unclear. In addition, many *GBA* carriers never get PD. *GBA* modifiers may help answer this conundrum. PD PRS is higher in *GBA* carrier cases compared to carrier controls, with variants near *CTSB* and *SNCA* showing potential gene-gene interaction with *GBA* (Blauwendraat et al. 2020). Nevertheless, clinical trials have started for *GBA* targeted therapies, all trying increase GCase production or activity. One uses glucosylceramide synthase inhibitor GZ/SAR402671 (ClinicalTrials.gov identifier NCT02906020), while others are using ambroxol hydrochloride (ClinicalTrials.gov identifier NCT02941822 and NCT02914366).

Patient-specific dosage and management of side effects is an important aspect of personalized medicine. Genes that influence the patient response often are involved in pathways that interact with the treatment in question. Many of the current PD treatments focus on supplying the brain with additional dopamine, either by providing the body with precursor molecules (levodopa), metabolic enzyme inhibitors (rasagiline), or dopamine

receptor agonists (ropinirole). As such, genes associated with treatment effectiveness are involved in pathways that interact with dopamine and metabolism of dopamine precursors. For instance, *DDC* and *COMT* encode enzymes that metabolize levodopa to dopamine, and variations in both are associated with dosage and side effects of levodopa (Bialecka et al. 2008; de Lau et al. 2012; Cheshire et al. 2014). Dopamine transporter gene *DAT* has been associated with psychosis with levodopa treatment (Kaiser et al. 2003) and dopamine receptor genes, including *DRD2* and *DRD3*, have been associated with side effects in levodopa and MAO-B inhibitors (Masellis et al. 2016; Rieck et al. 2012; Krishnamoorthy et al. 2016). In addition, there is evidence that monogenic PD patients have varied response to deep brain stimulation therapy (DBS) depending on the gene and variant in question; the *LRRK2* p.G2019S variant has shown positive outcomes to DBS, while *LRRK2* p.R1441G has shown poor outcomes (Kuusimäki et al. 2019).

Future Directions

Genomics Need Diversity

Most work in genomics has been done in subjects of Northern European Ancestry (Popejoy and Fullerton 2016) and PD genetic research is no exception (Foo et al. 2017). This lack of diversity reveals three limitations of our current approach: We don’t understand the applicability of genetic risk and PRS across populations; the LD structure of a single ancestral group means that it is difficult to fine map risk loci, and there is missing novel ancestry underlying specific genetic risk.

Expanding our investigation to more diverse populations is the right thing to do. Given our discussion of the potential impact of individualized genetic risk on treatment, it is critical that we understand genetic risk in individuals of varied genetic backgrounds, so that we can treat everyone effectively. A clear benefit of the expansion of this effort is the potential to identify rare but informative ancestry specific risk alleles and the genes these alleles influence, providing new therapeutic targets; however, this work also affords the ability to perform trans ethnic fine mapping, an approach that facilitates the reduction of risk regions to smaller credible intervals, thus simplifying their functional characterization.

Merely adding additional non-European participants will not be enough to remove the current bias. We will have to produce reference data and develop genetic tools specifically tailored to underserved populations. The current PD GWAS includes large amount of data from genotyping arrays designed around European populations (Nalls, Bras, et al. 2015; Blauwendraat et al. 2017; Bycroft et al. 2018). Designing arrays based on more global population or use of whole-genome sequencing in conjunction with diverse participant population will be crucial to reducing systematic European bias. Outside of PD, there has been at least one study on an underrepresented population that found a rare SNP with an effect on both the underrepresented and European populations (Fumagalli et al. 2015). In the same manner, PD may have “missing heritability” ready to be discovered through the study of non-European populations.

The good news is that there is a growing push to include diverse ancestral populations in genetics work. Pan-continental programs such as H3 Africa (H3Africa Consortium et al.

2014) have already begun establishing networks of international labs in genetically understudied regions. In the United States, the *All of Us* initiative is building a diverse genetic database that encompasses the population of the United States, including historically underrepresented populations (Investigators and The All of Us Research Program Investigators 2019). In the PD genetics field, pilot genomic studies have started to arise; the Michael J Fox Foundation (MJFF) has recently committed pilot support across non-European populations (Williams, Bandmann, and Walker 2018) including initiatives to extend large scale genotyping efforts to Latin Americans (LARGE-PD) (Zabetian, Mata, and Latin American Research Consortium on the Genetics of PD (LARGE-PD) 2017), Africans, African-Americans, the Luxembourg-German-Indian Alliance on Neurodegenerative diseases and Therapeutics (Lux GIANT) and East-Asians under the wing of the International Parkinson Disease Genomics Consortium (IPDGC; https://pdgenetics/org). We envisage that funding agencies will incentivize studying diverse populations and PD genetics research will make in-roads with non-European academia to establish collaborative large-scale genetic studies.

Conclusion

Within two decades, PD genetics has come a long way, from the field doubting the role of genetics in PD to an increased understanding its impact on PD risk, onset, progression, and treatment response, as well as phenotypic etiologies and causal comorbidities. Yet only a fraction of the heritability is known and the relationship between genetics and PD pathology is poorly understood. The nascent movement to expand this work at scale and to encourage diverse participation in PD genetics research will not only reduce systematic health disparities but also promote discoveries of the missing pieces of PD genetics.

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Highlights:

- A total of 90 risk loci have been associated with PD to date representing 16–36% of the heritable component of the disease.
- The number of familial and early onset cases with no known genetic cause remains high and the validation of novel genes remains extremely challenging.
- PD genetics is disproportionately based on studying populations of European ancestry. Diversity will not only reduce systematic health disparities but also promote discoveries of the missing pieces of PD genetics.

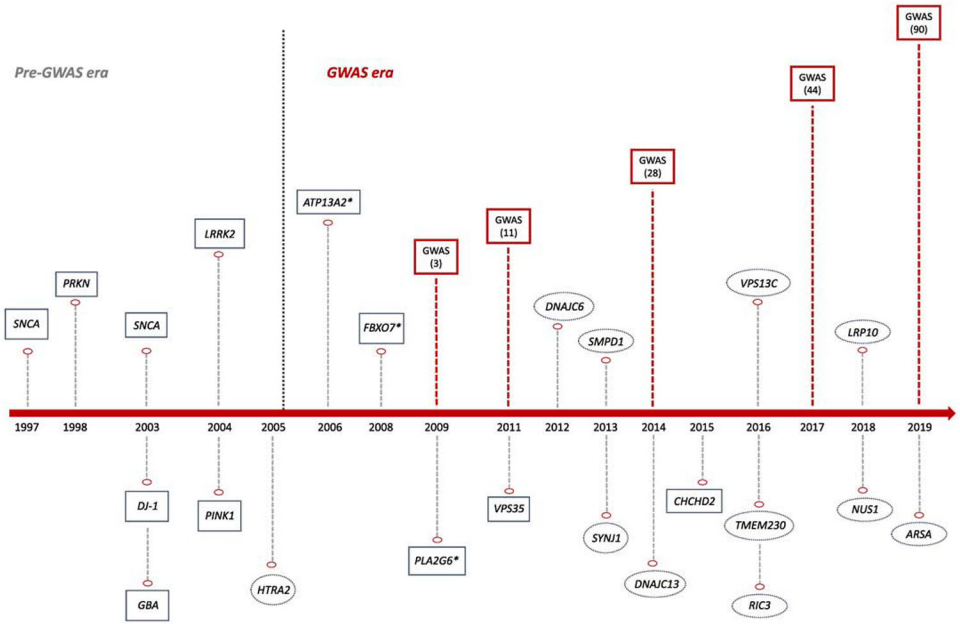

Figure 1.

The genetics of Parkinson disease over time.

Red squares represent genome-wide association studies and number of discovered risk loci in brackets. * indicate genes associated with atypical parkinsonism related syndromes. Green squares represent controversial or not widely validated genes linked to typical Parkinson disease

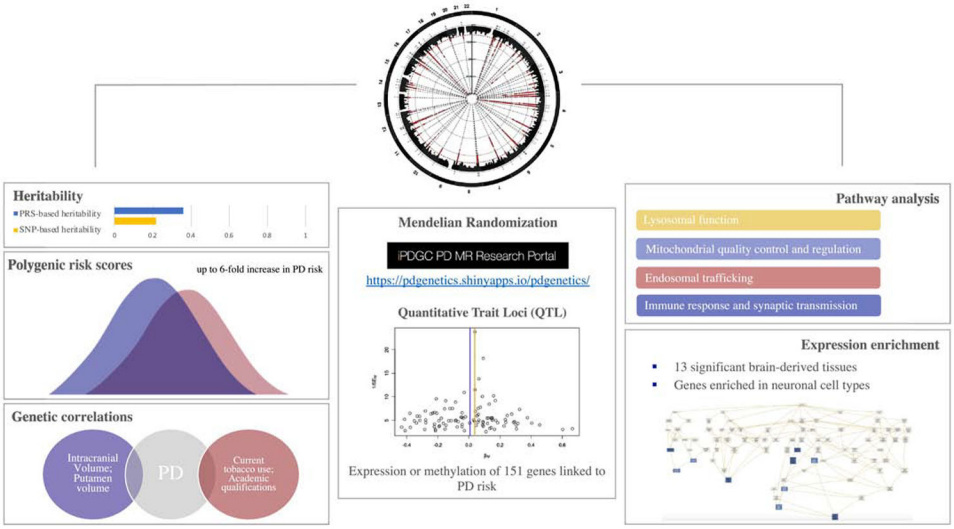

Figure 2.
Characterizing the genetic architecture of Parkinson disease.