Personal View

Uncovering the Genetic Basis of Parkinson's Disease Globally: From Discoveries to the Clinic

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Knowledge on the genetic basis of Parkinson's disease (PD) has grown tremendously since the discovery of the first monogenic form of PD in 1997, and the subsequent identification of multiple other causative genes and associated loci. Genetic studies provide insights into the phenotypic heterogeneity and global distribution of the disease. By shedding light on the biological mechanisms underlying PD, they facilitate the identification of new biomarkers and therapeutic targets. Several clinical trials of genetics-informed therapies are ongoing or imminent. International programs that are inclusive of populations underrepresented in PD genetics research are fostering collaboration and capacity-building, and have generated novel findings. Many challenges remain for genetics research in these populations, and addressing them provides opportunities to obtain a more complete and equitable picture of PD globally. All these advances increasingly facilitate the integration of genetics into the clinic to improve patient management and personalized medicine delivery.

Introduction

The last three decades have seen much progress in the understanding of the genetic architecture of Parkinson's disease (PD),[1-3] and knowledge regarding the biological mechanisms underlying PD, in particular the role of alpha-synuclein aggregation, mitochondrial and lysosomal dysfunction, and maladaptive immune responses, has increased remarkably.[4,5] These advances are anticipated to enable the development of disease-modifying therapies, the lack of which remains the biggest unmet need for most neurodegenerative conditions.[6] Such success has already been demonstrated in several areas of medicine, particularly oncology, where a focus on genetically defined subtypes of disease has culminated in the advent of novel effective therapeutics.[5,6]

Technologies to interrogate the genetic basis of human phenotypic traits and diseases continue to advance at a rapid pace, with next-generation sequencing costs reducing significantly. More widespread genetic testing has also been driven by collaborative PD genetics research programs.[7-13] The increasing availability of genetic testing for patients with PD,[1,7-14] and intense activity in the PD biomarker[15-20] and clinical trial[5,6,10,21-23] spaces, are bringing genetics to the mainstream of day-to-day clinical and research practice.

On an international scale, most genetics and genomics research have primarily focused on populations of European ancestry, resulting in the relative absence of non-European (also referred to as "underrepresented" [**Panel 1**]) populations in large-scale studies.[24-26] In this Personal View, we provide an update on the genetics associated with PD, and the global distribution and clinical presentation, emphasizing genetic findings in underrepresented populations. We also cover recent findings on the genetic and biological basis of "idiopathic" PD.[1-4] Genetic understanding can enhance the delivery of personalized precision medicine in clinical practice and we propose research priorities towards that aim.

Panel 1: **"Underrepresented populations" in genetics research - a term in need of further refinements**

Across medicine and health, ~80% of individuals in genome-wide association studies (GWASs), as of 2019, were of European ancestries (despite comprising only ~16% of the world population).[24,25] The latest figures show that the imbalance has not reduced but in fact widened: 94.5% European, 3.7% Asian, 0.4% Hispanic or Latino, 0.2% African, and 0.7% other/mixed ancestries (https://gwasdiversitymonitor.com, accessed 22 March 2024).

Thus, non-European populations are typically designated in publications on genetics and genomics as "underrepresented".[24-26] However, this practice has several caveats. Although rich and technologically advanced European nations (mainly the United Kingdom, Germany, France, and Italy) and the United States of America (USA) have pioneered and performed many genetic studies,[24-26] it should be noted that other (particularly Eastern) European countries have scarcely or never been explored from this perspective at all.[27] While populations such as Icelanders and Finnish have been intensively studied, it has to be acknowledged that these are quite unique genetically owing to their relative isolation and homogeneous gene pools resulting from historical factors such as founder effects and limited external gene flow, and have been a rich source of genetic discoveries.[27] On the other hand, there have been a considerable number of genetics/genomics studies from several non-European populations, in particular East Asians such as in the Japanese and Han Chinese populations (in mainland China, Taiwan, and Singapore).[25,26]

An alternative approach to equating non-European with "underrepresented" populations is to list countries by income. Accordingly, low- and middle-income countries (as per the classification of income per capita by the World Bank: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups) can be denoted as underrepresented.[11] However, this is also not ideal. For example, while Japan, Taiwan, and Singapore are high-income, China, which is currently considered an (upper-)middle-income country, has produced numerous genetics/genomics studies, e.g., in a

systematic review of publications on PD genetics in underrepresented populations through October 2021 (*n*=1,037), China accounted for a large number (*n*=469) of the papers.[26] Conversely, many countries designated as high-income, such as in the Middle East (e.g., Saudi Arabia), South and Central America (e.g., Chile), Southeast Asia (e.g., Brunei), and Oceania (e.g., Guam), have few publications on genetics overall and PD genetics specifically.[26] Furthermore, there are sizeable communities in high-income countries that are currently very underrepresented in genetics research.[24-26] These include people of African or Latino descent in the USA, indigenous groups (e.g., Aborigines in Australia and Maori in New Zealand), and immigrant/refugee groups in Europe (e.g., Afghans in the USA or Germany, or Roma in Slovakia).[24-26]

Moving forward, we propose that the following factors should be taken into account when considering whether populations are underrepresented in genetics research: ancestral origin, degree of admixture, country of residence, access to healthcare, access to research studies, the extent to which the population in question has been studied before, and perhaps even how much of the data are available for sharing with the international research community. All stakeholders should have a say in these discussions.

Monogenic and "idiopathic" PD

The discovery of a pathogenic variant in the alpha-synuclein (*SNCA*) gene in 1997 indisputably confirmed a genetic cause in a subset of PD patients.[1-4] There are now several well-established PD genes that cause monogenic/Mendelian forms of PD. In these patients, the cause of PD is attributed to rare pathogenic variant(s) in a single gene.[1-4] These genes include *SNCA*, *LRRK2*, and *VPS35*, which have been linked to autosomal dominant PD sometimes with reduced penetrance (**Panel 2**), and *PRKN*, *PINK1*, and *PARK7*/*DJ-1*, which have been linked to autosomal recessive, typically early-onset, PD (EOPD, <50 years) (genes listed in order of chronological discovery).[1-3] Very recently, *RAB32* has been described as a novel PD gene causing autosomal dominant PD (see **Figure 1** for a timeline of progress in unravelling the genetic architecture of PD).[41,42]

Panel 2: Genetic status within the new biological research classifications of Parkinson's disease, and the concept of penetrance

The development of fluid, tissue, and imaging biomarkers is now sufficiently advanced to allow the objective identification of genetic risk, pathological processes (particularly α-synucleinopathy), and neurodegeneration, before the onset of PD clinical features.[15-18] These biomarkers enable the critical process of moving the field from a purely clinical, to a biological approach, to the disease. Two frameworks have been recently published, aiming to enable preclinical and pathogenic-subtype classification and diagnosis.[17,18]

In the "SynNeurGe" scheme proposed by Hoglinger and colleagues,[17] PD-linked genes and variants are categorized into three groups, according to their degree of penetrance:

Group 1, consisting of fully penetrant pathogenic variants: dominantly-inherited *SNCA* triplications and missense variants; and recessively-inherited biallelic *PRKN*, *PINK1*, and *PARK7*/*DJ-1* missense, truncating, and structural variants.

Group 2, consisting of pathogenic variants with reduced penetrance but still conferring a strong predisposition to PD: dominantly inherited *SNCA* duplications; and pathogenic missense variants e.g., in *LRRK2* and *VPS35*. The penetrance of pathogenic variants may depend on age, ancestry/geography, modifier variants, and environmental factors, and has been best studied in *LRRK2*-PD (discussed further below).[3,14,28-34]

Group 3, consisting of heterozygous severe *GBA1* pathogenic variants that are associated with an intermediate predisposition to develop PD. There is an ongoing discussion about whether *GBA1*

variants should be considered "causal" with autosomal dominant transmission and markedly reduced penetrance (but reportedly as high as 21% and 30% at ages 70 and 80 years, respectively),[10,35] or as risk factors with increased odds ratios (ORs) for PD from ~1.4 to 30-fold.[9,36-38] These scenarios may depend on specific types of *GBA1* variants and their frequency in a given population, with variants having a minor allele frequency (MAF) >1% being considered as risk variants and not as pathogenic.

Thus, mild *GBA1* pathogenic variants and other common risk variants that increase PD risk[2,38,39] are not presently considered for the classification of "Genetic PD", due to their much smaller (and individually unpredictable) effect sizes.

The "neuronal α-synuclein disease integrated staging system (NSD-ISS)" proposed by Simuni and colleagues[18] is anchored on the presence of neuronal α-synucleinopathy. Currently, genotype is not considered within this system, aside from fully penetrant pathogenic variants in *SNCA* (the gene that encodes α-synuclein), which are established to manifest with neuronal α-synuclein disease pathology (designated as "stage 0"). Individuals who do not have detectable neuronal α-synuclein disease, including a substantial proportion of *LRRK2*-PD and the majority of *PRKN*-PD patients,[5,15,17,18,31,37,40] are excluded from the NSD-ISS.

Other autosomal recessive forms of early- or juvenile-onset parkinsonism related to *PLA2G6*, *ATP13A2*, *FBXO7*, *SYNJ1*, *DNAJC6*, *VPS13C*, *PTPA*, and *DAGLB* (listed in order of approximate frequency), may present initially as PD but are usually accompanied by atypical features such as early dementia, intellectual disability, epileptic seizures, pyramidal signs, or gaze palsy.[43,44] These disorders usually also have an even earlier age at onset (median 24 years) compared to *PRKN*-, *PINK1*- and *DJ-1*-related cases, with median ages at onset of 31, 32 and 27 years, respectively.[43-45] Notably, most of the original discoveries of autosomal recessive atypical parkinsonian disorders were made in underrepresented populations: *ATP13A2* in Chilean and Jordanian; *FBX07* and *SYNJ1* in Iranian; *DNAJC6* in Arab-Palestinian; *VPS13C* in Turkish; *PTPA* in South African and Libyan; and *DAGLB* in Chinese populations. This could be due to the higher rates of consanguinity and larger family sizes in many of these populations, which facilitate identification of the causal genetic variants through linkage analysis and segregation. Analysis of the Movement Disorder Society Genetic Mutation Database (MDSGene; www.mdsgene.org, which collates English-language reports of patients with monogenic movement disorders) reveals that the global number of reported patients with autosomal recessive atypical parkinsonian disorders (and to some extent also autosomal recessive EOPD) in underrepresented populations outnumber those in European-ancestry populations (**Figure 2**, indicated by red segments of the pie charts in the bottom 2 rows).

The proportion of PD patients harbouring pathogenic variants has been variably estimated at ~5-15%,[2,3,12,13,17,46] but could be considerably higher (>40-50%) in selected populations[47-49] (described further below), or lower in other (e.g., community-based)[50] studies. The yield also depends on the number of genes tested,[10] for example whether focusing on established PD-linked genes[12,50] or screening a larger neurodegenerative panel with ≥50 genes.[13]

While genetic studies initially focused on familial PD, genome-wide association studies (GWASs) in large case-control samples have enabled investigations of the association between common genetic variants, typically single nucleotide polymorphisms (SNPs), and, very recently, also structural variants (duplications, deletions, or inversions of stretches of DNA), with the risk of "idiopathic" PD.[1,2,8,39,51-53] This denotes the more typical scenario of the condition occurring sporadically later in life, wherein a complex interplay of genetic, environmental, aging-related, and other factors is believed to underlie disease development.[1-4] So far, >100 risk signals have been discovered in PD.[1,2,8,39,52] These studies, which use genotyped and genotype-imputed data from hundreds of thousands to several million SNPs, without any *a priori* hypothesis, have provided important insights into the genetic architecture of idiopathic PD based on an increasing number of included individuals (**Figure 1**).[1,2,8,39,52] Multiple genes/loci and biological pathways associated with PD have been identified, including those involved

in immune-inflammatory mechanisms, protein misfolding and aggregation, endosomal-lysosomal and mitochondrial function, membrane and intracellular trafficking, cytoskeleton assembly, synaptic transmission, lipid metabolism, post-translational protein modifications, and apoptosis.[2,4,8,54,55] New findings will continue to accrue as PD sample sizes increase into the hundreds of thousands, as seen in other diseases.[56] However, for many loci, their effects on downstream molecular pathways remain to be elucidated, and this is a bottleneck to obtaining mechanistic insights and translational progress.[1,2,4,8,39]

One remarkable finding in the PD genetics field, and recognized in some other disorders with both monogenic and polygenic forms, is an apparent convergence of mechanisms underlying monogenic and complex forms of the disease.[57] Several of the genes discussed earlier causing monogenic PD/parkinsonism are also detected in GWASs (e.g., *SNCA*, *LRRK2*, *GBA1*, *VPS13C*).[1,2,8,39,57] These GWAS signals in the vast majority of cases map to non-coding, mostly intergenic, genomic regions, thought to result in relatively subtle alterations in gene (and ultimately protein) expression, rather than causing changes in protein sequence.[1,8,39,56,57] Thus, for example, risk variants in *SNCA* and *LRRK2* may result in small increases in the expression or activity of their respective proteins, leading to a convergent pathogenesis with monogenic forms involving multiplications of *SNCA* (with ≥1.5-fold increase in *SNCA* expression) or kinase-activating mutations in *LRRK2*.[5,19,57] This notion that genes containing mutations that cause disease are also involved in the pathogenesis of sporadic disease, presumably through an overlapping mechanism, is the "pleomorphic risk locus" hypothesis.[57] An important implication of this convergence is that future genetics-targeted therapies found to be useful in monogenic PD could also potentially be deployed in the much larger group of idiopathic PD.[4,5,29,57] However, genetic and/or other molecular stratification of participants in clinical studies for the predominant pathomechanism(s) (e.g., "autophagy/lysosomal-" or "mitochondrial-related" PD) would likely need to be performed in this more heterogeneous group of patients.[4,5,19,57,58]

PD genes commonly encountered in clinical practice

In the following sections, we focus on the common and well-established PD genes, particularly those that are being targeted in ongoing and imminent clinical trials.[5,6,10,12,20-23] We begin by discussing *LRRK2*-PD, the most common form of autosomal dominant PD, followed by PD associated with variants in *GBA1*, which is the most frequently encountered PD risk gene in most populations studied to date. This is followed by *PRKN*- and *PINK1*-related PD, which are the commonest autosomal recessive forms of PD. Our discussion highlights some lesser-known epidemiological aspects of classical PD genes in underrepresented populations, and genotype-phenotype correlations that are highly relevant for clinicians. For a recent systematic review of publications on PD genetics in underrepresented populations through October 2021, readers are referred **to reference 26**.

LRRK2

Monogenic (autosomal dominant) *LRRK2*-PD has a high prevalence in selected populations. Thought to have arisen from ancient founder events in the Middle East and Europe several millennia ago, the *LRRK2* p.G2019S variant has a frequency of ~40% in familial as well as sporadic PD cases in the Arab-Berber population in North Africa (Tunisia, Morocco and Algeria),[48] and ~15% among Ashkenazi Jewish patients with PD.[14,28] The prevalence is ~2% overall in European patients, with a South-to-North gradient, e.g., higher prevalence in Spain and Portugal and lower in Scandinavia.[29] The frequency is <2% overall in South America, but ranges from 0.2% in Peru to 4.2% in Uruguay, and is associated with the amount of South and Eastern European ancestry.[14,29,59] Another variant, p.R1441G, is concentrated in the Spanish Basque population, again thought to have arisen from a common founder, and accounting for around half of the familial PD cases there.[29,60] The p.R1441C variant is quite frequent (4% of PD patients) in southern Italy.[61]

In contrast, monogenic *LRRK2*-PD and in particular the p.G2019S variant is rare or absent in Asian populations (including South Asians; Chinese in mainland China and Taiwan; Koreans; Central Asians; and Southeast Asians in Singapore, Malaysia, and Vietnam).[46,49,62] The p.G2019S variant was found in 0.2-0.5% of Japanese PD patients, similar to the p.I2020T variant.[63] The recently discovered likely pathogenic p.N1437D variant was detected in 0.8% among mainland Chinese autosomal dominant PD.[46]

Similarly, few or no known pathogenic *LRRK2* mutations have been reported in patients of African ancestry in the sub-Saharan countries of Nigeria, Ghana, Zambia, and South Africa, although the sample sizes of these studies have been relatively small (total *n*~400), and the targeted screening for specific variants could have missed other known rare variants or new pathological variants.[9,64] Future systematic analyses of *LRRK2* variants in globally diverse samples will likely shed light on many more relevant variants.[65]

The penetrance of pathogenic *LRRK2* variants highly depends on age.[3,14,28-32,60] Most studies have focused on the p.G2019S variant,[3,14,28-32] with the largest one reporting a 49% cumulative incidence of PD by age 80 years.[14] Penetrance is also influenced by ancestry/geography,[29] as elegantly shown in a comparative study between Tunisian Arab-Berbers and Norwegians with the following estimates: 31% vs. 3% by age 50 years, to 86% vs. 43% by age 70 years, in Tunisia vs. Norway, respectively.[30] In a study of Ashkenazi Jewish p.G2019S carriers, the penetrance was found to be only ~25% by age 80 years.[28] Population-specific penetrance is probably influenced by many factors, including genetic background such as modifier variants and environmental factors, and estimates may differ on account of differences in access to health care and movement disorders neurological expertise at different centres that can result in ascertainment bias.[14,29,31-34]

The clinical phenotype of *LRRK2*-PD, particularly p.G2019S which has been the most widely studied, is for the most part indistinguishable from idiopathic PD, with slightly more benign disease features and progression including a lower rate of dementia and longer survival.[29,40] Interestingly, however, although it is commonly stated that *LRRK2*-PD has a comparable or slightly earlier age at onset vs. idiopathic cases,[5] a recent extensively updated MDSGene review revealed that 30% of (*n*=862) patients with pathogenic or likely pathogenic *LRRK2* variants had EOPD.[66]

In addition to the rare pathogenic variants that act with reduced penetrance, several common variants (MAF >1%) within *LRRK2* have been nominated as genetic risk factors.[1-3,29,39] The *LRRK2* "Asian" risk variants p.G2385R and p.R1628P are prevalent in some Asian populations: East Asians, including Chinese (both variants), Japanese (p.G2385R) and Koreans (p.G2385R); Thais (p.R1628P); Vietnamese (p.R1628P); and Malays (p.R1628P). These are each present in up to ~10% of patients, vs. approximately half that frequency in non-PD controls.[29,62] On the whole, *LRRK2* Asian variant carriers also seem to be clinically indistinguishable from idiopathic PD, although studies have been limited in sample size and results have sometimes conflicted.[29,62] It has been suggested that these risk variants (particularly when present in combination) might confer an earlier onset of PD,[67] and motor function may be worse with more frequent motor fluctuations, among p.G2385R carriers.[68] Higher-powered, systematic studies will allow more definitive conclusions regarding the impact of *LRRK2* Asian risk variants on the clinical phenotype and progression.

Besides *LRRK2*, the other main established causes of autosomal dominant PD, related to *SNCA* and *VPS35*, overall appear to be very rare.[49,69,70] To our knowledge, global differences in frequency or clinical phenotype have not been observed, except possibly for *SNCA* p.A53T, the most common *SNCA* missense mutation, in Greece (accounting for 5% of familial PD or sporadic EOPD cases) and *VPS35* p.D620N in Japan (1% of index patients with autosomal dominant PD).[69,70]

GBA1

Heterozygous *GBA1* variants currently represent the commonest identifiable genetic factor underlying PD globally.[12,13,71,72] *GBA1*-PD has a frequency of ~4-20% in most PD populations studied so far.[5,12,13,37,59,73,74] The link between Gaucher's disease (a multisystem lysosomal storage disorder caused by biallelic mutations in *GBA1*) and parkinsonism was initially studied systematically in Ashkenazi Jewish-ancestry patients.[75] This population has been considered to have the highest frequency (~20%) of *GBA1*-PD, associated with heterozygous *GBA1* variants.[37,73,76] Remarkably, a common, non-coding *GBA1* variant, rs3115534-G, was recently found in ~50% of West African PD patients, conferring an OR for PD of 1.6.[9]

"Severe" *GBA1* variants (which result in neuronopathic Gaucher's disease in homozygous/compound heterozygous carriers and are associated with more pronounced reductions in glucocerebrosidase [GCase] enzyme activity), such as p.L483P (also known as p.L444P), are associated with higher odds for PD development (OR>10) and more rapid disease progression, compared to "mild" variants (that are associated with non-neuronopathic Gaucher's disease in homozygous/compound heterozygous carriers and less reduced GCase activity), such as p.N409S (also known as p.N370S, with OR 2.2-7.8 for PD development).[5,37,38] Meanwhile, "risk" variants such as p.E365K (also known as p.E326K) and p.T408M (also known as p.T369M) are associated with a less increased risk of PD (OR<2, but >1) and do not cause Gaucher's disease in the biallelic state.[5,37,38] As observed with *LRRK2*, variants in other genes and polygenic modifiers have been shown to modify *GBA1*-PD disease penetrance.[5,36,37]

The mutational spectrum of *GBA1* varies according to ancestry with, for example, the "mild" p.N409S variant accounting for the majority (~70%) of *GBA1* variants among Ashkenazi Jewish patients.[37,73,76] In contrast, in East Asians (e.g., Chinese), the "severe" p.L483P variant appears to be predominant, reported by some authors to comprise the majority of pathogenic *GBA1* variants.[71,74] In India, a broad spectrum of *GBA1* variants was reported, with p.L483P being the most common, accounting for ~1/3 of variant carriers.[72] A Latin American Research Consortium on the Genetics of PD (LARGE-PD) study also found a predominance of p.L483P in Peru (65% of *GBA1*-PD cases), whereas in Colombia, p.L483P and p.N409S were ~25% each, with a (severe) population-specific variant (p.K237E, also known as p.K198E) accounting for ~50% of *GBA1*-PD patients.[38,77]

Patients with *GBA1*-PD may experience an overall more aggressive clinical course with a less favourable prognosis, with worse "axial" motor and cognitive-behavioural features, and poorer survival.[5,37,40,74] Variant carriers may also be at heightened risk of suboptimal outcomes after deep brain stimulation surgery (DBS).[78] These include outcomes related to cognition, axial motor features, function, quality of life, and reduction of dopaminergic medications[78] (~20% on average in some although not all[79] studies, vs. 30-50% in overall cohorts treated with subthalamic nucleus DBS). The frequency of *GBA1*-PD in patients presenting for DBS is not trivial, with studies documenting an over-representation of carriers in DBS cohorts (~12-20%).[78,79] This is likely because of their younger age and occurrence of troublesome motor response complications,[37,74] which are the major selection criteria for DBS.

PRKN* and *PINK1

PRKN-related PD is the most common form of autosomal recessive PD and has a global distribution.[45] Soon after its initial description in mostly consanguineous Japanese families with autosomal recessive juvenile PD, the condition was found in patients of various ancestries, with frequencies ranging from ~1-15% among EOPD cohorts.[45,49,80,81] However, there may yet be undiscovered clusters of *PRKN*-related PD, or other forms of monogenic PD, for example, among indigenous populations that have rarely been included in genetics research.[3,26] This has been exemplified recently by a high prevalence (>50%) of pathogenic *PRKN* variants found among indigenous Kadazan-Dusun EOPD patients in the East Malaysian state of Sabah.[3] Whether this remarkably high frequency reflects the occurrence of consanguinity in this historically isolated population, is a subject of ongoing investigation. In the MDSGene database, Iran has the highest number of *PRKN* patients according to country of origin (accounting for 13% of cases), with studies estimating rates of consanguineous unions ~40-80% in the country, in common with many other MENASA (Middle East, North Africa, and South Asia) nations.[45,80]

Although overall *PINK1*-related PD is much less common globally compared to *PRKN*,[45] a pathogenic *PINK1* missense variant (p.L347P) was found to be relatively common with a 7% prevalence among Malay EOPD patients (Malays number around 200 million in Southeast Asia).[49,82] There is interest in exploring this further in geographically close populations, such as Filipinos and Pacific Islanders/Polynesians, who are thought to share an "Austronesian" ancestry.[49,82] An early study reported a high heterozygous carrier rate of p.L347P (3/50=6%) among Filipinos, suggesting that this

specific variant could be an important cause for PD among Filipinos (who number ~110 million, of whom >10% live outside the Philippines in >100 countries).[49,62,82]

PARK7/*DJ-1*-related PD is the least frequent of the autosomal recessive forms of PD, with even fewer reported cases compared, for example, to *SNCA* or *VPS35*.[45,69]

Patients with autosomal recessive forms of PD, particularly biallelic *PRKN* carriers, have a relatively benign disease course, sometimes running over 50 years or more, and a favourable outcome can generally be expected from device-aided therapies.[40,45,47,49,81] In large part this is because they have less extra-nigral pathology and, therefore, overall are dopa-responsive and uncommonly have dementia (although recent studies suggest that autonomic dysfunction may be more common than previously recognized).[4,5,40,45,47,49,81] Motor response complications are common in *PRKN*-related PD and can be pronounced.[45,47,49] However, recent analyses of large numbers of patients revealed that *PRKN* patients are at lower risk of motor response complications compared to mutation-negative patients, after accounting for confounding factors such as young age at onset and/or long disease duration.[80,81]

Integration of genetics into the clinic

Obtaining genetic diagnosis through next-generation sequencing

Currently, a major barrier to the integration of genetics knowledge into neurology clinics is the lack of availability and access to genetic testing, especially in underrepresented populations (**Panel 3**). In the context of PD, opportunities for genetic testing have improved substantially over the past several years, driven in part by research programs,[7-13,15,49,50,74,82,85] which typically provide return of genetic results to collaborating investigators. The reducing cost of genetic testing has also resulted in greater access to clinical and direct-to-consumer testing,[14] albeit still significantly limited in low- and middle-income countries.[11] Encouragingly, multiple studies suggest a high interest among PD patients and their relatives to participate in PD genetics studies,[10-13,86,87,88] although data regarding patient (and clinician) attitudes towards, and knowledge of, genetic testing for PD are scarce from underrepresented populations.[11]

The decision of whom to test, and which type of genetic test to obtain, will depend on the individual patient and setting. PD genetic testing pathways for neurologists have been proposed,[10,87] although this is an evolving area that will undergo updating. Testing has a higher yield when targeting individuals with earlier onset of PD, a positive family history, and/or from high-risk ethnic groups. However, PD variant carriers are often clinically indistinguishable from non-carriers at the individual level, and the development of personalized medicine with increasing clinical actionability of genetics knowledge has caused a shift in perspective with some authors recently suggesting that all patients should be offered screening as a routine part of patient evaluation and care in PD.[12,13]

There are some caveats surrounding genetic testing, including possible adverse psychological effects and concerns surrounding genetic privacy and discrimination.[10,11,85-88] There are also concerns about potentially inaccurate results from research testing, which may not match the same levels of compliance with stringent regulations and quality control standards applied to clinical laboratories. Increasingly, researchers are calling for mechanisms to be put in place to verify research results in certified clinical laboratories,[85,86] and in some large initiatives (e.g., the PD GENEration [PD GENE] Study and the Rostock International PD Study [ROPAD], **Appendix Table 1**), genetic testing is performed, at the outset, in accredited laboratories.[12,13] On the whole, it seems appropriate that genetic results that are medically actionable and/or robustly associated with the phenotype can and should be returned to research participants who consent to receive such results. This process should be guided by the ethical principles of autonomy, beneficence, nonmaleficence, honesty, and reciprocity.[51,85-89] PD patients, at-risk individuals, and advocates desire transparent communication and feedback throughout the research process,[88] which may include results that are unclear such as genetic variants of uncertain significance (VUS; i.e., changes in a gene's DNA sequence that have an unknown effect on a person's health), and

this should be respected. Better engagement with research participants will also improve recruitment and retention, including of other family members.

Next-generation sequencing technologies are now widely employed, and WGS allows the comprehensive detection of variants in coding and noncoding DNA regions.[90] Long-read sequencing further improves the detection of structural variations compared to standard short-read WGS, and these relatively unexplored types of genomic variation have already shown relevance to PD in recent studies.[52,53,91] These new technologies are anticipated to improve the detection rate of pathogenic variants in known PD genes, and accelerate the discovery of novel PD genes. As an example of the former, recently, "heterozygous" *PRKN* cases were solved by identifying cryptic second mutations that were previously undetected, using long-read sequencing.[91] There has been much excitement in recent years of new discoveries for monogenic causes of late-onset dementia, cerebellar ataxia, and sensory neuropathy, e.g., related to non-coding repeat expansions in *NOTCH2NLC*, *FGF14*, and *RFC1*, respectively, and it remains to be seen if a similar scenario using these advanced tools will unfold in PD.[92]

Panel 3: **Underrepresented populations in PD genetic studies**

An important limitation of PD genomics/genetics studies is that these have mainly, until very recently, been carried out in European-ancestry populations, and to a lesser extent in East Asian populations, but largely not included other ancestries.[1,26,39] **Figure 1** shows that there are substantially more GWASs, and with much larger samples sizes, in European-ancestry populations compared to others populations such as East Asians, Latinos, and Africans (with some populations, e.g., Middle Eastern, having no PD GWAS to date). **Figure 3**, depicting the participation of countries in various international PD genetics research programs and consortia, similarly shows an underrepresentation of non-European populations, which for example account for only ~10% of the ~4K PD gene mutation carriers in the Michael J. Fox Foundation Global Genetics Parkinson's Disease Project (MJFF GGPD Study) on monogenic PD.[69]

There are myriad challenges for genetics research in underrepresented populations. These range from participant recruitment and the collection and processing of clinical data and biosamples, to genotyping/sequencing and analysis, and the interpretation and return (disclosure) of genetic results. Although studies of underrepresented populations are often challenging to conduct, efforts to promote diversity in genetic studies are vital to obtain a more complete and equitable picture of PD globally, and to achieve progress in the diagnosis, management, risk prediction, and prevention of PD across global populations. Conversely, failure to do so will result in genetic technologies inadvertently exacerbating, rather than reducing, existing health disparities.[24,25,83,84]

Fortunately, a "diversity, equity and inclusion (DEI)" mindset has gained wider recognition in recent years. Collaborative programs are promoting outreach efforts to include investigators, patients, and families from Africa, Asia, and South and Central America, among others. These have also improved capacity and infrastructure, and generated insights that are making an impact on the global PD genetics landscape.[7-9,26,30,32,33,41,44,48,49,54,64,68,69,73,74,77,80,82]

A prime example of these collaborative efforts is the Global Parkinson's Genetics Program (GP2). GP2 was created in late 2019 with the objective of developing a more complete understanding of PD pathogenesis, by democratising genetics/genomics discovery through inclusivity, and making this knowledge globally available and actionable.[7-9,26] A specific goal is to include a wide diversity of patients and researchers, with a strong emphasis on local and regional capacity-building.[7-9,26] Substantial progress has been made towards achieving the aim of recruiting ≥50K non-European-ancestry participants, out of a total sample of 200K.[7-9]

Current utility of enhanced PD genetics knowledge in the clinic

In practical terms, the determination of the genetic factor(s) underlying PD in the patients for whom we care often has relevant clinical impact. Specifically, PD genetics knowledge has clinical utility in: (1) improving the diagnosis of young/juvenile-onset cases and/or patients with atypical clinical features; (2) assisting in family and life planning; (3) potentially allaying anxiety, fear or guilt; (4) understanding the disease course and in prognostication; and (5) selecting and/or stratifying patients for treatments such as DBS.

The very early (sometimes juvenile) onset and/or occurrence of atypical features (e.g., presentation with craniocervical dystonia or a very long history of tremors in autosomal recessive EOPD) often lead to diagnostic "odysseys" over many years or even decades[49,93] and can involve potentially harmful misdiagnoses, e.g., as a functional tremor or functional gait disorder.[93] What ensues then are missed opportunities for proper early management including pharmacotherapy and family counselling/planning, resulting in a loss of function/life quality, unemployment, and even termination of pregnancy.[49] The latter could arise because of an erroneous assumption that a very early onset of PD portends a similar affliction in the offspring, and might be circumvented by more precise information about reproductive risks (specifically, autosomal recessive disorders being unlikely to manifest in children, particularly if there is no consanguinity between the patient and partner).[10,49,87] Better patient understanding of an underlying genetic cause can empower patients and help, in some instances, to allay guilt and anxiety that PD developed because of something the patient had done in the past (a belief held by nearly half of both PD patients and caregivers in one study conducted in urban Malaysia).[94]

A sensitive, culturally-appropriate, and nuanced approach (e.g., acknowledging the remaining uncertainties in predicting prognosis at an individual level) is needed when sharing genetic results with patients and families, preferably delivered by a trained clinician or genetic counsellor.[10,51,85-90,95] The authors would like to caution against "genetic determinism", i.e., the perception that phenotypes are exclusively controlled by an individual's genes, and highlight that there are many factors (genetic, epigenetic, environmental, psychosocial, etc.), most still poorly understood, that contribute to substantial variability (even with the same genetic variant) to a person's condition and his/her experience of it.[51] Multiple other issues require consideration in the genetic counselling process, including the possibility of stigma arising from test results (e.g., affecting marriage prospects) and the potential implications for family members; these have been extensively discussed in other publications.[10,51,85-90,95] A genomic multidisciplinary team approach, incorporating expertise in clinical evaluation, human genetics, bioinformatics, functional genomics, and genetic counselling, is advantageous to maximize diagnostic yield and improve patient management,[90,95] especially in more complex situations requiring considerable judgment and extrapolation. One example is in the interpretation of rare or newly discovered variants, including VUS.[90,95]

Now, when encountering a patient with EOPD, clinicians are advised to exercise caution in automatically deferring to the prevailing notion that "younger patients exhibit a more gradual disease progression" when conducting prognostic evaluations.[96] Rather, clinicians should consider that the disease trajectory depends in significant part on genetic factors. The statement may be true for *PRKN*-related PD and perhaps the other forms of autosomal recessive EOPD,[3,5,40,45,47,49,80-82] but is much less likely to be the case for *GBA1*- (or *SNCA*)-related PD[3,5,31,37,40,70,74] which often also cause EOPD,[5,35,49,59,69-71] but are associated with more rapid progression, likely reflecting, at least in part, a greater burden of Lewy body pathology.[4,5,31,37,40] Information on prognosis provided to patients and their families can help to shape forward-looking treatment plans[10] including, for patients at heightened risk, adoption of lifestyle, rehabilitative, and medical measures to try and delay the onset, or mitigate the effects, of falls and cognitive impairment. While the generally poorer response to DBS in *GBA1*-PD should not automatically preclude DBS as a potential treatment option for such patients (as the procedure could still confer substantial benefit in motor function and quality of life),[79] it does provide clinicians and families with more information to enable informed decision-making regarding life-changing - but invasive and costly[62] - treatments.

For the field to advance in understanding genotype-phenotype correlations, there needs to be more systematic phenotyping efforts using standardized/harmonized tools which will facilitate cross-cohort

analyses.[3,65] Guidelines are being developed for improved phenotype reporting in the genomic era.[7] The study of subtypes of PD, e.g., more benign vs. aggressive disease with the earlier development of gait and balance problems or dementia, or the responsivity to treatment, will generate new medical and biological insights. In this regard, longitudinal[40,81] and not just cross-sectional[45,66,70] data will be invaluable. Besides using conventional rating scales and patient-reported outcome measures, these efforts can be supported by technological advances, described further below.[97]

The clinical utility of PD genetics will likely expand in the near future into personalized therapeutics and lifestyle modification strategies for affected, as well as at-risk, variant carriers. Disease prevention can be a particularly important concern for at-risk persons,[88] and emerging studies suggest that lifestyle modifications might mitigate PD risk.[3,33,62,88,98,99] One example is the observation that caffeine consumption may be especially beneficial in *LRRK2* variant carriers, with one large study showing recently that asymptomatic *LRRK2* Asian risk variant carriers who are non-caffeine drinkers have up to 8x greater PD risk compared to wildtype-caffeine drinkers.[99] This finding may have significant public health implications[84] given their high frequency in multiple Asian populations, as described above.[29,62,67,68,99] Ultimately, with rapid advances integrating genetics/genomics with multiple layers of big and deep data (electronic health records, sensors, imaging, and 'omics, including exposomics and epigenomics), supported by advanced analytics, a scenario could be envisaged in which whether, and when, a person develops PD can be accurately forecast at an individual level.[3,15-18,97,98] This will open up the possibility of targeted primary and secondary preventative strategies in pre-symptomatic individuals.

Translation of genetics to facilitate therapeutic development

Currently, the most prominent gap in the PD field is the lack of effective disease-modifying treatments which can slow or even halt the progression of the disease by addressing its underlying biology,[6] and thus translate genetic findings into improved outcomes for patients. The early recruitment and stratification of participants by genetic status will hopefully start to curtail the failures of disease-modification trials in PD. Two likely major reasons for the long list of negative studies are that the disease has already advanced too far for therapies to arrest the pathogenic cascade, even in patients with clinically "early" PD; and that these trials have been performed approaching PD as a single entity, despite the fact that multiple aetiologies - linked to variable biological mechanisms - account for the disease.[4] Both these aspects are addressable with genetics. Regarding the former point, genetic variants can serve as the earliest definable upstream cause or predisposition to PD, and can be used with other biological markers (e.g., of synucleinopathy and/or neurodegeneration) to enable trials at very early stages of the pathological process (see also **Panel 2**).[16-18]

The prospect of participating in genetics-informed clinical trials is becoming increasingly relevant for PD patients and at-risk individuals,[5,6,10,12,13,15-18,21-23,37] and is an important source of engagement and hope for patients and families.[88] As shown in **Table 1**, current genetics-informed clinical trials primarily target *LRRK2* and *GBA1*-related pathways (six studies each), with fewer targeting *PRKN*/*PINK1* pathways (two studies). For *LRRK2* (and possibly also *VPS35* and *RAB32*), the main strategy currently is to correct the increased LRRK2 kinase activity by applying LRRK2 kinase inhibitors.[4-6,19,21,29,66] For *GBA1*, a major aim is to upregulate GCase activity (the rationale of "substrate reduction" to reduce the accumulation of glycolipid substrates that is standard therapy for Gaucher's disease, appears less attractive now for *GBA1*-PD with the negative results of the venglustat study, despite demonstrating target engagement).[4-6,22,23,37] For *PRKN*- or *PINK1*-related mitochondrial dysfunction, "mitochondrial enhancers" are being tested.[4,5]

However, even within "genetically-defined" PD, there may be a need for further stratification, for example for *GBA1* variants of different severities with different trajectories in disease progression (or with different effects on GCase structure and function),[5,37,38] or for *LRRK2* mutations that have a variant-dependent effect on functional outcomes in terms of LRRK2 kinase activity and other downstream biomarkers such as urine bis(monoacylglycero)phosphate (BMP) levels.[19,20,29] It has been argued, for example, that trials recruiting severe *GBA1* variant carriers may require a smaller sample size and/or

shorter duration, compared to trials recruiting mild or risk variant carriers.[5,37,38] It will also be important for trial arms to be balanced for different severities of variants.[5,37,38]

When considering future therapeutic development for common risk variants (such as the *LRRK2* Asian risk variants or the West African *GBA1* rs3115534-G variant), it could be argued, based on experience in drug development outside the PD field, that their (relatively small) genetic effect sizes may belie significant biological importance and potential druggability.[56,101]

Genetics-informed clinical trials face multiple obstacles, including slow recruitment. As evident from **Table 1**, few genetics-informed clinical trials (4/14=29%) currently enrol participants from outside North America and Europe. This lack of diversity contributes to delays in trial completion, exacerbates disparities, and limits our ability to generalize study results.[62,102] For example, in the first large-scale trial of a targeted treatment in *GBA1*-PD, recruitment of the 221 *GBA1* mutation-positive participants (>90% of whom were European-ancestry) took >4 years.[23] Recruitment should therefore be broadened, especially considering that other global populations have enriched cohorts of genetic PD involving *LRRK2*, *GBA1*, *PRKN*, and *PINK1*, as discussed earlier. Ongoing genetic testing of global populations with the identification of "new" cohorts with genetic forms of PD are of great value to rapidly identify and recruit patients for targeted biomarker studies and genetics-informed clinical trials. Ideally, the consenting process for these large-scale genetic projects should include consent for participants to be recontacted for future clinical trials.[85] Many promising strategies to promote clinical trial recruitment in underrepresented populations have been proposed.[102] These include the creation of truly global clinical trial networks, and having prespecified recruitment goals (e.g., ≥10-30% participants from underrepresented populations). The PD GENEration Study is an example of an initiative incorporating several of these measures, and in 2024 is extending its scope from North to South America, and beyond.

Conclusions and future directions

Genetics is becoming an increasingly powerful and available tool to understand and predict the risk of PD, its progression, and response to treatment, and brings us closer to providing personalized precision medicine. To fully harness the power of genetics/genomics in PD, it is crucial that we identify the broadest range of genetic variations across and within populations that influence the disease. There are myriad challenges for genetics research in underrepresented populations, and also rich opportunities, which are discussed further in **Table 2**.

These discoveries will provide critical information on molecular pathways, potential biomarkers, therapeutic targets, and disease expression (penetrance and clinical phenotype), which might differ across worldwide populations. PD genetics/genomics research will require interdisciplinary team science, involving a wide range of expertise and data, and engaging clinical, academic, philanthropic, industry, and regulatory/governmental partners, to make substantial advances possible. In all these efforts, an "open science/community resource" framework, with transparent and reproducible methods, will maximize yield and promote discovery. Concurrent measures to safeguard patient confidentiality and ensure fairness to contributing researchers, and respectful consideration of local cultural norms, are paramount to building trust and guaranteeing sustainable progress.[109]

Finally, as a field, it is important that we strive to ensure that the whole genetics/genomics research enterprise - being a flagship of international scientific collaboration - should result in fair prospects to promote health among the global community of patients and families, irrespective of geographical location, socioeconomic status, race, or gender.[84] Crucially, these efforts should include opportunities for participation in clinical trials of genetics-informed therapies, and access to newly developed and affordable treatments.

Search strategy and selection criteria

We searched PubMed for relevant English-language articles published between Jan 1, 2017 and July 1, 2024, using the following terms: “Parkinson’s disease”, in combination with “genetics” or “genomics”. We also checked reference lists in relevant articles and personal files. Articles published in the past five years were prioritized, although seminal older publications that were deemed important to provide context and enhance understanding were also included. Selected review articles were cited to provide readers with further details and references. The final reference list was generated on the basis of the relevance to the objectives of this Personal View.

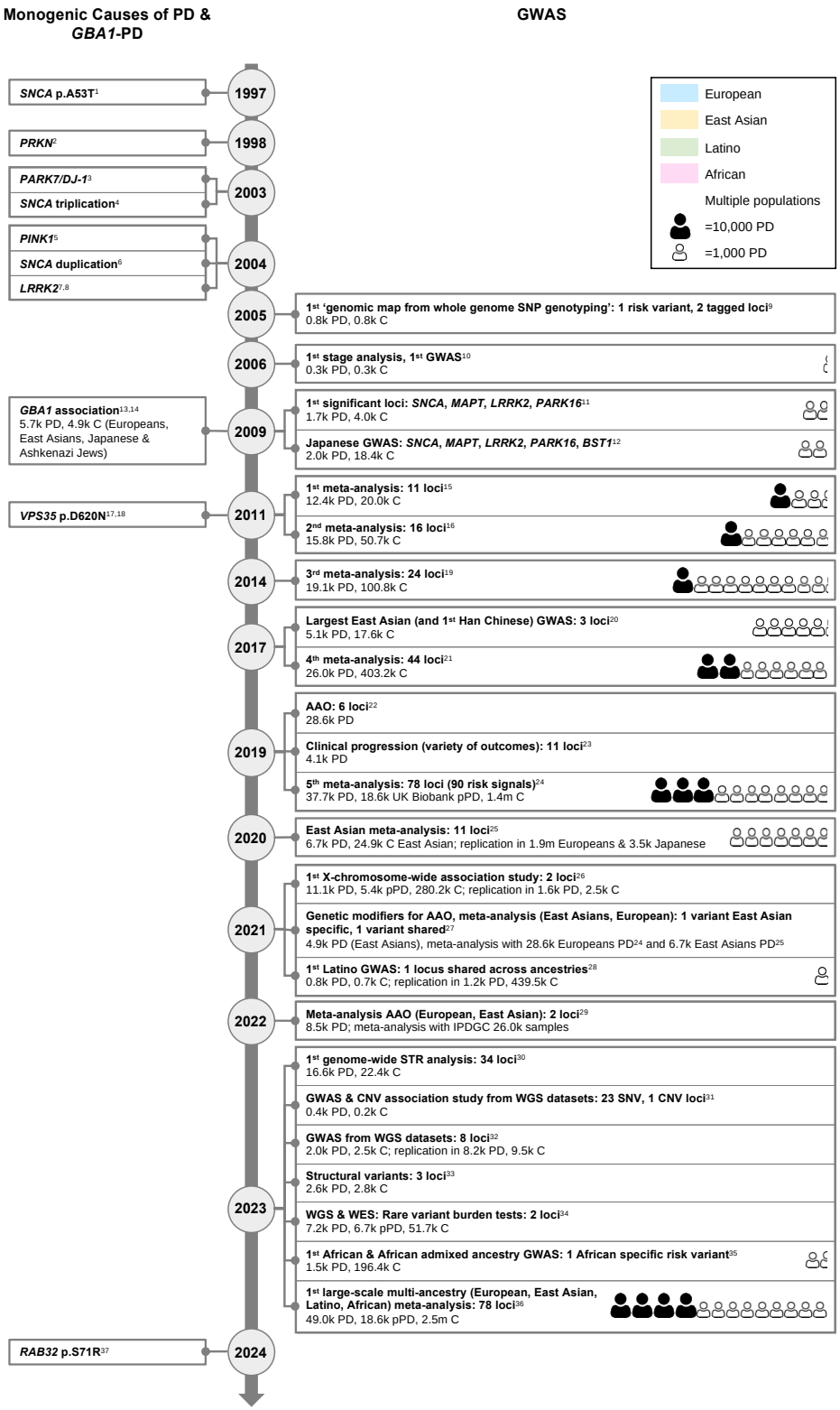

***Figure 1*: A brief historical timeline of Parkinson's disease (PD) genetics and genomics research**

Discoveries of monogenic causes of PD are shown on the left. On the right, genome-wide association studies (GWASs) are depicted. Over time, these have increased in size (human icons are depicted for the main GWASs/meta-GWASs for PD risk), ancestral diversity, resolution (recently employing next-generation sequencing technologies including WES, WGS, and even long-read WGS), and scope (investigating not only disease risk, but also phenotypic features such as AAO, disease progression, and mortality - we list here only studies on AAO). Studies are listed according to the date/year of journal acceptance. For context, the first GWASs (for cardiovascular and ophthalmic disease) were published in 2002 and 2005, respectively. Supporting references can be found in **Appendix Figure 1**. AAO=Age at onset; C=Control cases; CNV=Copy number variant; k=thousand (rounded to the closest 100); m=million (rounded to the closest 100,000); PD=Parkinson's disease cases; pPD=Proxy Parkinson's disease cases; SNV=Single nucleotide variant; STR=Short-tandem repeat; WES=Whole exome sequencing; WGS=Whole genome sequencing.

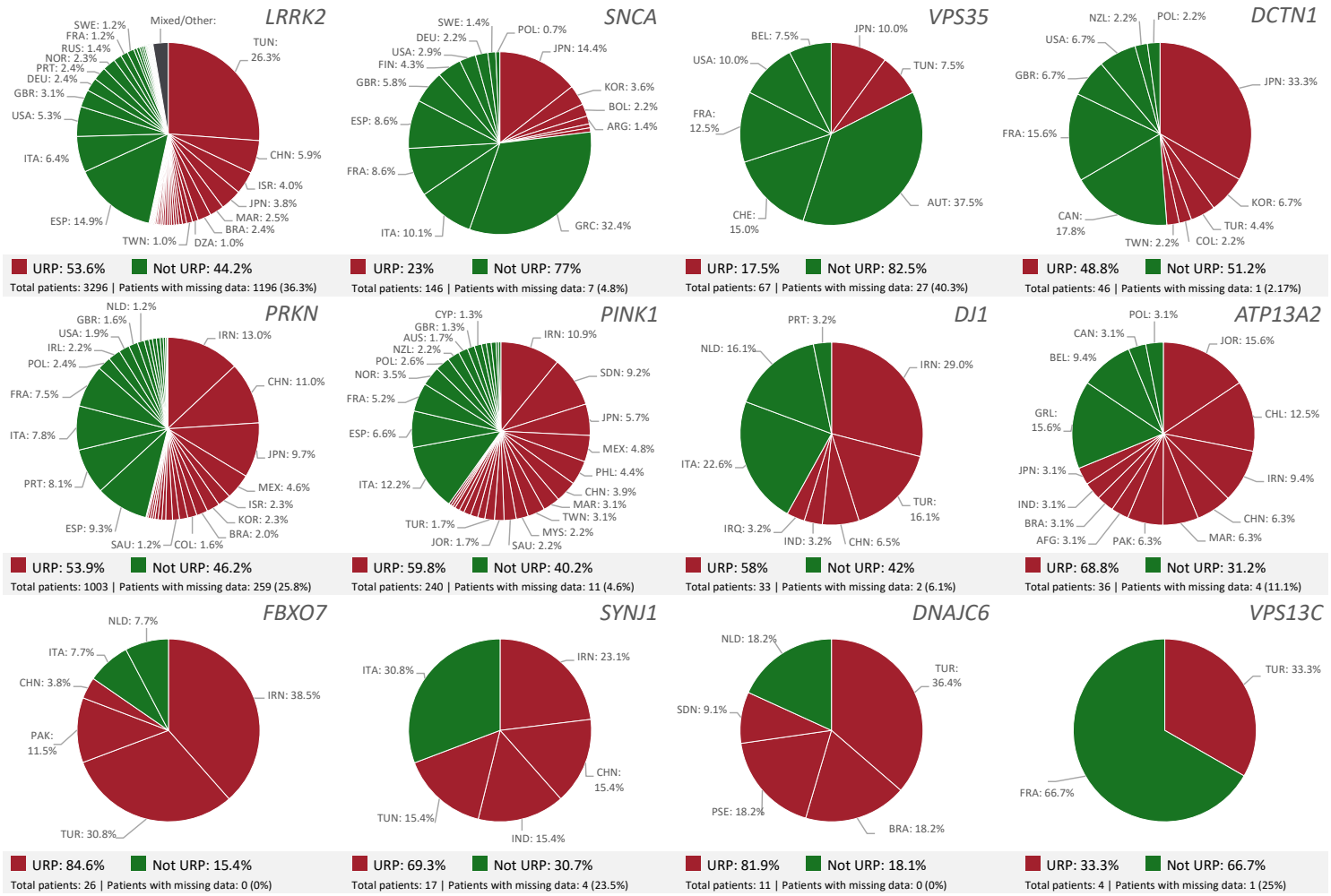

Figure 2: **A comparison of autosomal dominant (top row) and autosomal recessive (bottom two rows) forms of PD and atypical parkinsonian disorders in underrepresented populations (URPs) vs. European-ancestry populations, using the MDSGene database**

These pie charts, derived from the MDSGene database (www.mdsgene.org, accessed on 30 May 2024) show relatively higher frequencies in underrepresented populations (depicted in red) vs. European-ancestry populations (green) of *LRRK2*-PD and autosomal recessive forms, especially the atypical parkinsonian disorders related to *ATP13A2*, *FBX07*, *SYNJ1*, and *DNAJC6*. An important caveat is that the sample sizes for the latter conditions are currently small. MENASA (Middle East, North Africa, and South Asia) countries (e.g., Iran, Turkey, Jordan, and Palestine from the Middle East; Tunisia, Morocco, and Sudan from North Africa; and India and Pakistan from South Asia), comprise a relatively large proportion of the cases in underrepresented populations. The counts denote the numbers of patients with "possibly pathogenic", "probably pathogenic", and "definitely pathogenic" variants, according to MDSGene pathogenicity scoring.

Country abbreviations are based on the International Organization for Standardization (ISO) three-letter codes (https://www.iso.org/obp/ui/#search): AFG=Afghanistan; ARG=Argentina; AUS=Australia; AUT=Austria; BEL=Belgium; BLR=Belarus; BOL=Bolivia; BRA=Brazil; CAN=Canada; CHE=Switzerland; CHL=Chile; CHN=China; COL=Colombia; CRI=Costa Rica; CUB=Cuba; CYP=Cyprus; CZE=Czechia; DEU=Germany; DNK=Denmark; DZA=Algeria; ECU=Ecuador; EGY=Egypt; ESP=Spain; EST=Estonia; FIN=Finland; FRA=France; FRO=Faroe Islands; FSM=Federated States of Micronesia; GBR=United Kingdom; GRC=Greece; GRL=Greenland; GTM=Guatemala; HUN=Hungary; IND=India; IRL=Ireland; IRN=Iran; IRQ=Iraq; ISR=Israel; ITA=Italy; JOR=Jordan; JPN=Japan; KAZ=Kazakhstan; KOR=South Korea; LBY=Libya; LKA=Sri Lanka; LTU=Lithuania; MAR=Morocco; MEX=Mexico; MLT=Malta; MYS=Malaysia; NLD=Netherlands; NOR=Norway; NZL=New Zealand; PAK=Pakistan; PER=Peru; PHL=Philippines; POL=Poland; PRI=Puerto Rico; PRT=Portugal; PSE=Palestine; RUS=Russian Federation; SAU=Saudi Arabia; SDN=Sudan; SRB=Serbia; SVK=Slovakia; SWE=Sweden; TUN=Tunisia; TUR=Turkey; TWN=Taiwan; URY=Uruguay; USA=United States; ZAF=South Africa; ZMB=Zambia.

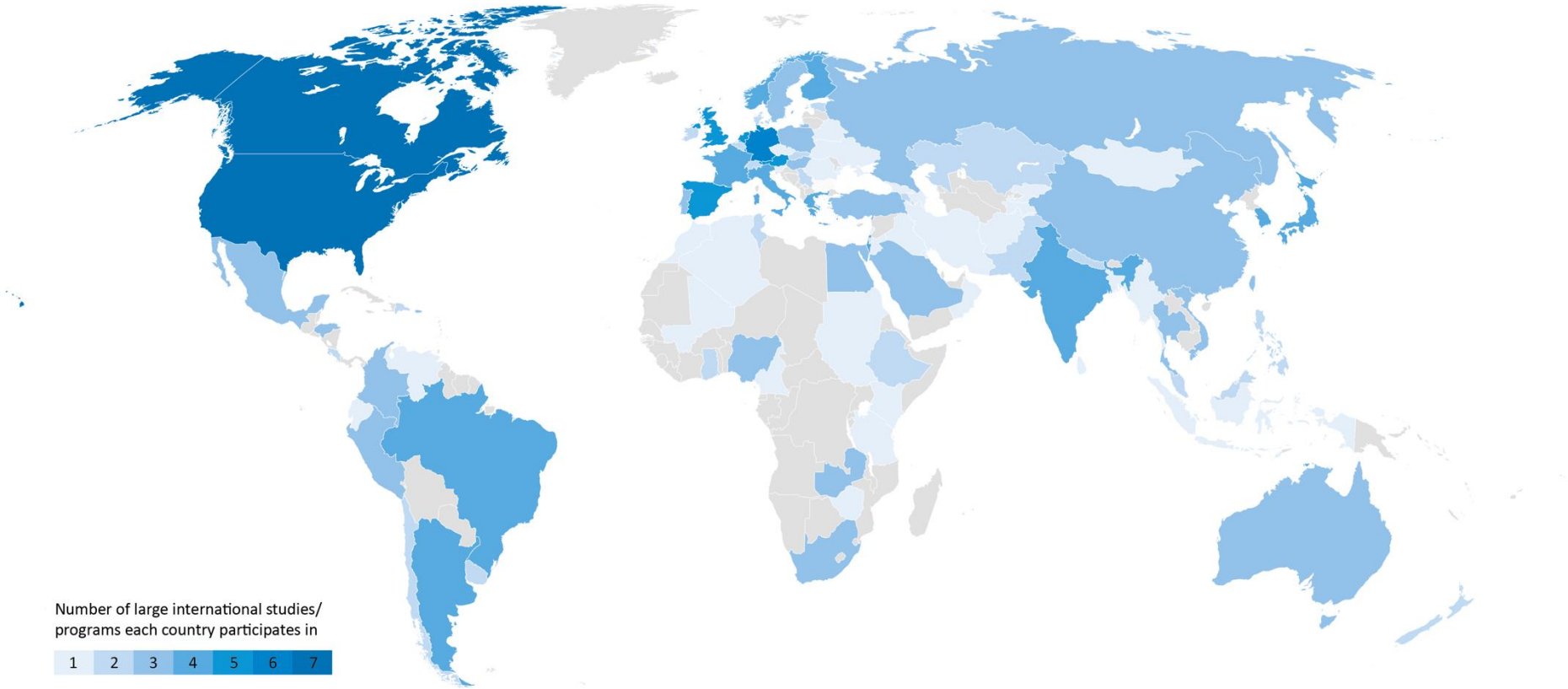

***Figure 3*: World map of countries participating in ongoing, large international Parkinson's disease genetic research studies, programs, and consortia**

The map highlights countries in which centers are involved in international studies, programs and consortia from the field of Parkinson's disease (PD) genetics, including the Global Parkinson's Genetics Program (GP2), the Michael J. Fox Foundation Global Genetics Parkinson's Disease Project (MJFF GGPD), the Movement Disorder Society Genetic Mutation Database (MDSGene), the International Parkinson's Disease Genomics Consortium (IPDGC), the Latin American Research Consortium on the Genetics of PD (LARGE-PD), the Luxembourg-German-Indian Alliance on Neurodegenerative diseases and Therapeutics (Lux-GIANT) Consortium, PD GENEration (PD GENE) Study, and the Parkinson's Progression Markers Initiative (PPMI). These studies/programs were selected based on international reach, relatively large size (involving ≥10 centres), and ongoing presence. The different shades of blue reflect the number of studies/programs the highlighted country is involved in (as of 8 February 2024). The darker the shade of blue, the more studies/programs the respective country is participating in. A listing of studies/programs and included countries can be found in **Appendix Table 2**.

Trial ID, Sponsor, Study Location	Study Design and Intervention	Core Eligibility Criteria	Primary Outcome Measure(s)	Study Status; Publication(s)
Gene target population: *LRRK2*				
· **NCT03710707** · Denali Therapeutics · USA 8 centres	· Randomized, double-masked, parallel assignment · **DNL201** 30mg or 50mg TID PO for 42d vs. matching placebo	· Sporadic PD; **PD patients with *LRRK2* variants** · DaT scan deficit consistent with PD; Age 30-80y; H&Y 1-3; MoCA ≥24; Absence of significant pulmonary disorders	· Treatment-emergent AEs and SAEs (laboratory tests, ECG, vital signs, neurological examination)	· Start: 04-12-2018 · End: 06-12-2019 · Status: "Completed" · Jennings et al. *Sci Transl Med* 2022[21]
· **NCT05009199** · Invicro · USA 1 centre	· Non-randomized, single group · **Caffeine** in repeated PO doses · After a caffeine wash-out ≥24h, participants receive a single injection of [18F]MNI-444 followed by brain PET scan of up to 90m to establish baseline adenosine A2A receptor binding	· **Non-manifesting carriers with *LRRK2* pathogenic/risk variants** · Age ≥30y; Absence of DaTscan deficit	· Pharmacodynamics and pharmacokinetics of multiple doses of oral caffeine on striatal binding of the adenosine A2A receptor ligand [18F]MNI-444	· Start: 26-04-2021 · End: 12-05-2022 · Status: "Completed"
· **NCT05355064** · Neuromed IRCCS · Italy 1 centre	· Non-randomized, single group, open-label · **Trehalose** 4g/d PO for 24w	· Idiopathic PD; **PD patients with *LRRK2* variants** · Age 18-80y; H&Y >1	· Safety and AEs (laboratory tests and physical/neurological examination)	· Start: 05-2022 (estimated) · Status: "Not Yet Recruiting"
· **NCT05348785** · Biogen · USA 33 centres; Austria 2; Canada 5, China 4; France 9; Germany 12; Israel 3; Italy 9; Japan 5; Netherlands 3; Poland 6; Spain 10; UK 6	· Randomized, double-blind, parallel assignment · **BIIB122/DNL151** 225mg/d PO for 48-144w, vs. matching placebo	· Early-stage PD patients; **PD patients with pathogenic *LRRK2* variants who completed early termination visit of NCT05418673** · Age 30-80y; PD duration ≤2y; OFF mH&Y 1-2; OFF MDS-UPDRS II+III ≤40	· Time to confirmed worsening (i.e., a worsening event sustained over 2 consecutive assessments) in MDS-UPDRS Parts II+III over the treatment period up to 144w	· Start: 19-04-2022 · Status: "Recruiting"

· **NCT05418673** · Biogen · USA 12 centres; France 5; Germany 2; Italy 1; Spain 6; UK 1	· Randomized, double-blind, parallel assignment · **BIIB122/DNL151** 225mg/d PO for up to 180w, vs. matching placebo	· **PD patients with pathogenic *LRRK2* variants** · Age 30-80y; PD duration ≤5y; OFF mH&Y 1-2.5; OFF MDS-UPDRS II+III ≤40	· Time to confirmed worsening (i.e., a worsening event sustained over 2 consecutive assessments) in MDS-UPDRS Parts II+III over the treatment period up to 180w	· Start: 26-08-2022 · End: 27-07-2023 · Status: "Terminated" by Sponsor*
· **ChiCTR2200064198** · The First Affiliated Hospital of Zhengzhou University · China 1 centre	· Randomized, double-blind, parallel assignment · Donor **fecal microbiota transplantation (FMT)** vs. autologous FMT	· ***De novo* PD patients with *LRRK2* variants** · Age 18-75y; H&Y 2-3; Absence of other PD genetic variants; Absence of family history of PD; Absence of use of probiotics or antibiotics within 3m prior to trial	· Change in MDS-UPDRS and H&Y scores	· Start: 20-09-2022 · Status: "Recruiting"
Gene target population: *GBA1*				
· **NCT02941822** · University College London · UK 1 centre	· Non-randomized, single group, open label · **Ambroxol** with increasing dose from 60 to 300mg TID PO over 28d, then 420mg TID to 6m	· **PD patients with and without heterozygous *GBA1* mutations** · Age 40-80y; H&Y 1-3	· CSF and blood GCase and ambroxol levels	· Start: 12-2016 · End: 05-2018 · Status: "Completed" · Mullin et al. *JAMA Neurol* 2020[22]
· **NCT02906020** · Sanofi-Genzyme · USA 19 centres; Austria 1; Canada 3; France 1; Germany 2; Greece 1; Israel 4; Italy 5; Japan 5; Norway 1; Portugal 2; Singapore 2; Spain 2; Sweden 1; Taiwan 1; UK 2	· Randomized, double-blind, parallel assignment · Part 1: **GZ/SAR402671 (venglustat)** PO with increasing dose of 4, 6 and 15mg for 4w · Part 2: Venglustat QD with dose determined in part 1 for 52w, vs. matching placebo	· **PD patients with heterozygous *GBA1* mutations** · RBD by PSG or questionnaire; Age 18-80y; PD symptoms ≥2y; H&Y ≤2; MoCA ≥20; No concomitant *LRRK2* p.G2019S mutation; Absence of cortical or posterior subcapsular cataract	· Part 1: Treatment-emergent AEs and SAEs (laboratory tests, ECG, vital signs, neurological and physical examination including ophthalmological abnormalities) · Part 2: Change from baseline to 52w in MDS-UPDRS II+III	· Start: 15-12-2016 · End: 27-05-2021 · Status: "Completed" · Peterschmitt et al. *J Parkinson Dis* 2022;[100] Giladi et al. *Lancet Neurol* 2023[23]
· **NCT04127578** · Prevail Therapeutics · USA 5 centres; Israel 4	· Non-randomized, sequential assignment, open label · Single dose of **LY3884961** (dose level 1 or 2), administered intra-	· **PD patients with heterozygous *GBA1* mutations** · Age 35-80y; OFF H&Y 3-4; MoCA ≥14; Negative screening	· From baseline to 5y: Treatment-emergent AEs and SAEs, including brain and spine MRI and NCS	· Start: 03-01-2020 · Status: "Recruiting"

	cisterna magna, followed by methylprednisolone IV 6 pulses over 3m	for *M. tuberculosis*; Absence of unstable autoimmune disease	· From baseline to 24m: Treatment-emergent immunogenicity of AAV9, GCase, and NfL in blood; and immunogenicity of AAV9 and GCase in CSF	
· **NCT05287503** · Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta · Italy 3 centres	· Randomized, double-blind, parallel assignment · **Ambroxol** hydrochloride 1200mg/d (400mg TID) PO for 52w (with initial titration from 200mg/d for the first 25d) vs. matching placebo	· **PD patients with heterozygous *GBA1* mutations** · Age 21-80y; PD symptoms >5y; H&Y ≤3	· Change from baseline to 52w in MoCA, and conversion rate from normal cognitive function (PD-N) to mild cognitive impairment (PD-MCI) and from PD-N or PD-MCI to Parkinson-Dementia (PD-D)	· Start: 15-02-2022 · Status: "Recruiting"
· **NCT05819359** · Bial R&D Investments · USA 28 centres; Canada 2; France 6; Germany 6; Italy 9; Netherlands 3; Poland 3; Portugal 4; Spain 7; Sweden 2; UK 5	· Randomized, double-blind, parallel assignment · **BIA 28-6156** 10mg or 60mg/d PO vs. matching placebo	· **PD patients with heterozygous *GBA1* mutations** · Age 35-80y; PD duration 1-7y; mH&Y ≤2.5; MoCA ≥22	· Time from baseline to clinically meaningful progression on MDS-UPDRS II and III over the treatment period up to 78w	· Start: 31-03-2023 ·Status: "Recruiting"
· **NCT05830396** · University Medical Center Groningen · Netherlands 1 centre	· Randomized, double-blind, parallel assignment · **Ambroxol** 1800mg/d PO for 48w (with initial titration from 600mg/d over 2w), followed by 12w washout period, vs. matching placebo	· **PD patients with heterozygous *GBA1* mutations** · Age ≥18y; PD duration ≤10y	· Change from baseline to 60w in MDS-UPDRS III	· Start: 05-2023 · Status: "Recruiting"
Gene target population: *PRKN*/*PINK1*				
· **DRKS00015880** · Universitätsklinikum Schleswig-Holstein Campus Lübeck · Germany: Multi-centre	· Randomized, double-blind, parallel assignment · QuinoMit Q10 fluid ubiquinone emulsion (equivalent dosage of	· **PD patients with homozygous or heterozygous *PRKN*/*PINK1* mutations;** PD patients with polygenic mitochondrial profile (based on eight predefined SNPs);	· Change from baseline to 24w in MDS-UPDRS III	· Start: 15-12-2018 · Status: "Recruiting"

	1200mg **Coenzyme Q10**) TID PO for 6m, vs. matching placebo	PD patients without polygenic mitochondrial profile · Age ≥18y; MMSE ≥24; Absence of treatment with coenzyme Q10 within 3m prior to trial		
· **DRKS00019932** · Universitätsklinikum Schleswig-Holstein Campus Lübeck · Germany 1 centre	· Randomized, double-blind, parallel assignment · **Vitamin K2** (MK-7) 1mg/d PO for 7d, vs. matching placebo	· **PD patients with biallelic *PRKN*/*PINK1* mutations**; non-genetic PD patients; healthy controls · Age ≥18y; Absent of treatment with vitamin K2 or vitamin K-antagonist within 1m prior to trial	· Change in magnetic resonance spectroscopic measurements of adenosine triphosphate and phosphocreatine	· Start: 03-02-2020 · Status: "Not recruiting"

***Table 1*: Clinical trials recruiting subjects with specific Parkinson's disease genetic variants**

A systematic search was conducted on two international clinical trial registries, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int) (last accessed on 22 March 2024), using the following search terms for the following conditions: *LRRK2*, *GBA1*, *SNCA*, *VPS35*, *Parkin*/*PRKN*, *PINK1*, and *PARK7*/*DJ-1*. One trial on *GBA1*-PD was withdrawn without any enrolled participants (NCT02758730) and is not included in this table. AEs=Adverse events; d=Day; DaT=Dopamine transporter; ECG=Electrocardiogram; GCase=Glucocerebrosidase; H&Y=Hoehn and Yahr; m=Month; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; mH&Y=Modified Hoehn and Yahr; MoCA: Montreal Cognitive Assessment; NCS=Nerve conduction study; NfL=Neurofilament light chain; PD=Parkinson's disease; PO=Per oral intake; PSG=Polysomnography; RBD=Rapid eye movement sleep behavior disorder; SAEs=Serious adverse events; SNPs=Single nucleotide polymorphisms; w=Week; y=Year. *This trial was terminated due to the sponsor's decision to revise the trial plans for BIIB122, and not due to safety concerns.

Challenges	Opportunities and Successes
1. Generating genetic (and accompanying clinico-demographic and other biomarker) data	
· The mutational spectrum and frequency of genetic variants, which differ depending on the cohort ancestry, are unknown in many underrepresented populations. For example, autosomal recessive forms of PD/parkinsonism may be more common in underrepresented populations but remain underreported.[3,43-45,82] The vast majority of families with an autosomal dominant pattern of transmission also remain unsolved in most underrepresented populations, in part because of the rarity of monogenic *LRRK2*-PD (e.g., in Asians and Africans).[3,46,49,62-64,66,70] · Because of the lack of research on monogenic PD in underrepresented populations, the more relevant genes/variants in these populations may not be translated into biomarker discoveries or therapeutic targets. · Similarly, there is a lack of research into the polygenic factors underlying PD in non-European populations,[8,9,26,39,52,54] which results in poorer disease prediction and targeted management for these populations.	· Collaborative programs promoting outreach to diverse populations will help to determine the frequency of known pathogenic variants in patients across the world. New causative genes likely remain to be identified in underrepresented populations, since in many families, variants are not detected in established or candidate genes.[3,26] Recently, for example, large clinico-genomics datasets that included African and Asian families were utilized in the discovery and validation of new monogenic causes of PD (*RAB32* p.S71R and *PSMF1*).[41,103] · The study of different populations can help to discover, fine-map, and assess heterogeneity at, disease risk loci.[2,8,9,51,54] For example, studies in East Asians, Latinos, and Africans have identified novel PD risk loci not found in European-ancestry patients, despite their relatively smaller sample sizes, and increased fine-mapping resolution of causal variants at known PD loci.[2,8,9,51,54] Recently, efforts to combine East Asian, Latino, and African datasets in the first large-scale multi-ancestry meta-analysis (MAMA) of PD GWASs, yielded 12 novel PD risk loci.[8]
· There are challenges with participant recruitment and clinical data collection. Barriers to physical access to some participants exist due to poor transportation infrastructure and geographical obstacles.[11,49] Clinicians may lack specialist training in PD and related movement disorders which in turn affects diagnostic accuracy.[11,62] Clinics are frequently overcrowded and the time available for patient evaluations may be very limited due to human resource limitations.[62] Most clinician-researchers in underrepresented populations do not have protected time to conduct research, including collection of samples and data. The lack of electronic health records or databases render systematic clinical data collection challenging.	· Helpful measures could include the provision of reimbursements (e.g., to help offset participants' travel costs); training of clinicians and researchers (e.g., in the use of diagnostic criteria and brief clinical rating scales which may be particularly helpful for researchers facing severe time constraints); and funding for clinic assistants.[7,62,102,104] · For true engagement to occur, collaborative programs need to work closely with underrepresented populations regarding their specific needs and gaps, as the readiness level and barriers can be different, and unique to each population.
· There is limited research funding and laboratory infrastructure in many underrepresented populations. · Some centres in low- and middle-income countries face problems with the initial steps of biosample storage and DNA extraction. In most cases, collections are limited to biosamples that are relatively easier to process/store (instead of, e.g., samples such as peripheral blood mononuclear cells or patient-derived fibroblasts, that can permit deeper exploration of genetic findings), resulting in fewer opportunities to participate in large international biomarker studies, and potentially also clinical trials (since various molecular markers are being employed for patient selection/stratification and/or to demonstrate target and pathway engagement of putative treatments).[4,5,15-23,37] · Institutional/governmental regulations on sample and data collection and sharing across countries can pose significant hurdles.[7]	· Helpful measures could include the provision of funding for equipment purchase (e.g., ultralow-temperature freezer) and laboratory assistants. · Advanced biobanking requires significant funding, human resource support, planning, and coordination. The recent enrolment of an African site as a PPMI collaborating centre is an example of diversification efforts; participants from Malaysia are being recruited for biosample collections of *LRRK2* Asian risk variants, with funding support from the MJFF. · Researchers can benefit from assistance with ethics board applications to permit international sample/data sharing. · Studying populations outside their ancestral country of origin (e.g., Chinese in Taiwan, Malaysia, Singapore, and the USA; Indians in the USA, Malaysia, and the United Kingdom; Afghans in the USA and Germany; or Uzbeks in Kyrgyzstan) can help to circumvent the problem of the inability to send samples/data out of these countries.

	Studying underrepresented populations in countries with stronger healthcare and research infrastructure (e.g., immigrant groups in North America and Europe) can also be an effective strategy.
2. Interpreting genetic data	
· Deciphering the pathogenicity of variants can be challenging. The underrepresentation of non-European-ancestry groups in current genomics databases leads to a much higher frequency of VUS in these populations, since the background population frequencies of detected variants are unknown.[11,83] · Studying the co-segregation of a genetic variant with disease in affected and unaffected family members is useful; however, extended pedigrees may not be available and this is also more difficult to perform in resource-limited contexts.[11,90] Likewise, large case-control datasets may not be available to test for gene/variant-disease associations, and functional studies are expensive and complex to undertake.[11,90] · Multidisciplinary genomics team[90,95] access currently remains very limited in underrepresented populations.	· Initiatives to create population-based genomics databases are underway in underrepresented populations, such as the Human Heredity and Health in Africa Consortium (H3Africa, across multiple African countries), the GenomeAsia 100K Project (across multiple Asian countries), GenomeIndia, the SG10K Consortium (Singapore), the Taiwan Biobank, the Mexico Biobank, and the Oceanian Genome Variation Project (across multiple Pacific Island nations) (see **Appendix Table 1** for weblinks). · Various online tools relating to PD genetics have become publicly available to assist in the interpretation of genetic variants and genotype-phenotype correlations[38,43,45,66,70] (**Appendix Table 1**). As an example, the recently updated MDSGene review since the last one in 2017 on *LRRK2* variants included >10x more (292 vs. 23) variants, and is a useful resource for clinicians, genetic counsellors/clinical geneticists, and researchers.[66] · Large-scale or even full variant spectrum functional testing is becoming available for selected genes.[19,105] · There should be collaborative opportunities for functional assaying, e.g., of LRRK2 kinase and glucocerebrosidase enzyme (GCase) activities.[19,20] Recently, the field witnessed the rapid investigation of a novel African-ancestry PD GWAS hit (*GBA1* rs3115534-G)[9] by a concerted international collaboration.[106] A variety of tools (including long-read DNA and RNA sequencing and CRISPR editing) were utilized to reveal a novel mechanism (intronic branchpoint disruption) for increased PD risk, opening up a potential therapeutic target for a very common genetic variant in a very underserved population.[106]
· There is a lack of expertise in handling large/complex datasets, with a major shortage of geneticists and bioinformaticians in underrepresented populations.[26] · Computing infrastructure for the storage and analysis of large datasets is expensive to set up and maintain.	· From its inception, GP2 has prioritized capacity building in genetics/genomics analyses and bioinformatics in underrepresented populations.[9,26,59] Ongoing initiatives include the creation of online training modules, in-person data science and clinical workshops, mentorship of teams by experienced researchers, and provision of funding for degrees for trainees (e.g., to pursue PhD or Master in Genetics Data Science) or travel for training opportunities. · Access to cloud computing platforms hosted by large research consortia or collaborators in high-income countries could be shared with researchers in underrepresented populations.
· Current genotyping arrays and polygenic scores (which aggregate the small effects of many genetic risk variants in predicting relevant phenotypes/clinical outcomes) are Eurocentric and are not optimal for use in non-European-ancestry populations; the accuracy of polygenic scores	· Improved genotyping tools, such as the NeuroBooster Array (NBA), are designed to capture global diversity.[108] · Leveraging multi-ancestry datasets and analytical innovations (e.g., in statistical methods and software tools) will capture a broader range of genetic variation associated with PD, and improve the accuracy of polygenic scores.[1,2,8,39]

decreases with increasing genetic distance from the discovery population.[24,25,39,107] · Clinical implementation of polygenic scores is still in its infancy even in sophisticated healthcare settings, and much more development of clinical polygenic score assays, including reporting workflow, is needed.	· Besides forecasting the development of PD, emerging studies show the potential utility of polygenic scores in predicting the age at disease onset; motor progression; development of dyskinesias, cognitive decline/dementia, or impulse control disorders; response to medical and surgical therapies (i.e., pharmacogenomics and surgicogenomics); as well as mortality.[1-3,107]
3. Returning genetic data	
· There is a major lack of genetic counsellors/clinical geneticists in underrepresented populations, who ideally would be involved in pre- and post-test counselling.[10,11,85-87] · Many clinicians receive only rudimentary education in genetics/genomics, and may lack the knowledge and skills to effectively communicate genetic findings, and incorporate these into the care of the patient and family.[10,11,85-87] · In some communities with poor biological knowledge of diseases and prevalent superstitions, patients with genetic disorders and their families can be considered "cursed," with extremely negative psychosocial repercussions.[11] · Countries may lack legal protections against genetic discrimination (e.g., regarding insurance or employment).[10,11,85-87]	· Efforts are needed to increase the availability and accessibility of genetic counselling; one step would be establishing accredited training pathways for genetic counsellors/clinical geneticists.[11] At the same time, training should be provided to a broader audience (including neurologists and PD nurses) to provide some level of genetic counseling.[10,11,85-87] The creation of guidelines for clinicians and checklists for PD genetic discussions with minimum talking points could be helpful.[85,87] · The knowledge and readiness of healthcare workers and patients can be improved through outreach and educational programs.[10,11,83,85-87] Increasing health literacy on the potential biological risks of consanguinity can reduce the burden of autosomal recessive disorders, and has to be conducted sensitively considering local cultural values.[11] · Advocacy and engagement with stakeholders, including policymakers, health and research institutes, medical and patient-support organizations, and industry partners, are essential in shifting healthcare and social policies to enhance support for patients living with genetic disorders, reduce stigma, and enact protections against genetic discrimination.[11]

***Table 2*: Challenges and opportunities of genetics research in underrepresented populations**

GP2=Global Parkinson's Genetics Program; GWAS=Genome-wide association study; MJFF=Michael J. Fox Foundation; PD=Parkinson's disease; PPMI=Parkinson's Progression Markers Initiative; VUS=Variants of uncertain significance.

Contributors
SYL designed the study, searched the literature, did the data collection, analysis, and interpretation, and wrote the first draft of this Review, including the Panels and Table 2. AAA, TST and SYL designed and drafted Figure 1. CK, LML, and NB designed and drafted Figures 2 and 3. AHT designed and drafted Table 1. All authors contributed to the final revisions of the manuscript.

Declaration of interests
SYL is an employee at the University of Malaya. He has received stipends from the International Parkinson and Movement Disorder Society (MDS) as Chair of the Asian-Oceanian Section, and Science Advances as Associate Editor (Neuroscience). He reports consultancies from the Michael J. Fox Foundation (MJFF), the Aligning Science Across Parkinson's-Global Parkinson's Genetics Program (ASAP-GP2), and Neurotorium Editorial Board; honoraria for lecturing from the MDS, Lundbeck, Eisai, and Medtronic; and research grants from the Malaysian Ministry of Education Fundamental Research Grant Scheme and the MJFF.

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IM reports receiving research grants from the National Institutes of Health (1R01NS112499), the MJFF, and the ASAP-GP2. He is also a member of the MDS-PAS Executive Committee and the PDGENEration Latino Advisory Council from the Parkinson's Foundation and has received honoraria as speaker from the MDS.

LML reports receiving support from the Bachmann-Strauss Dystonia & Parkinson Foundation as part of a research fellowship. She also received a travel stipend to attend the Samuel Belzberg Dystonia Symposium in 2023.

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AJN is employed by Queen Mary University of London (QMUL). He reports grants from Parkinson's UK, Barts Charity, Cure Parkinson's, National Institute for Health and Care Research, Innovate UK, Solvemed, the Medical College of Saint Bartholomew's Hospital Trust, Alchemab, and the MJFF. He reports consultancy and personal fees from AstraZeneca, AbbVie, Profile, Bial, Charco Neurotech, Alchemab, Sosei Heptares, Umedeor, and Britannia, outside the submitted work. He has share options in Umedeor.

WL reports research grants from the National Natural Science Foundation of China and the Science Technology Department of Zhejiang Province, China.

RO has received travel grants from the MDS in 2022 and 2023, and received a research grant in 2022 and travel support to attend the annual GP2 meeting in 2022 and 2023 from ASAP-GP2.

ABS is employed by the National Institutes of Health. He has received grants from the MJFF, and is a member of the scientific advisory board of Cajal Neuroscience.

CB is a federal employee of the National Institutes of Health, National Institute on Aging. He reports receiving research grants from the MJFF and ASAP-GP2.

CK is the recipient of research grants from the German Research Foundation, ASAP-GP2, and the MJFF. She has received travel grants and faculty honoraria from the MDS, and stipends as Deputy Editor of Movement Disorders and Science Advances, as well as a member of the Science Committee of the Else Kroener Fresenius Foundation. She serves as a medical advisor to Centogene, Takeda, and Retromer Therapeutics, and has received speakers' honoraria from Bial and Desitin.

AAA, KL, TST, YWT, SBC, JCEO, and NB have no conflicts of interests to declare.

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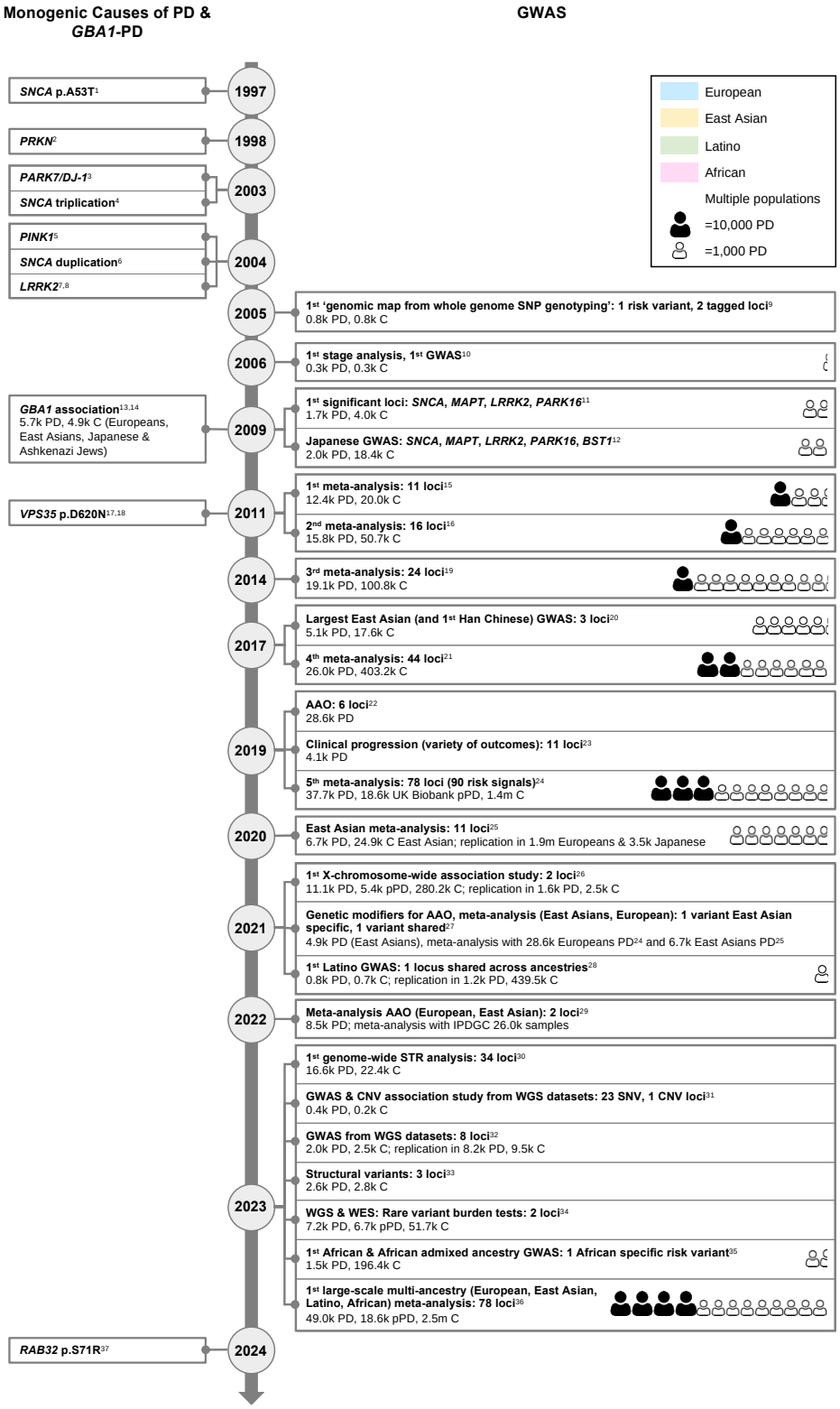
Appendix



Appendix Figure 1: **A brief historical timeline of Parkinson's disease (PD) genetics and genomics research (identical to Figure 1 in the main manuscript, but here with a complete list of citations).**

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Resource/Website/References	Year established	Objectives/Features
Accelerating Medicines Partnership (AMP) Program in PD (AMP-PD) website https://amp-pd.org/ Iwaki et al. *Mov Disord*. 2021	2018	Aims to facilitate broad sharing of data and analyses with the biomedical community to advance identification and validation of diagnostic, prognostic, and/or disease progression biomarkers for PD Provides a platform for researchers to access and perform *in situ* analysis of large-scale clinical and genomics (and other omics e.g., transcriptomic) data harmonized across multiple cohort studies (including PPMI, PDBP, HBS, BioFIND, etc.)
Foundational Data Initiative for Parkinson's Disease (FOUNDIN-PD) website https://www.foundinpd.org/ Bressan et al. *Cell Genom.* 2023	2023	Provides an interactive tool to access and analyze multi-layered omics data of iPSC-derived dopaminergic neurons with different genetic risk backgrounds (e.g., including pathogenic and risk variants in *GBA1*, *LRRK2* and *SNCA*) from PPMI participants
***GBA1*-PD browser** https://pdgenetics.shinyapps.io/GBA1Browser Parlar et al. *Mov Disord.* 2023	2022	Aims to inform and support basic, translational, and clinical research on *GBA1*-PD Generates a comprehensive database for *GBA1* variants (including variant classification and associated disease risk)
Global Parkinson's Disease Program (GP2) website https://gp2.org/ GP2 *Mov Disord.* 2021 Lange et al. *NPJ PD.* 2023 Towns et al. *NPJ PD.* 2023	2020	Provides an overview of GP2 objectives and progress to date; including information about Working Groups, opportunities (to contribute samples/data, apply for projects, and regarding training and employment, etc.), and directory of members Approved researchers can also explore individual-level GP2 genetics data using the GP2 Cohort Browser Application (https://gp2.org/spotlight-introducing-the-new-gp2-cohort-browser-application/)
International Parkinson's Disease Genomics Consortium (IPDGC) website https://pdgenetics.org/ IPDGC. *J Parkinson Dis.* 2020	2009	Provides an overview of IPDGC objectives and progress to date; including links to downloadable datasets, and directory of members
Movement Disorder Society Genetic Mutation Database (MDSGene) website www.mdsgene.org Lill et al. *Mov Disord*. 2016 Kasten et al. *Mov Disord*. 2018 Trinh et al. *Mov Disord*. 2018	2016	Aims to help movement disorder specialists follow and interpret the growing number of publications on genetic movement disorders Systematically and regularly collates and curates published genetic mutations (including their potential pathogenicity) and associated movement disorder phenotypes (genotype-phenotype correlations) The user-friendly platform allows exploration of data using various filters (e.g., patients with a specific mutation) and graphical summaries that are easily generated "on the fly"
Michael J. Fox Foundation Global Genetic Parkinson's Disease Project (MJFF GGPD) online resource https://gp2networkdev.wpengine.com/monogenic-resource-map/ Vollstedt et al. *PLoS One* 2023	2022	Aims to build a global network of centers working on monogenic PD to foster collaborative research, and help establish clinical trial-ready cohorts Collates information on the availability of data, biomaterials, and facilities relating to monogenic PD
Parkinson's Disease Mendelian Randomization Research Portal	2019	

https://pdgenetics.shinyapps.io/MRportal/ Noyce et al. *Mov Disord.* 2019		Aims to provide a new resource for the PD research community to add causal insights to associations using Mendelian randomization* Provides a publicly accessible platform that includes summary statistics of SNPs from a total of 5,839 GWASs of exposures
PD DNA Variant Browser https://pdgenetics.shinyapps.io/VariantBrowser/ Kim et al. *Mov Disord.* 2021	2021	Aims to enable researchers to rapidly query specific PD-associated genes and variants (e.g., whether a variant is enriched in PD cases) Provides exonic summary data from multiple large-scale genotyping and sequencing case-control projects
PD GENEration (PD GENE) Study website https://www.parkinson.org/advancing-research/our-research/pdgeneration Cook et al. *Genet Med.* 2023	2019	Provides plain language explanations (in English and Spanish) of why PD genetic testing is important, and study progress to date; the site contains links for people with PD in the USA (and also Canada, Puerto Rico, and the Dominican Republic) to participate in CLIA and CAP-certified PD genetic testing and genetic counseling, either in-person at designated sites or even from home via telehealth
PD GWAS Locus Browser https://pdgenetics.shinyapps.io/GWASBrowser/ Grenn et al. *Mov Disord*. 2020	2020	Aims to provide guidance to the research community on prioritization of causal genes and potential mechanisms at each locus for follow-up functional studies Catalogs all significant PD GWAS signals, and gathers data for all genes 1Mb upstream and downstream of each variant
Parkinson's Progression Marker Initiative (PPMI) website https://www.ppmi-info.org/about-ppmi PPMI. *Prog Neurobiol.* 2011 Marek et al. *Ann Clin Transl Neurol.* 2018	2010	Makes data of international biomarker-defined cohorts (with an emphasis on early disease or even presymptomatic at-risk subjects) rapidly available to qualified researchers, including individual-level clinical, imaging, genetic, omics, biomarker, and sensor data; also shares biospecimens
Rostock International Parkinson's Disease Study (ROPAD) website https://www.centogene.com/pharma/clinical-trial-support/rostock-international-parkinsons-disease-study-ropad Skrahina et al. *Mov Disord*. 2020 Westenberger et al. *Brain*. In press.	2019	Provides an overview of the study, which aims to conduct genetic screening in up to 25K participants (PD patients and relatives of *LRRK2* variant-positive patients) from North and South America, Europe and Israel Provides a physician portal for access to clinical trials

***Appendix Table 1*: Online resources specifically related, or highly relevant, to Parkinson's disease (PD) genetics**

Resources are presented in alphabetical order. BioFIND=Fox Investigation for New Discovery of Biomarkers in PD; CAP=College of American Pathologists (CAP) (most diagnostic laboratories undertake CAP accreditation as a voluntary step, serving as a stamp of excellence and a third-party approval of the laboratory practices); CLIA=Clinical Laboratory Improvement Amendments (through which the Centers for Medicare and Medicaid Services [CMS] regulates human laboratory testing in the United States); HBS=Harvard Biomarkers Study; IPDGC=The International Parkinson's disease Genomics Consortium; iPSC=Inducible pluripotent stem cells; K=1,000; Mb=Megabase; MJFF=Michael J. Fox Foundation; PDBP=Parkinson's Disease Biomarkers Project (https://pdbp.ninds.nih.gov/PD-BRAC-Cohorts); SNPs=Single nucleotide polymorphisms. *Mendelian randomization is an observational research approach that uses variation in genes of known function as a proxy for an exposure (for example, to a drug), risk factor or phenotypic trait, to predict its causal effects on health outcomes. Since genetics are (mostly) fixed at conception, this method is less likely to be affected by confounding or reverse causation than are conventional observational studies.

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Weblinks for various genomics databases listed in Table 1 are as follows: the Human Heredity and Health in Africa Consortium (H3Africa, https://h3africa.org), the GenomeAsia 100K Project (https://www.genomeasia100k.org), GenomeIndia (https://genomeindia.in/), the SG10K Consortium (https://www.npm.sg/partners/sg10k/), the Taiwan Biobank (TWB, https://www.biobank.org.tw), the Mexico Biobank (MXB, http://www.mxbiobank.org), and the Oceanian Genome Variation Project (OGVP, https://arxiv.org/pdf/2405.09216).

	GP2	IPDGC	LARGE-PD	Lux-GIANT	MDSGene	MJFF GGPD	PD GENE	PPMI	Total
Afghanistan									1
Algeria									1
Argentina									4
Armenia									2
Australia									3
Austria									5
Azerbaijan									1
Bangladesh									1
Belarus									1
Belgium									2
Brazil									4
Cameroon									1
Canada									6
Chile									2
China									3
Colombia									3
Costa Rica									2
Czech Republic									1
Denmark									2
Dominican Republic									2
Ecuador									1
Egypt									3
Estonia									2
Ethiopia									2
Faroe Islands									1
Finland									4
France									4
Georgia									1
Germany									6
Ghana									2
Greece									4
Grenada									1
Honduras									3
Hungary									3
India									4
Indonesia									1
Iran									1
Iraq									1
Ireland									2
Israel									4
Italy									4
Japan									4
Jordan									1
Kazakhstan									2
Kenya									1
Kuwait									1
Kyrgyzstan									1
Lebanon									1
Luxembourg									4
Malaysia									3
Mali									1
Mexico									3
Mongolia									1

Morocco									1
Myanmar									1
Nepal									2
Netherlands									5
New Zealand									2
Nigeria									3
Norway									4
Oman									1
Pakistan									2
Peru									3
Poland									3
Portugal									3
Puerto Rico									3
Romania									1
Russia									3
Samoa									1
Saudi Arabia									3
Serbia									2
Singapore									2
Slovakia									2
Slovenia									1
South Africa									3
South Korea									4
Sudan									1
Spain									5
Sri Lanka									1
Sudan									1
Sweden									3
Switzerland									2
Taiwan									3
Tajikistan									1
Tanzania									1
Thailand									3
The Philippines									2
Tunisia									2
Turkey									3
Ukraine/ Poland									1
United Kingdom									5
United States									7
Uruguay									2
Venezuela									1
Vietnam									3
Zambia									3
Zimbabwe									1

***Appendix Table 2*: Listing of international research studies, programs, and consortia on the genetics of Parkinson's disease, and participating countries, as illustrated in the Figure 3 world map**

These studies/projects were selected based on international reach, relatively large size (involving ≥10 centres), and ongoing presence. Data sources: The Global Parkinson's Genetics Program (GP2) Cohort Dashboard:

https://gp2.org/cohort-dashboard-advanced/; the Michael J. Fox Foundation Global Genetics Parkinson's Disease Project (MJFF GGPD) – countries with participating institutions: Vollstedt et al. *Mov Disord*. 2023;38(2):286-303. doi: 10.1002/mds.29288 (Figure 3B); the Movement Disorder Society Genetic Mutation Database (MDSGene) – countries with reported variant carriers: https://www.mdsgene.org/; the International Parkinson's Disease Genomics Consortium (IPDGC) – currently included countries: https://pdgenetics.org/about; the Latin American Research Consortium on the Genetics of PD (LARGE-PD) – currently included countries: https://large-pd.org/centers/; the Luxembourg-German-Indian Alliance on Neurodegenerative diseases and Therapeutics (Lux-GIANT) Consortium: https://lux-giant.com/research/; PD GENEration (PD GENE) Study – clinical sites: Cook et al. *Brain*. 2024 (in press); and the Parkinson's Progression Marker Initiative (PPMI) – clinical sites: https://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites. Online databases were accessed on 30 May 2024. Non-European "underrepresented" countries are highlighted in red and bold in the first column.