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 has grown tremendously since the discovery of the first monogenic form, caused by a mutation in α-synuclein, and with the subsequent identification of multiple other causative genes and associated loci. Genetic studies provide insights into the phenotypic heterogeneity and global distribution of Parkinson's disease. By shedding light on the underlying biological mechanisms, genetics facilitates the identification of new biomarkers and therapeutic targets. Several clinical trials of genetics-informed therapies are ongoing or imminent. International programmes in populations who have been under-represented in Parkinson's disease genetics research are fostering collaboration and capacity-building, and have already generated novel findings. Many challenges remain for genetics research in these populations, but addressing them provides opportunities to obtain a more complete and equitable understanding of Parkinson's disease globally. These advances facilitate the integration of genetics into the clinic, to improve patient management and personalised medicine.

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Introduction

The past three decades have seen much progress in the understanding of the genetic architecture of Parkinson's disease[1–3] and knowledge regarding its biological mechanisms. In particular, evidence on the role of α-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.[6] Such success has already been shown in several areas of medicine, particularly oncology, in which a focus on genetically defined disease has culminated in the advent of effective therapeutics.[5,6] Technologies to interrogate the genetic basis of phenotypic traits and diseases continue to advance, while the cost of next-generation sequencing has decreased substantially; genetic testing has also been driven by collaborative Parkinson's disease genetics research programmes.[7–13] The increasing availability of genetic testing[1,7–14] and intense research efforts on Parkinson's disease biomarkers[15–20] and clinical trials[5,6,10,21–23] are bringing genetics to the mainstream of day-to-day clinical practice.

On an international scale, most genetics research has focused on populations of European ancestry, resulting in the relative absence of non-European (also referred to as under-represented; panel 1) populations in large-scale studies.[24–26] In this Personal View, we provide an update on the genetics of Parkinson's disease, emphasising findings in populations who are under-represented. We also cover up-to-date findings on the genetic and biological basis of sporadic Parkinson's disease.[1–4] Genetic understanding can enhance the delivery of personalised medicine in clinical practice, and we propose research priorities towards that aim.

Monogenic and sporadic Parkinson's disease

The discovery of a mutation in the α-synuclein (*SNCA*) gene in 1997 indisputably proved a genetic cause in a subset of patients with Parkinson's disease.[1–4] Several genetic causes behind monogenic or Mendelian forms of Parkinson's disease are now well established. In these patients, the cause of Parkinson's disease is attributed to rare pathogenic variants in a single gene.[1–4] These genes, in chronological order of discovery, include *SNCA*, *LRRK2*, and *VPS35*, which have been linked to autosomal dominant Parkinson's disease sometimes with reduced penetrance; and *PRKN*, *PARK7* (also known as *DJ-1*), and *PINK1*, which have been linked to autosomal recessive, typically early-onset, Parkinson's disease (onset age <50 years).[1–3] In 2024, *RAB32* has been described as a novel gene causing autosomal dominant Parkinson's disease.[28,29] A timeline of progress in unravelling the genetic architecture of Parkinson's disease is provided in the appendix (pp 1–3).

Other autosomal recessive forms of early-onset or juvenile-onset parkinsonism related to *PLA2G6*, *ATP13A2*, *FBXO7*, *SYNJ1*, *DNAJC6*, *VPS13C*, *PTPA*, and *DAGLB* (listed in order of their approximate frequency), can present as Parkinson's disease, but are usually accompanied by atypical features, such as early dementia, intellectual disability, epileptic seizures, pyramidal signs, or gaze palsy.[30,31] These disorders usually have an even earlier age at onset (median age 24 years) than *PRKN*-related, *PINK1*-related, and *DJ-1*-related cases, with median ages at onset of 31, 32, and 27 years, respectively.[30–32] Notably, most of the original discoveries of genetic variants associated with autosomal recessive atypical parkinsonism were made in otherwise under-represented 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 observation could be due to the high rates of consanguinity and large family size in many of these populations, which facilitate identification of the causal genetic variants. The Movement Disorder Society Genetic Mutation Database

Panel 1: Populations who are under-represented in genetics research: a term in need of refinement

Approximately 80% of individuals in genome-wide association studies (GWAS), as of 2019, were of European ancestries (despite comprising only about 16% of the world population).[24,25] The latest figures from March, 2024, show that the imbalance has not decreased but, in fact, has widened: 94·5% of individuals in GWAS were of European ancestry, 3·7% of Asian ancestry, 0·4% of Hispanic or Latino ancestry, 0·2% of African ancestry, and 0·7% of other or mixed ancestries. Thus, non-European populations are usually designated as under-represented.[24–26] However, although rich and technologically advanced European nations (mainly France, Germany, Italy, and the UK) and the USA have pioneered genetic studies,[24–26] other (particularly eastern) European countries have scarcely or never been explored from this perspective.[27] Populations such as those from Finland and Iceland have been intensively studied, but they 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] A considerable number of genetic studies have been done in non-European populations, in particular east Asian populations, such as in the Han Chinese (in China, Singapore, and Taiwan) and the Japanese populations.[25,26]

Low-income and middle-income countries (as per the classification of income per capita by the World Bank) can be denoted as under-represented.[11] However, this terminology is not ideal. For example, Japan, Singapore, and Taiwan are high-income countries, whereas China is currently considered an upper-middle-income country but has produced numerous genetics studies. In a systematic review of publications on Parkinson's disease genetics in populations who are under-represented through October, 2021 (n=1037), China accounted for a large number (n=469) of the papers.[26] Conversely, many countries designated as high-income, such as those in the Middle East (eg, Saudi Arabia), South America and Central America (eg, Chile), Southeast Asia (eg, Brunei), and Oceania (eg, Guam), have produced few publications on genetics overall and Parkinson's disease genetics specifically.[26] Furthermore, sizeable communities in high-income countries are under-represented in genetics research.[24–26] These communities include people of African or Hispanic descent in the USA, indigenous groups (eg, Aboriginal people in Australia and Maori people in New Zealand), and migrant and refugee groups in Europe (eg, Afghan people in Germany or Roma people in Slovakia).[24–26]

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

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(MDSGene), 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 early-onset Parkinson's disease) in populations who are otherwise under-represented outnumber those in European-ancestry populations (figure 1).

The proportion of patients with Parkinson's disease harbouring pathogenic variants has been variably estimated at approximately 5–15%,[2,3,12,13,17,33] but could be considerably higher (>40–50%) in some populations,[34–36] or lower in other (eg, community-based)[37] studies. The yield also depends on the number of genes tested,[10] for example, if focusing on established Parkinson's disease-linked genes[12,37] or when screening for the presence of a neurodegenerative panel with 50 genes or more.[13]

Although genetic studies initially focused on familial Parkinson's disease, genome-wide association studies (GWAS) have enabled investigations of the association between common genetic variants, typically single nucleotide polymorphisms (SNPs), and in the past 1–2 years, also structural variants (duplications, deletions, or inversions of stretches of DNA), with the risk of idiopathic Parkinson's disease.[1,2,8,38–41] Idiopathic in this context denotes the more typical scenario of the condition occurring sporadically later in life, wherein a complex interplay of genetic, environmental, ageing, and other factors is believed to underlie disease development.[1–4] So far, more than 100 genetic variants have been shown to increase the risk of Parkinson's disease.[1,2,8,38,40] These studies, which use genotyped and genotype-imputed data from hundreds of thousands to several million SNPs, without any a priori hypothesis, have provided insights into the genetic architecture of idiopathic Parkinson's disease.[1,2,8,38,40] Multiple pathways associated with Parkinson's disease have been identified, including those involved in immunoinflammatory 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.[2,4,8,42,43] New findings will continue to accrue as sample sizes for this type of study increase into the hundreds of thousands, as seen in other diseases.[44] However, for many loci, their effects on downstream molecular pathways remain to be elucidated.[1,2,4,8,38]

One remarkable finding, which is also recognised in other disorders, is an apparent convergence of mechanisms underlying monogenic and complex forms of the disease.[45] Several of the genes that cause monogenic Parkinson's disease are also detected in GWAS (eg, *SNCA*, *LRRK2*, *GBA1*, and *VPS13C*).[1,2,8,38,45] These GWAS signals usually map to non-coding, mostly intergenic, genomic regions, thought to result in relatively subtle alterations in gene (and ultimately protein) expression rather than in changes in protein sequence.[1,8,38,44,45] Thus, for example, risk variants in *SNCA* and *LRRK2* could 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* (where SNCA expression was at least 1·5 times higher) or kinase-activating mutations in *LRRK2*.[5,19,45] This notion that mutated genes that cause Parkinson's disease are also involved in the pathogenesis of sporadic disease is known as the pleomorphic risk locus hypothesis.[45] An important implication of this convergence is that future gene-targeted therapies found to be useful in monogenic Parkinson's disease could also potentially be deployed in the much larger group of

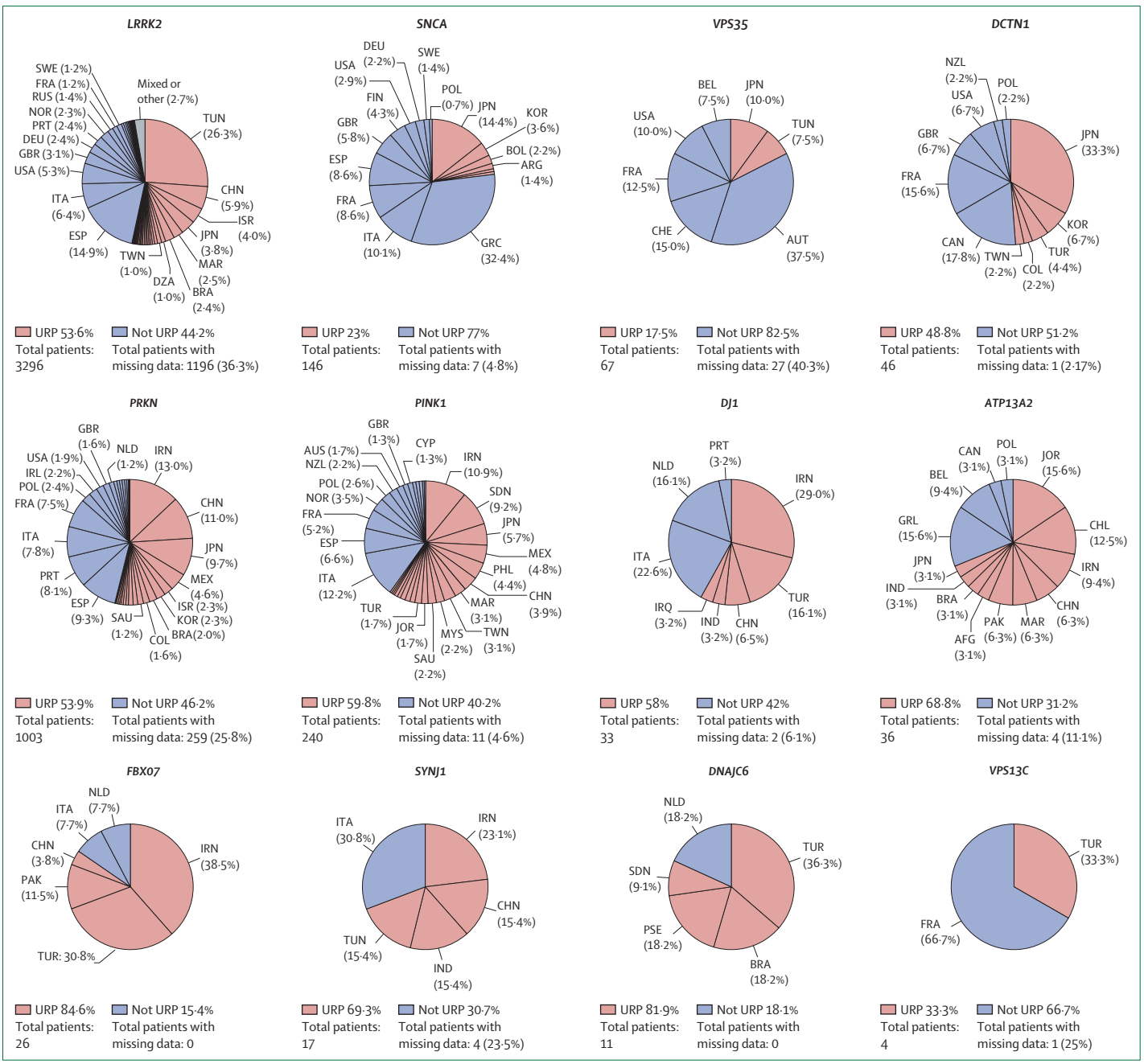

Figure 1: **Genetic forms of Parkinson's disease in different populations.**
These pie charts, derived from the MDSGene database on May 30, 2024, show relatively higher frequencies in populations who are under-represented (depicted in red) than in populations of European ancestry (depicted in blue) of *LRRK2* Parkinson's disease 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 these atypical parkinsonian disorders are small. Countries in the Middle East, North Africa, and South Asia have a relatively large proportion of cases. The counts denote the numbers of patients with possibly pathogenic, probably pathogenic, and definitely pathogenic variants, according to the MDSGene pathogenicity scoring. Country abbreviations are based on the ISO three-letter codes. ISO=International Organization for Standardization. URP=under-represented population

patients with idiopathic Parkinson's disease.[4,5,45,46] However, further stratification of participants on the basis of the predominant mechanisms (eg, lysosomal or mitochondrial-related) would likely be needed in clinical studies of this more heterogeneous group of patients.[4,5,19,45,47]

Genotypes commonly encountered in clinical practice

In this section, we focus on common and well established Parkinson's disease genes, particularly those that are being targeted in clinical trials.[5,6,10,12,20–23] We discuss *LRRK2*-related Parkinson's disease, which is the most common form of

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See Online for appendix

For the **GWAS Diversity Monitor** see https://gwasdiversitymonitor.com

For the **World Bank classification** see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

For **MDSGene** see www.mdsgene.org

For the **ISO country codes** see https://www.iso.org/obp/ui/#search

autosomal dominant Parkinson's disease, followed by Parkinson's disease associated with variants in *GBA1*, which is the most frequently encountered risk gene in most populations studied to date. *PRKN*-related and *PINK1*-related Parkinson's disease are the most common autosomal recessive forms. We also highlight some lesser-known epidemiological aspects in populations who are under-represented in genetic studies, and genotype–phenotype correlations that are highly relevant for clinicians. For a systematic review in this area, we refer readers to the review by Schumacher-Schuh and colleagues, which includes evidence reported up until 2021.[26]

LRRK2

Autosomal dominant *LRRK2* Parkinson's disease has a high prevalence in some populations. Thought to have arisen from ancient founder events in the Middle East and Europe several millennia ago, the *LRRK2* p.Gly2019Ser variant has a frequency of approximately 40% in familial and sporadic cases in the Arab–Berber population in North Africa (Algeria, Morocco, and Tunisia),[35] and approximately 15% among Ashkenazi Jewish patients with Parkinson's disease.[14,48] The prevalence is approximately 2% overall in European patients, with a south-to-north gradient (ie, higher prevalence in Portugal and Spain, and lower prevalence in Scandinavia).[46] The frequency is less than 2% overall in South America, but ranges from 0·2% in Peru to 4·2% in Uruguay, and is associated with southern and eastern European ancestry.[14,46,49] Another variant, p.Arg1441Gly, is prevalent in the Spanish Basque population, again thought to have arisen from a common founder, and accounts for around half of the familial cases in the region.[46,50] The p.Arg1441Cys variant is quite frequent (about 4% of patients with Parkinson's disease) in southern Italy.[51]

By contrast, *LRRK2* Parkinson's disease and, in particular, the p.Gly2019Ser variant, is rare or absent in Asian populations (including in South Asia; mainland China and Taiwan; Korea; Central Asia; and Singapore, Malaysia, and Vietnam).[33,36,52] The p.Gly2019Ser variant was found in only 0·2–0·5% of Japanese patients with Parkinson's disease, similar to the p.Ile2020Thr variant.[53] The p.Asn1437Asp variant, discovered in 2020 and likely to be pathogenic, was detected in 0·8% of cases of autosomal dominant Parkinson's disease in mainland China.[33] Similarly, few *LRRK2* mutations have been reported in patients of African ancestry in Ghana, Nigeria, South Africa, and Zambia, although the sample sizes of these studies have been relatively small (total approximately 400 patients), and the targeted screening for specific variants could have missed new pathological variants.[9,54] Future systematic analyses of *LRRK2* variants in globally diverse cohorts will probably shed light on further relevant variants.[55]

The penetrance of pathogenic *LRRK2* variants depends on age.[3,14,46,48,50,56–58] Most studies have focused on the p.Gly2019Ser variant,[3,14,46,48,56–58] with the largest one reporting a 49% cumulative incidence of Parkinson's disease by age 80 years.[14] Penetrance is also influenced by ancestry and other factors,[46] as elegantly shown in a comparative study between Tunisian Arab–Berber and Norwegian cohorts with the following estimates: 31% versus 3% by age 50 years, and 86% versus 43% by age 70 years, in Tunisia versus Norway, respectively.[56] In a study of Ashkenazi Jewish carriers of the p.Gly2019Ser mutation, the penetrance was found to be approximately 25% by age 80 years.[48] Population-specific penetrance is probably influenced by many factors, including both genetic background and environmental factors, and estimates could differ also on account of differences in access to health care and neurological expertise of movement disorders at different centres, that can result in ascertainment bias.[14,46,57–60]

The clinical phenotype of *LRRK2* Parkinson's disease, particularly the p.Gly2019Ser variant that has been most widely studied, is indistinguishable from sporadic Parkinson's disease, with slightly more benign symptomatology and progression, including a lower incidence of dementia and longer survival.[46,61] However, although it is commonly stated that *LRRK2* Parkinson's disease has a similar or slightly earlier age at onset compared with sporadic cases,[5] a MDSGene review published in 2024 revealed that 265 (31%) of 863 patients with pathogenic or probably pathogenic *LRRK2* variants had early-onset Parkinson's disease.[62]

In addition to the rare pathogenic variants with reduced penetrance, several common variants (minor allele frequency >1%) within *LRRK2* are considered genetic risk factors for Parkinson's disease.[1–3,38,46] The *LRRK2* risk variants p.Gly2385Arg and p.Arg1628Pro are prevalent in Asia, including in Chinese (both variants), Korean (p.Gly2385Arg), Japanese (p.Gly2385Arg), Malay (p.Arg1628Pro), Thai (p.Arg1628Pro), and Vietnamese (p.Arg1628Pro) populations. In these regions, these risk variants are each present in up to approximately 10% of patients, and they are about half as frequent in those who do not have Parkinson's disease.[46,52] On the whole, carriers of p.Gly2385Arg or p.Arg1628Pro also seem to be clinically indistinguishable from patients with sporadic Parkinson's disease, although studies have been limited in sample size and results have sometimes conflicted.[46,52] These risk variants (particularly when present in combination) might confer an earlier onset,[63] and it has been suggested that motor function might be worse with more frequent motor fluctuations in carriers of the p.Gly2385Arg variant, than in non-carrier patients.[64] Larger systematic studies will allow more definitive conclusions regarding the effect of p.Gly2385Arg and p.Arg1628Pro on clinical phenotype and disease progression.

Besides *LRRK2*, the other main established genetic causes of autosomal dominant Parkinson's disease are mutations in *SNCA* and *VPS35*, but these mutations are very rare.[36,65,66] To our knowledge, global differences in frequency or clinical phenotype have not been reported,

except for *SNCA* p.Ala53Thr, the most common *SNCA* missense mutation, which accounts for about 5% of familial Parkinson's disease or sporadic early-onset Parkinson's disease cases in Greece, and *VPS35* p.Asp620Asn in Japan (1% of index patients with autosomal dominant Parkinson's disease).[65,66]

GBA1

Heterozygous *GBA1* variants are the most common genetic factor underlying Parkinson's disease globally.[12,13,67,68] *GBA1* Parkinson's disease has a frequency of approximately 4–20% in most cohorts studied so far.[5,12,13,49,69–71] The link between Gaucher's disease (a lysosomal storage disorder caused by biallelic mutations in *GBA1*) and parkinsonism was initially studied in patients of Ashkenazi Jewish ancestry.[72] This population has been considered to have the highest frequency (approximately 20% of all cases) of *GBA1* Parkinson's disease, which is associated with heterozygous *GBA1* variants.[69,70,73] Remarkably, the common non-coding *GBA1* variant rs3115534-G has been found in approximately 50% of west African patients with Parkinson's disease, conferring an odds ratio (OR) for Parkinson's disease of 1·6.[9]

Severe *GBA1* variants, which result in neuronopathic Gaucher's disease in homozygous or compound heterozygous carriers and are associated with more pronounced reductions in glucocerebrosidase activity (eg, p.Leu483Pro, also known as p.Leu444Pro), are associated with higher odds for Parkinson's disease (OR higher than 10) and more rapid disease progression than mild variants. Mild *GBA1* variants are associated with non-neuronopathic Gaucher's disease in homozygous or compound heterozygous carriers and less reduced glucocerebrosidase activity (eg, p.Asn409Ser, also known as p.Asn370Ser, with OR 2·2–7·8 for Parkinson's disease development).[5,69,74] Meanwhile, risk variants such as p.Glu365Lys (also known as p.Glu326Lys) and p.Thr408Met (also known as p.Thr369Met) are associated with a less increased risk of Parkinson's disease (OR less than 2 but more than 1) and do not cause Gaucher's disease in the biallelic state.[5,69,74] As observed with *LRRK2*, variants in other genes and polygenic modifiers have been shown to modify *GBA1* penetrance.[5,69,75]

The mutational spectrum of *GBA1* varies according to ancestry with, for example, the mild p.Asn409Ser variant accounting for the majority (approximately 70%) of variants among patients of Ashkenazi Jewish ancestry.[69,70,73] By contrast, in Chinese patients, the severe p.Leu483Pro variant appears to be predominant.[67,71] In India, many *GBA1* variants have been reported, with p.Leu483Pro being the most common, and accounting for approximately a third of carriers.[68] A Latin American Research Consortium on the Genetics of Parkinson's Disease (LARGE-PD) study[76] also found a predominance of p.Leu483Pro in Peru (65% of *GBA1* Parkinson's disease cases), whereas in Colombia, p.Leu483Pro and p.Asn409Ser accounted for approximately 25% of *GBA1* Parkinson's disease cases each, with a severe population-specific variant p.Lys237Glu, also known as p.Lys198Glu, accounting for the remaining cases.[74,76]

Patients with *GBA1* Parkinson's disease can have a more aggressive clinical course with less favourable prognosis, with worse motor and cognitive-behavioural features, and poorer survival than patients with sporadic Parkinson's disease.[5,61,69,71] Variant carriers can also be at heightened risk of suboptimal outcomes after deep brain stimulation (DBS).[77] These suboptimal outcomes include those related to cognition in particular, but possibly also axial motor features, function, quality of life, and reduction of dopaminergic medications (reduction of dopaminergic medications being approximately 20% on average in some studies versus 30–50% in overall cohorts treated with DBS of the subthalamic nucleus).[77,78] The frequency of *GBA1* Parkinson's disease in patients eligible for DBS is not trivial, with studies documenting an over-representation (approximately 12–20%) of carriers in cohorts of DBS-treated patients.[77,78] This over-representation probably occurs because carriers are younger and have troublesome motor complications,[69,71] which are major selection criteria for DBS.

PRKN and *PINK1*

PRKN Parkinson's disease is the most common autosomal recessive form of the disease and has a global distribution.[32] Soon after its initial description in consanguineous families of Japanese ancestry with autosomal recessive juvenile (onset age <21 years) Parkinson's disease, the condition was found in patients of various ancestries, with frequencies ranging from approximately 1–15% among cohorts of patients with early-onset disease.[32,36,79,80] However, there might yet be undiscovered clusters of *PRKN* Parkinson's disease, or other forms of monogenic Parkinson's disease, for example, among indigenous populations that have rarely been included in genetics research.[3,26] This scenario has been exemplified by a high prevalence (more than 50%) of pathogenic *PRKN* variants found among indigenous patients of Kadazan-Dusun ethnicity with early-onset Parkinson's disease 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 investigation. In the MDSGene database, Iran has the highest number of patients with *PRKN* Parkinson's disease worldwide according to country of origin (accounting for about 13% all cases), with studies estimating frequencies of consanguineous marriage to be approximately 40–80% in the country, similar to those in many nations in the Middle East, North Africa, and South Asia.[32,79]

Overall, *PINK1* Parkinson's disease is much less common globally than *PRKN* Parkinson's disease.[32] However, a pathogenic *PINK1* missense variant (p.Leu347Pro) was found to be relatively common, with a 7% prevalence among patients of Malay ethnicity with early-onset Parkinson's disease (there are approximately

Panel 2: **Populations who are under-represented in large genetic studies**

An important limitation of Parkinson's disease genetics studies is that they have mainly been carried out in populations of European ancestry, and to a lesser extent in East Asian populations, but largely not included other ancestries.[1,26,38] Many more GWAS, and with much larger samples sizes, have been done in populations of European ancestry than in other populations, such as those of East Asian, African, and Hispanic ancestries. No Parkinson's disease GWAS to date has been done in populations with Middle Eastern ancestry. In international Parkinson's disease genetics research programmes and consortia, similarly, there is under-representation of non-European populations. For example, non-European populations account for only approximately 10% of about 4000 participants in the Michael J Fox Foundation Global Genetics Parkinson's Disease Project on monogenic Parkinson's disease.[65]

Although studies of populations who are under-represented are often challenging to conduct, efforts to promote diversity are vital to obtain a more complete and equitable understanding of Parkinson's disease globally, and to achieve progress in the diagnosis, management, and prevention of Parkinson's disease worldwide. Conversely, failure to do so will result in genetic technologies inadvertently exacerbating, rather than reducing, health disparities.[24,25,82,83]

Collaborative programmes are promoting outreach efforts to include investigators, patients, and families from Africa, Asia, and South and Central America, among other regions. These programmes have also improved capacity and infrastructure, and generated valuable insights.[9,36,56,65,70,79] A prime example of these collaborative efforts is the Global Parkinson's Genetics Program (GP2). GP2 was created in late 2019, with the objectives of developing a more complete understanding of Parkinson's disease genetics and pathogenesis, through inclusivity, and making this knowledge globally available and actionable.[7,8,9,26] A specific goal of GP2 is to include a wide diversity of patients and researchers, with a strong emphasis on local and regional capacity-building.[7,8,9,26] Substantial progress is being made towards achieving the aim of recruiting at least 50 000 participants of non-European ancestry, out of a total sample of 200 000.[7,8,9]

200 million people of Malay ethnicity in Southeast Asia).[36,81] There is interest in exploring this missense variant further in geographically close populations, such as those of Filipino ancestry and those of Pacific Islander or Polynesian ancestry, who are thought to share an Austronesian ancestry.[36,81] An early study reported a relatively high frequency of heterozygous p.Leu347Pro carrier status among neurologically healthy volunteers of Filipino ancestry (three [6%] of 50 volunteers were carriers), suggesting that this specific variant could be an important cause for Parkinson's disease among this group (approximately 110 million people, of whom more than 10% live outside the Philippines in over a hundred countries).[36,52,81]

PARK7-related or *DJ-1*-related Parkinson's disease is the least frequent of the autosomal recessive forms of Parkinson's disease, with even fewer reported cases compared with, for example, *SNCA* or *VPS35*.[32,65]

Patients with autosomal recessive forms of Parkinson's disease, particularly carriers of biallelic *PRKN* mutations, have a relatively benign disease course, sometimes lasting over 50 years or more, and a favourable outcome can generally be expected from device-aided therapies (ie, DBS or infusions of dopaminergic medications).[32,34,36,61,80] Predominantly, this comparatively good disease course occurs because these patients have less extra-nigral pathology and, therefore, respond well to levodopa and do not usually have dementia (although a study published earlier in 2024 suggests that autonomic dysfunction might be more common in these patients than previously recognised).[4,5,32,34,36,61,80] Motor complications are common in *PRKN* Parkinson's disease and can be pronounced.[32,34,36] However, analyses of large numbers of patients published in 2020[79] and 2024[80] revealed that patients with *PRKN* mutations are at lower risk of motor complications than patients without these mutations, after accounting for confounding factors such as younger age at onset or longer disease duration.

Integration of genetics into the clinic

Currently, a major barrier to the integration of genetics into neurology clinics is insufficient availability of and access to genetic testing, especially for some populations (panel 2). Opportunities for genetic testing have improved substantially over the past several years, driven in part by research programmes,[9,12,13,15,36,84] which typically provide genetic findings to collaborating investigators. The reducing cost of genetic testing has also resulted in greater access to clinical and direct-to-consumer testing,[14] but access is still inadequate in low-income and middle-income countries.[11] Encouragingly, multiple studies suggest a high interest among patients with Parkinson's disease and their relatives to participate in genetics studies,[10–13,85–87] although data from populations who are under-represented regarding patient (and clinician) attitudes towards, and knowledge of, genetic testing are scarce.[11]

The decision of whom to test and which type of genetic test to obtain will depend on the individual patient and setting. Clinical pathways have been proposed,[10,86] although genetic testing is still an evolving area. Testing has a higher yield when targeting individuals with earlier onset Parkinson's disease, with a positive family history, from ethnic groups at higher risk, or with a combination of these characteristics. However, the clinical presentations of carriers of variants are often indistinguishable from those of non-carriers, and the development of personalised medicine has caused a shift in perspective, with some specialists now suggesting that all patients should be offered screening as a routine part of their evaluation and care.[12,13]

Genetic testing has caveats, including potential adverse psychological effects and concerns surrounding privacy and discrimination.[10,11,84–87] Other concerns relate with the potentially inaccurate results from research testing, which might not match the stringent 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,[84,85] and in some large initiatives (eg, the PD Generation [PD GENE] study and the Rostock International PD Study [ROPAD]; appendix p 5), genetic testing is performed in accredited

laboratories.[12,13] It seems appropriate that genetic findings that are medically actionable and robustly associated with the phenotype should be returned to research participants who consent to receive such information. This process should be guided by the ethical principles of autonomy, beneficence, nonmaleficence, honesty, and reciprocity.[39,84–88] Patients with Parkinson's disease, individuals who are at risk, and other stakeholders have called for transparent communication and feedback throughout the research process,[87] which might include results that are unclear, such as genetic variants of uncertain significance (VUS), that is, changes in a DNA sequence that have an unknown effect on a person's health. Better engagement with research participants will also improve recruitment and retention, including of family members.

Next-generation sequencing technologies are now widely used, and whole-genome sequencing (WGS) allows the comprehensive detection of variants in both coding and non-coding DNA regions.[89] Long-read sequencing further improves the detection of structural variations, compared with standard short-read WGS, and these relatively unexplored types of genomic variation have already shown relevance to Parkinson's disease in studies in the past 1–2 years.[40,41,90] These new technologies are anticipated to improve the detection of pathogenic variants in known Parkinson's disease genes, and accelerate the discovery of novel Parkinson's disease genes. For example, apparently heterozygous *PRKN* cases were solved by identifying cryptic second mutations using long-read sequencing that were previously undetected.[90] There has been much excitement in the past half-decade about new discoveries of monogenic causes of dementia, cerebellar ataxia, and sensory neuropathy (eg, 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 techniques will unfold for Parkinson's disease.[91]

In practical terms, the identification of the genetic factors underlying Parkinson's disease often has a clinical impact. Specifically, genetics knowledge has clinical utility in: (1) improving the diagnosis of young patients or those with other atypical clinical features; (2) assisting in family and life planning; (3) potentially allaying anxiety, fear, or guilt; (4) understanding the disease course and its prognostication; and (5) selecting or stratifying patients for treatments such as DBS.

The very early (sometimes juvenile) onset or occurrence of atypical features, or both (eg, presentation with craniocervical dystonia or a long history of tremors in autosomal recessive early-onset Parkinson's disease), often lead to so-called diagnostic odysseys over many years or even decades,[36,92] and can involve potentially harmful misdiagnoses (eg, functional tremor or functional gait disorder).[92] What ensues then are missed opportunities for proper early management, including treatment and family counselling or planning, which can result in a loss of function and life quality, unemployment, and even termination of pregnancy.[36] Termination of pregnancy could arise because of an erroneous assumption that having early onset of Parkinson's disease 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).[10,36,86] Better patient understanding of an underlying genetic cause can empower patients and help, in some instances, to allay guilt and anxiety that Parkinson's disease developed because of something the patient had done in the past (a belief held by nearly half of both patients with Parkinson's disease and caregivers in one study conducted in urban Malaysia).[93]

A sensitive, culturally-appropriate, and nuanced approach (eg, acknowledging uncertainties in predicting prognosis) is needed when sharing genetic findings with patients and families, preferably delivered by a trained clinician or genetic counsellor.[10,39,84–89,94] We would like to caution against genetic determinism (ie, the perception that phenotypes are exclusively controlled by an individual's genes) and highlight that there are many factors (eg, genetic, epigenetic, environmental, and psychosocial), most of which are still poorly understood, that contribute to substantial variability, even with the same genetic variant.[39] Multiple other issues require consideration in the genetic counselling process, including the possibility of stigma arising from test results (eg, affecting marriage prospects) and the potential implications for family members. These issues have been extensively discussed in other publications.[10,39,84–89,94] A genomic multidisciplinary team approach, incorporating expertise in clinical evaluation, human genetics, bioinformatics, functional genomics, and genetic counselling is advantageous to maximise diagnostic yield and improve patient management,[89,94] especially in complex situations requiring considerable judgment. One example is the interpretation of rare or newly discovered variants, including VUS.[89,94]

In patients with early-onset Parkinson's disease, clinicians are advised to exercise caution in deferring to the prevailing notion that younger patients exhibit a more gradual disease progression when conducting prognostic evaluations.[95] Rather, clinicians should consider that the disease trajectory depends in a substantial part on genetic factors. The statement could be true for *PRKN* Parkinson's disease and perhaps the other forms of autosomal recessive early-onset Parkinson's disease,[3,5,32,34,36,61,79–81] but is much less likely to be true for *GBA1* or *SNCA* Parkinson's disease,[3,5,57,61,66,69,71] which often also cause early-onset Parkinson's disease,[5,36,49,65–67,96] but are associated with more rapid progression, probably reflecting, at least in part, a greater burden of Lewy body pathology.[4,5,57,61,69] Information on prognosis provided to patients and their families can help to shape forward-looking treatment plans,[10] including the adoption of lifestyle, rehabilitative, and medical measures to mitigate the effects of falls and cognitive

Panel 3: Genetic status within the new biological research classifications of Parkinson's disease

The development of fluid, tissue, and imaging biomarkers is now sufficiently advanced to allow the identification of genetic risk, pathological processes (particularly α-synucleinopathy), and neurodegeneration, before the onset of Parkinson's disease clinical features.[15–18] These biomarkers will facilitate a biological approach to diagnosis, instead of clinical criteria. Two new biological frameworks aim at enabling classification and diagnosis.[17,18]

In the SynNeurGe criteria, proposed by Hoglinger and colleagues,[17] Parkinson's disease-linked genetic variants are classified into three categories, according to their penetrance and pathogenic effect. The first category consists of fully penetrant pathogenic variants. These variants include dominantly inherited *SNCA* triplications and missense variants, and recessively inherited biallelic *PRKN*, *PINK1*, and *PARK7* or *DJ-1* missense, truncating, and structural variants. The second category consists of pathogenic variants with reduced penetrance but still conferring a strong predisposition to Parkinson's disease, that is, dominantly inherited *SNCA* duplications and pathogenic missense variants (eg, in *LRRK2* and *VPS35*). The penetrance of pathogenic variants might depend on age, ancestry and geography, modifier variants, and environmental factors, and has been best studied in *LRRK2* Parkinson's disease[3,14,46,48,56–60] The third category consists of heterozygous severe *GBA1* pathogenic variants that are associated with an intermediate predisposition to develop Parkinson's disease. There is an ongoing discussion about whether *GBA1* variants should be considered causal, with autosomal dominant transmission and markedly reduced penetrance (but as high as 21% and 30% at ages 70 and 80 years, respectively),[10,96] or as risk factors, with increased odds ratios for Parkinson's disease from approximately 1·4 to 30-fold.[9,69,74,75] These scenarios would depend on specific types of *GBA1* variants and their frequency in a given population, with variants having a minor allele frequency of more than 1% being considered as risk variants and not as pathogenic. Thus, mild *GBA1* pathogenic variants and other common risk variants that increase risk of Parkinson's disease[2,38,74] are not considered in the endorsed genetic categories in the SynNeurGe criteria, due to their much smaller (and unpredictable) effect sizes than the other pathogenic variants discussed.

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 pathology. In this framework, carriers of a fully penetrant *SNCA* variant are considered at stage 0 of the disease. Individuals who do not have detectable neuronal α-synuclein disease, including a substantial proportion of patients with *LRRK2* Parkinson's disease and the majority of patients with *PRKN* Parkinson's disease,[5,15,17,18,57,61,69] are excluded from the NSD-ISS.

impairment. Although the generally poorer response to DBS in *GBA1* Parkinson's disease should not preclude it as a treatment option, because the procedure could still confer substantial benefit in motor function and quality of life,[77] genetic information enables informed decision making regarding life-changing, but invasive and costly,[52,78] treatments.

For the field to advance in understanding genotype–phenotype correlations, systematic phenotyping efforts using standardised or harmonised tools will facilitate cross-cohort analyses.[3,55] Guidelines are being developed for improved phenotype reporting in the genomic era.[7] The study of subtypes of Parkinson's disease (eg, 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[61,80] and not just cross-sectional[32,62,66] data will be invaluable. Besides using conventional rating scales and patient-reported outcome measures, these efforts can be supported by technological advances.[97]

The clinical utility of Parkinson's disease genetics will probably expand in the near future into personalised therapeutics and lifestyle modification strategies. Disease prevention can be a particularly important concern for people at risk,[87] and emerging studies suggest that lifestyle modifications might mitigate Parkinson's disease risk.[3,52,59,87,98,99] One example is the observation that caffeine consumption might be especially beneficial in carriers of *LRRK2* variants, with one large study showing that carriers of the Asian p.Gly2385Arg and p.Arg1628Pro *LRRK2* risk variants who were asymptomatic and did not have drinks with caffeine have up to eight times greater risk of developing Parkinson's disease than those who had drinks with caffeine and did not carry the risk variants.[99] This finding could have implications[83] given the high frequency of these risk variants in multiple Asian populations.[46,52,63,64,99] Ultimately, with rapid advances integrating genetics and genomics with 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 Parkinson's disease could be accurately forecast at an individual level.[3,15–18,97,98] This predictive ability will open up the possibility of targeted primary and secondary preventive strategies in individuals who are pre-symptomatic.

Translation of genetics into therapeutics

The most prominent gap in the Parkinson's disease field is the lack of disease-modifying treatments,[6] and thus the translation of genetic findings into improved outcomes for patients. The early recruitment and stratification of participants by genetic status will hopefully curtail some of the failures of disease-modification trials. Two probable reasons for these failures are the disease stage of participants (which might be already advanced for therapies to arrest the pathogenic cascade, even in patients with clinically early Parkinson's disease, eg, within 4 years of diagnosis),[100] and that these trials have been done by approaching Parkinson's disease as a single entity, despite the fact that multiple causes—linked to variable biological mechanisms—account for the pathogenesis.[4] Both these aspects can be addressed with genetics. Genetic variants can serve as the earliest definable upstream cause or predisposition to Parkinson's disease, and can be used with other biological markers (eg, of synucleinopathy or neurodegeneration) to enable recruitment at very early stages of the pathological process (panel 3).[16,17,18]

	Study design and intervention	Inclusion criteria	Primary outcome	Status
Gene target population: *LRRK2*				
NCT03710707; USA, eight centres	Randomised, double-blind, parallel assignment; DNL201 30mg or 50mg three times a day orally for 42 days *vs* matching placebo	Sporadic Parkinson's disease; patients with Parkinson's disease with *LRRK2* variants; DaT scan deficit consistent with Parkinson's disease; age 30–80 years; Hoehn and Yahr scale 1–3; MoCA ≥24; absence of significant pulmonary disorders	Treatment-emergent AEs and SAEs (laboratory tests, ECG, vital signs, and neurological examination)	Start date April 12, 2018; end date June 12, 2019; trial completed[21]
NCT05009199; USA, one centre	Non-randomised, single group; caffeine in repeated oral doses; after a caffeine wash-out for ≥24 h, participants receive a single injection of [^{18}F]MNI-444 followed by brain PET scan of up to 90 min to establish baseline adenosine A2A receptor binding	Carriers of *LRRK2* pathogenic or risk variants who are non-manifesting; age ≥30 years; absence of DaT scan deficit	Pharmacodynamics and pharmacokinetics of multiple doses of oral caffeine on striatal binding of the adenosine A2A receptor ligand [^{18}F]MNI-444	Start date April 26, 2021; end date May 26, 2021; trial completed
NCT05355064; Italy, one centre	Non-randomised, single group, open-label; trehalose 4 g per day orally for 24 weeks	Idiopathic Parkinson's disease; patients with Parkinson's disease with *LRRK2* variants; age 18–80 years; Hoehn and Yahr scale >1	Safety and AEs (laboratory tests, physical examination, and neurological examination)	Estimated start date May, 2022; but trial not recruiting yet
NCT05348785; Austria, two centres; Canada, five centres; China, four centres; France, nine centres; Germany, 12 centres; Israel, three centres; Italy, nine centres; Japan, five centres; Netherlands, three centres; Poland, six centres; Spain, 10 centres; UK, six centres; USA, 33 centres	Randomised, double-blind, parallel assignment; BIIB122 (also known as DNL151) 225 mg per day orally for 48–144 weeks *vs* matching placebo	Patients with early-stage Parkinson's disease; patients with Parkinson's disease with pathogenic *LRRK2* variants who completed early termination visit of NCT05418673; age 30–80 years; Parkinson's disease duration ≤2 years; OFF modified Hoehn and Yahr scale 1–2; OFF MDS-UPDRS parts II and III ≤40	Time to confirmed worsening (ie, a worsening event sustained over two consecutive assessments) in MDS-UPDRS parts II and III over the treatment period up to 144 weeks	Start date April 19, 2022; recruiting
NCT05418673; France, five centres; Germany, two centres; Italy, one centre; Spain, six centres; UK, one centre; USA, 12 centres	Randomised, double-blind, parallel assignment; BIIB122 (also known as DNL151) 225 mg per day orally for up to 180 weeks *vs* matching placebo	Patients with Parkinson's disease with pathogenic *LRRK2* variants; age 30–80 years; Parkinson's disease duration ≤5 years; OFF modified Hoehn and Yahr scale 1·0–2·5; OFF MDS-UPDRS parts II and III ≤40	Time to confirmed worsening (ie, a worsening event sustained over two consecutive assessments) in MDS-UPDRS parts II and III over the treatment period up to 180 weeks	Start date Aug 26, 2022; end date July 27, 2023; terminated by sponsor*
ChiCTR2200064198; China, one centre	Randomised, double-blind, parallel assignment; donor *vs* autologous fecal microbiota transplantation	Patients with de novo Parkinson's disease with *LRRK2* variants; age 18–75 years; Hoehn and Yahr scale 2–3; absence of other Parkinson's disease genetic variants; absence of family history of Parkinson's disease; absence of use of probiotics or antibiotics within 3 months before trial	Change in MDS-UPDRS and Hoehn and Yahr scale scores	Start date Sept 20, 2022; recruiting
Gene target population: *GBA1*				
NCT02941822; UK, one centre	Non-randomised, single group, open-label; ambroxol with increasing dose from 60 mg to 300 mg three times a day orally over 28 days, then 420 mg three times a day to 6 months	Patients with Parkinson's disease with and without heterozygous *GBA1* mutations; age 40–80 years; Hoehn and Yahr scale 1–3	CSF and blood glucocerebrosidase and ambroxol levels	Start date December, 2016; end date May, 2018; trial completed[22]
NCT0290600; Austria, one centre; Canada, three centres; France, one centre; Germany, two centres; Greece, one centre; Israel, four centres; Italy, five centres; Japan, five centres; Norway, one centre; Portugal, two centres; Singapore, two centres; Spain, two centres; Sweden, one centre; Taiwan, one centre; UK, two centres; USA, 19 centres	Randomised, double-blind, parallel assignment; part 1: GZ/SAR402671 (venglustat) orally with increasing dose of 4, 6, and 15 mg for 4 weeks; part 2: venglustat daily with dose established in part 1 for 52 weeks *vs* matching placebo	Patients with Parkinson's disease with heterozygous *GBA1* mutations; RBD by polysomnography or questionnaire; age 18–80 years; Parkinson's disease symptoms ≥2 years; Hoehn and Yahr scale ≤2; MoCA ≥20; no concomitant *LRRK2* p.Gly2019Ser mutation; absence of cortical or posterior subcapsular cataract	Part 1: treatment-emergent AEs and SAEs (laboratory tests, ECG, vital signs, and neurological and physical examination including ophthalmological abnormalities); part 2: Change from baseline to 52 weeks in MDS-UPDRS parts II and III	Start date Dec 15, 2016; end date May 27, 2021; trial completed[23]
NCT04127578; Israel, four centres; USA, five centres	Non-randomised, sequential assignment, open-label; single dose of LY3884961 (dose level 1 or 2), administered intra-cisterna magna, followed by intravenous methylprednisolone in six pulses over 3 months	Patients with Parkinson's disease with heterozygous *GBA1* mutations; age 35–80 years; OFF Hoehn and Yahr scale 3–4; MoCA ≥14; negative screening for *Mycobacterium tuberculosis*; absence of unstable autoimmune disease	From baseline to 5 years: treatment-emergent AEs and SAEs, including brain and spine MRI and NCS; from baseline to 24 months: treatment-emergent immunogenicity of AAV9, glucocerebrosidase, and NfL in blood; and immunogenicity of AAV9 and glucocerebrosidase in CSF	Start date Jan 3, 2020; recruiting

(Table continues on next page)

	Study design and intervention	Inclusion criteria	Primary outcome	Status
(Continued from previous page)				
NCT05287503; Italy, three centres	Randomised, double-blind, parallel assignment; ambroxol hydrochloride 1200 mg per day (400 mg three times a day) orally for 52 weeks (with initial titration from 200 mg per day for the first 25 days) *vs* matching placebo	Patients with Parkinson's disease with heterozygous *GBA1* mutations; age 21–80 years; Parkinson's disease symptoms >5 years; Hoehn and Yahr scale ≤3	Change from baseline to 52 weeks in MoCA, and conversion rate from normal cognitive function to mild cognitive impairment and from normal cognitive function or mild cognitive impairment to Parkinson's disease dementia	Start date Feb 15, 2022; recruiting
NCT05819359; Canada, two centres; France, six centres; Germany, six centres; Italy, nine centres; Netherlands, three centres; Poland, three centres; Portugal, four centres; Spain, seven centres; Sweden, two centres; UK, five centres; USA, 28 centres	Randomised, double-blind, parallel assignment; BIA 28-6156 10 mg or 60 mg per day orally *vs* matching placebo	Patients with Parkinson's disease with heterozygous *GBA1* mutations; age 35–80 years; Parkinson's disease duration 1–7 years; modified Hoehn and Yahr scale ≤2·5; MoCA ≥22	Time from baseline to clinically meaningful progression on MDS-UPDRS parts II and III over the treatment period up to 78 weeks	Start date March 31, 2023; recruiting
NCT05830396; Netherlands, one centre	Randomised, double-blind, parallel assignment; ambroxol 1800 mg per day orally for 48 weeks (with initial titration from 600 mg per day over 2 weeks), followed by 12-week washout period *vs* matching placebo	Patients with Parkinson's disease with heterozygous *GBA1* mutations; age ≥18 years; Parkinson's disease duration ≤10 years	Change from baseline to 60 weeks in MDS-UPDRS part III	Start date May, 2023; recruiting
Gene target population: *PRKN* or *PINK1*				
DRKS00015880; Germany, multi-centre	Randomised, double-blind, parallel assignment; fluid ubiquinone emulsion (equivalent dosage of 1200 mg coenzyme Q10) three times a day orally for 6 months *vs* matching placebo	Patients with Parkinson's disease with homozygous or heterozygous *PRKN* or *PINK1* mutations; patients with Parkinson's disease with polygenic mitochondrial profile (based on eight predefined SNPs); patients with Parkinson's disease without polygenic mitochondrial profile; age ≥18 years; MMSE ≥24; absence of treatment with coenzyme Q10 within 3 months before trial	Change from baseline to 24 weeks in MDS-UPDRS part III	Start date Dec 15, 2018; recruiting
DRKS00019932; Germany, one centre	Randomised, double-blind, parallel assignment; vitamin K2 (MK-7) 1 mg per day orally for 7 days *vs* matching placebo	Patients with Parkinson's disease with biallelic *PRKN* or *PINK1* mutations; patients with non-genetic Parkinson's disease; healthy volunteers in a control group; age ≥18 years; absence of treatment with vitamin K2 or vitamin K antagonist within 1 month before trial	Change in magnetic resonance spectroscopic measurements of adenosine triphosphate and phosphocreatine	Estimated start date Feb 3, 2020; but trial not recruiting yet

We searched two clinical trial registries, ClinicalTrials.gov and the WHO ICTRP, using the following search terms: *LRRK2*, *GBA1*, *SNCA*, *VPS35*, *Parkin*/*PRKN*, *PINK1*, and *PARK7*/*DJ-1*. One trial on *GBA1* Parkinson's disease was withdrawn without any enrolled participants (NCT02758730) and is not included in this table. AEs=adverse events. DaT=Dopamine transporter. ECG=electrocardiogram. ICTRP=International Clinical Trials Registry Platform. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. MMSE=Mini-Mental State Examination. MoCA=Montreal Cognitive Assessment. NCS=nerve conduction study. NfL=Neurofilament light chain. RBD=rapid eye movement sleep behaviour disorder. SAEs=serious AEs. SNPs=single nucleotide polymorphisms. *This trial was terminated due to the sponsor's decision to revise the trial plans for BIIB122, and not due to safety concerns.

Table: **Clinical trials including participants with Parkinson's disease genetic variants**

For **ICTRP** see https://trialsearch.who.int

The prospect of participating in genetics-informed clinical trials is becoming increasingly relevant for patients with Parkinson's disease and individuals at risk,[5,21,22,23,69] and is a source of engagement and hope for patients and families.[87] As shown in the table, current genetics-informed clinical trials primarily target *LRRK2*-related and *GBA1*-related pathways, with fewer targeting *PRKN* or *PINK1* pathways. For *LRRK2* (and possibly also *VPS35* and *RAB32*), the main strategy is to correct the increased LRRK2 kinase activity by use of kinase inhibitors.[4,5,6,19,21,46,62] For *GBA1*, a major aim is to upregulate glucocerebrosidase activity.[4,5,6,22,69] The strategy to reduce the accumulation of glycolipid substrates, which is standard therapy for Gaucher's disease, appears to be less useful for *GBA1* Parkinson's disease after the negative results of the MOVES-PD part 2 venglustat study, despite exhibited target engagement.[23] For *PRKN*-related or *PINK1*-related mitochondrial dysfunction, so-called mitochondrial enhancers are being tested.[4,5]

Even within genetically defined Parkinson's disease, there might be a need for further stratification, for example for *GBA1* variants of different severities and with different trajectories in disease progression (or with different effects on glucocerebrosidase structure and function),[5,69,74] 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 levels.[19,20,46]

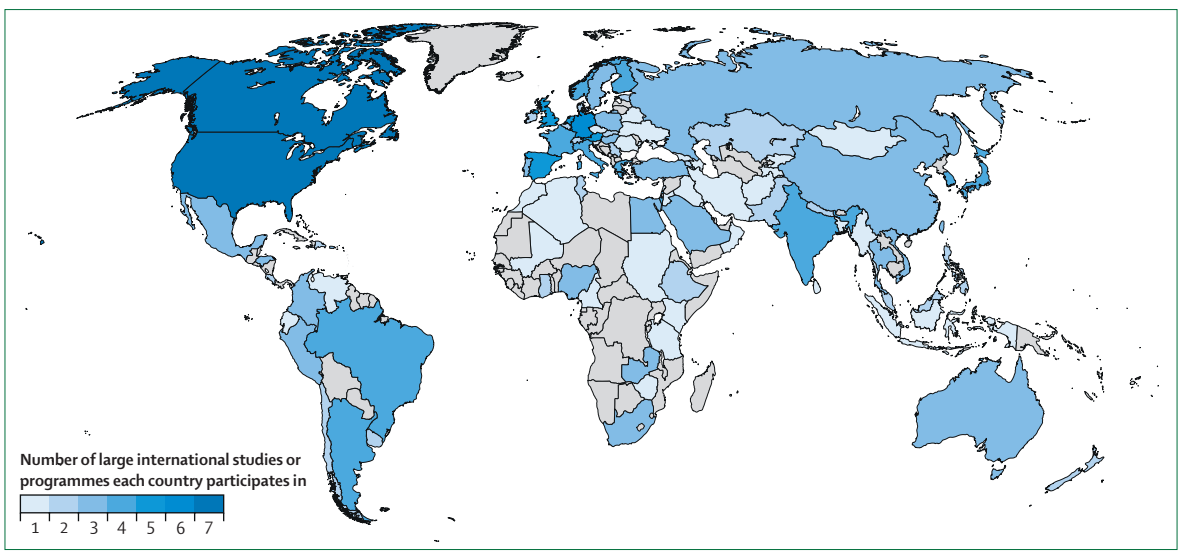

Figure 2: **Countries participating in ongoing, large international Parkinson's disease genetic research studies and consortia**
The map highlights countries in which academic centres are involved in international studies, programmes, and consortia, including the Global Parkinson's Genetics Program (GP2), 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, the PD Generation (PD GENE) study, and the Parkinson's Progression Markers Initiative (PPMI). These studies were selected based on international reach, and relatively large size of the network (involving at least ten centres). The different shades of blue reflect the number of studies or programmes in the country (as of Feb 8, 2024). The darker the shade of blue, the more studies or programmes the country is participating in. A listing of studies, programmes, and included countries can be found in the appendix (pp 7–9).

It has been suggested, for example, that trials recruiting carriers of severe *GBA1* variants could require a smaller sample size or shorter duration, compared with trials recruiting carriers of mild or risk variants.[5,69,74] It will be important also to balance the groups of the trial according to the severities of variants.[5,69,74] When considering therapeutic development for common risk variants (such as the *LRRK2* Asian p.Gly2385Arg and p.Arg1628Pro variants or the West African *GBA1* rs3115534-G variant), it could be argued that their (relatively small) genetic effect sizes could belie biological importance and potential druggability.[44,101]

Genetics-informed clinical trials face multiple obstacles, including slow recruitment. Few genetics-informed clinical trials (four [29%] of 14 trials; table) currently enrol participants from outside North America and Europe. This lack of diversity contributes to delays in trial completion, exacerbates disparities, and restricts our ability to generalise study results.[52,102] For example, in the first large-scale trial of a targeted treatment in *GBA1* Parkinson's disease, recruitment of 221 participants who carried a *GBA1* mutation (over 90% of whom were of European ancestry) took more than 4 years.[23] Recruitment should therefore be broadened, especially considering that other global populations have enriched cohorts of *LRRK2, GBA1, PRKN,* or *PINK1*-related Parkinson's disease. Ongoing genetic testing in previously under-studied populations, with the identification of new cohorts with genetic forms of Parkinson's disease, will be of value to recruit participants for 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.[84] Promising strategies to promote clinical trial recruitment in populations who are under-represented have been proposed.[102] These strategies include the creation of global clinical trial networks and prespecified recruitment goals (eg, at least 10–30% participants from populations who are under-represented). The PD Generation study is an example of an initiative incorporating these measures, and the study is extending its scope from North America to South America and beyond.

Conclusions and future directions

Genetics is becoming a powerful tool to understand and predict the risk of Parkinson's disease and its progression. Genetics brings us closer to providing personalised medicine, and it is crucial to identify the broadest range of variations that influence the disease across and within populations. There are myriad challenges for genetics research in populations who are under-represented, but also rich opportunities (appendix pp 10–14).

These discoveries will provide crucial information on molecular pathways, potential biomarkers, therapeutic targets, and disease expression (penetrance and clinical phenotype), which might differ across populations. Parkinson's disease research will require interdisciplinary teams, involving a wide range of expertise and data, and engaging clinical, academic, philanthropic, industry, and regulatory and governmental partners, to make substantial advances. In all these efforts, an open science and community resource framework, with transparent

Search strategy and selection criteria

We searched PubMed for 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 5 years were prioritised, 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.

and reproducible methods, will maximise 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.[103] Furthermore, it is important to ensure that genetics research—being a flagship of international scientific collaboration (figure 2)—results in fair prospects to promote health among the global community of patients and families, irrespective of geographical location, socioeconomic status, ethnicity, and gender.[83] Crucially, these efforts should include opportunities for participation in clinical trials of genetics-informed therapies, and access to newly developed and affordable treatments.

Contributors

SYL searched the literature and wrote the first draft of this Personal View, including the panels. CK, LML, and NB designed and drafted figures 1 and 2. AHT designed and drafted the table. AAA, TST, and SYL designed and drafted Appendix figure 1. All authors contributed to the final revisions of the manuscript.

Declaration of interests

SYL is an employee at the University of Malaya. SYL 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. AHT is an employee at the University of Malaya. AHT has received grants from and served as a consultant for the MJFF and the ASAP-GP2. AHT has received honoraria for lecturing from the MDS and Boehringer Ingelheim. NUO is employed by the College of Medicine, University of Lagos and receives institutional research grant support from the ASAP-GP2, the MJFF, and the UK National Institute for Health and Care Research for Parkinson's disease research including Parkinson's disease genetics studies. NUO has received honoraria as speaker from the MDS. HRM is employed by University College London. HRM reports paid consultancy from Roche, Aprinoia, AI Therapeutics, and Amylyx; lecture fees and honoraria from the *British Medical Journal*, Kyowa Kirin, and the MDS; research grants from Parkinson's UK, the Cure Parkinson's Trust, PSP Association, Medical Research Council, and the MJFF. HRM is a co-applicant on a patent application related to C9ORF72 (method for diagnosing a neurodegenerative disease; PCT/GB2012/052140). IM reports receiving research grants from the National Institutes of Health (1R01NS112499), the MJFF, and the ASAP-GP2. IM 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. JNF is an employee at Nanyang Technological University Singapore, and received the National Medical Research Council Open Fund Individual Research Grant (MOH-000559) and the Ministry of Education Academic Research Funds (MOE-T2EP30220-0005 and MOE-MOET32020-0004). ES is employed by the University of Dundee, UK and has received research funding from the MJFF, the Chief Scientist Office in Scotland, and UK Research and Innovation Medical Research Council. AJN is employed by Queen Mary University of London. AJN 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. AJN reports consultancy and personal fees from AstraZeneca, AbbVie, Profile, Bial, Charco Neurotech, Alchemab, Sosei Heptares, Umedeor, and Britannia, outside the submitted work. AJN 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 (NIH) USA, specifically the 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. CK 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. CK 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 declare no competing interests.

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