Am J Neurodegener Dis 2023;12(4):108-122
www.AJND.us /ISSN:2165-591X/AJND0151946

Review Article

Leveraging genetic diversity to understand monogenic Parkinson's disease's landscape in AfrAbia

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Received June 27, 2023; Accepted August 15, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Parkinson's disease may be caused by a single highly deleterious and penetrant pathogenic variant in 5-10% of cases (monogenic). Research into these mutational disorders yields important pathophysiological insights. This article examines the phenotype, genotype, pathophysiology, and geographic and ethnic distribution of genetic forms of disease. Well established Parkinson's disease (PD) causal variants can follow an autosomal dominant (*SNCA*, *LRRK2*, and *VPS35*) and autosomal recessive pattern of inheritance (*PRKN*, *PINK1*, and *DJ*). Parkinson's disease is a worldwide condition, yet the AfrAbia population is understudied in this regard. No prevalence or incidence investigations have been conducted yet. Few studies on genetic risk factors for PD in AfrAbia communities have been reported which supported the notion that the prevalence and incidence rates of PD in AfrAbia are generally lower than those reported for European and North American populations. There have been only a handful of documented genetic studies of PD in AfrAbia and very limited cohort and case-control research studies on PD have been documented. In this article, we provide a summary of prior conducted research on monogenic PD in Africa and highlight data gaps and promising new research directions. We emphasize that monogenic Parkinson's disease is influenced by distinctions in ethnicity and geography, thereby reinforcing the need for global initiatives to aggregate large numbers of patients and identify novel candidate genes. The current article increases our knowledge of the genetics of Parkinson's disease (PD) and helps to further our knowledge on the genetic factors that contribute to PD, such as the lower penetrance and varying clinical expressivity of known genetic variants, particularly in AfrAbian PD patients.

Keywords: AfrAbia, Parkinson's disease, monogenic, genetics, challenges, gaps, prospects

Introduction

Parkinson's disease (PD) affects one percent of the global population. It disproportionately affects the elderly and has severe consequences for their quality of life [1, 2]. It is believed that neuron mortality in vulnerable brain regions (particularly but not exclusively the substantia nigra) and the development of Lewy bodies in the few surviving neurons result from a complex interaction between genetic and environmental factors [3]. Resting tremor, bradykinesia, mood problems, olfactory dysfunction, and cognitive impairment are only some of the motor and non-motor symptoms of PD, a complex, diverse neurodegenerative condition. About 6.1 million individuals worldwide were living with PD in 2016 [4], and this number is anticipated to climb to 17.5 million by 2040 [5] due to an aging global population and greater lifespan. Dopamine replacement therapy (DRT) with levodopa or other dopamine agonists (DA) is the standard treatment for people with Parkinson's disease [6].

The overwhelming majority of PD cases have no identifiable cause. About 5-10% of all patients suffer from a monogenic form of PD [6, 7]. Almost 100 genetic risk loci have been associated with PD but most of our knowledge is based on EUR population-based studies [6]. High genetic heterogeneity underlies PD, in part due to the multiple rare mutations observed only in a single family or small groups [6]. Despite extensive and ongoing research, the pathogenic pathways underlying Parkinson's disease needs more explanation and better understanding [7, 8]. Due to the high genetic

heterogeneity of the disease and the difficulty in interpreting variants of uncertain significance, Next Generation Sequencing (NGS) technologies are widely used in diagnostics, but their application to Parkinson's disease (PD) is still limited to a small number of patients with a clear family history and a small number of causative mutations.

There are presently no disease-modifying therapeutics for PD, even though it is a widespread neurodegenerative condition for which we have only a limited grasp of the molecular and cellular disease foundation. Most cases of Parkinson's disease have a complicated genetic background. Strong evidence for the function of cholinergic pathway in causing Parkinson's disease is shown for the first time by mutations in RIC3, a chaperone of neuronal nicotinic acetylcholine receptor subunit-7 (CHRNA7). Intellectual incapacity, stiffness, seizures, myoclonus, dystonia, and a poor response to levodopa are only some of the (atypical) symptoms of early-onset X-linked parkinsonism [9]. CHCHD2, *LRP10*, *TMEM230, UQCRC1*, and *VPS13C* are only a few of the newly discovered genes for which replication studies are necessary to confirm such associations. Some genes (including *SNCA* and *LRRK2*) have been related to both Mendelian types of PD and enhanced vulnerability. Mutations in genes like glucocerebrosidase (*GBA1*) are intermediate between a single gene's involvement and a predisposition for the disease [10].

Recent hot topics include the investigation of regional and ethnic differences for PD gene mutations, the impact of heterozygous variants in recessive PD genes, the outcomes in individuals who co-inherit mutations in both *GBA1* and *LRRK2*, and the impact of the underlying genetic form on outcomes from deep brain stimulation. The purpose of this review is to increase our knowledge of the significance of genetics in PD and to disseminate that information worldwide so that it may be used. In addition to enhancing our current understanding of known genetic causes, such as reduced penetrance and variable clinical expressivity of known genetic variants in AfrAbia PD patients. It also, establishes an efficient infrastructure to speed up the discovery of novel monogenic causes of parkinsonism.

Genetic diversity in AfrAbia

Over the last two decades, more than 20 genes responsible for hereditary PD have been identified. At least five genes, including *SNCA* (*PARK1/4*), *LRRK2 (PARK8), VPS35 (PARK17), DNAJC13, and CHCHD2* [11, 12], have been implicated in autosomal dominant types of PD. LRRK2 is one of the main risk factors for PD in the EUR population. About 1.8% of healthy people, 3.6% of people with sporadic PD, and 10% of those with autosomal dominant familial PD are carriers [13]. So far, scientists have uncovered over 80 variations of the *LRRK2* gene [14]. Seven of these variations have been identified as harmful, with the *G2019S* mutation being the most frequent. This mutation is responsible for 5-6% of familial and 1-2% of sporadic PD cases [13, 15]. It's interesting to see how the prevalence of this mutation varies greatly by location and race. However, the Ashkenazi Jewish and North African communities had the greatest documented prevalence, with up to 20% and 40% of PD patients, respectively [16].

AfrAbia has a higher incidence of autosomal recessive neurodegenerative diseases due to high consanguinity rates. All these factors present opportunities for the neuroscience community in Africa to make advances in fundamental research and develop personalized treatments to improve brain health and well-being on the continent. While the high prevalence of mental, neurological, and substance-use disorders poses distinct challenges to the African neuroscience community [17, 18], it also presents enormous opportunities. Low physician-to-patient ratios, for instance, expose the average clinician to many patients, thereby increasing the potential for field-specific competence development. This increased clinical exposure generates locally pertinent study topics and enhances the viability of clinical studies, which benefits not only the African community but also the Global North. In Africa, it takes less time to recruit participants for clinical investigations on traumatic brain injury, for example, than in Europe. In conclusion, there are ample opportunities for clinically oriented neuroscience research to improve healthcare in Africa. Specific goals include enhancing developmental potential and mental health, as well as reducing mortality and neurological impairment. AfrAbia is composed of both Arab League and

African Union members. Historical and geographical influences connect the two contiguous territories of Africa and the Arab world on a cross-cultural level for more information, see [19].

For several reasons [20], people of European ancestry are overrepresented in genetic research, especially those pertaining to PD. The potential for novel gene discoveries, medicine development, and advances in treatment for multi-ethnic AfrAbian people may be jeopardised due to inadequate representation of AfrAbian groups in such research. PD prevalence rates have been observed to be higher in men across a variety of populations [4, 21]. Demographic differences in both monogenic and complex PD have been uncovered via genetic research. Different domains of function are associated with the two forms of the *LRRK2* protein [22]. Although the pathogenicity of PD may not be linked to kinase activity, people of East Asian descent (6-11% carrier prevalence) may benefit more from a PD medication that targets *LRRK2* than people of other ethnicities [23]. The need to learn about the effects of genetic differences across local populations [22, 24, 25] is a direct result of the discrepancy in occurrence across communities. Similar issues are also brought on by the *GBA*1 gene. The carrier frequencies of *GBA1* gene mutations vary considerably (3-31%) across ethnic groups [26], even when mutations are unique to one.

Rizig et al. [27] established *GBA1* as a unique genetic risk factor for PD in people of African heritage and those with some African ancestry. Both the mechanism and the associated risk are different in this startling finding compared to earlier study in Northern European groups. This finding underscores the need for the fair and equitable inclusion of people from different ancestries in clinical trials of treatments for complex diseases like PD and comes at a time when the field is shifting toward precision medicine. Given the unique genetics of these understudied groups, including them is an important step toward uncovering the underlying genetic causes of Parkinson's disease. This paves the way for future treatment options, including those based on RNA, with the goal of lowering lifetime risk.

Disparities across populations may contribute to sporadic PD. Some findings from research conducted on people of European ancestry were confirmed in one of the biggest East Asian GWAS on P, conducted by Foo et al. [28]. To highlight this, the authors identified two loci that had not been published in prior GWAS of people of European ancestry [28]. Although it is too early to draw conclusions about the functional importance of these results, they do underscore the need for more trials to shed light on the enigma of PD pathogenicity. Atypical PD and other neurological diseases are affected by the same variables. In this review, we provide a concise summary of the monogenic origin of PD with a focus on AfrAbia population.

Monogenic origin of PD in AfrAbia (Tables 1 and 2)

Numerous investigations have pointed up the lack of genetic research on African people [29-31]. **Table 1** provides a summary of all the studies that have been done and their results. Because of genetic founder effects, most of the research on the African continent has focused on patients from North African Arabic nations, where the prevalence of the *LRRK2 G2019S* mutation was reported to be as high as 41% of patients [32]. Despite several investigations, the mutation discovery rate in South African research is poor [29, 33-44]. Nigeria (30-32 studies), Tanzania (12 studies), Zambia (56 studies), and Ghana (57 studies) are the only other nations in Africa where genetic research has been documented. AfrAbian people have the oldest genomes and the highest genetic variety in the globe, making them a prime source for uncovering previously unknown aspects of the pathophysiology of PD [47].

Research into *LRRK2* and, more specifically, the *G2019S* mutation, has shown some intriguing results (**Table 1**). Black Africans have not been shown to have this mutation [38, 45, 46], despite its prevalence in North African Arabic communities. Eight of the 647 individuals tested in recent research in South Africa were discovered to be *G2019S*-carriers; all except one (whose grandpa was German) were of Ashkenazi Jewish descent [47]. *G2019S*-carriers in a study of African Arabic patients in Tunisia had the same PD symptoms as non-carriers but at a younger age at start (AAO), exhibited a more benign phenotype, and displayed less cognitive impairment [47]. The eight *G2019S* carriers in the South African cohort had a mean age at

Table 1. Published mutation screening studies in AfrAbian patients with Parkinson's disease [100]

Country	Patients and controls	Genes screened and method used	Main findings	Phenotype of mutation carriers	Reference
Algeria	1 multiplex family	PRKN (all 12 exons) PCR and gel electrophoresis	PRKN homozygous deletion of exons 8 and 9 found in 3 affected siblings	Young AAO (<45 years), good response to levodopa	Lücking et al., 1998
	106 patients	LRRK2 G2019S (exon 41) Sanger sequencing	G2019S found in 34 patients (32%)	G2019S carriers had a similar age at onset to that of non-carriers. Behavioural abnormalities, mostly depression and hallucinations, and sleep disorders were more frequent in G2019S carriers	Belarbi et al., 2010
	236 probands	LRRK2 G2019S (exon 41) Sanger sequencing	G2019S found in 84 patients (36%); (77 heterozygotes and 7 homozygotes)	Mean age at onset in probands was 48.9 ± 12.1	Troiano et al., 2010
Egypt	5 patients; 50 controls	GIGYF2 Asn56Ser and Asn457Thr; TaqMan assay	Asn457Thr found in one patient, heterozygous; Not present in controls	AAO 46 years presented with marked rigidity and bradykinesia and slight resting tremor, good response to levodopa	Zimprich et al., 2009
	113 patients (sporadic PD) 87 controls	LRRK2 G2019S PCR-RFLP/TaqMan assay	G2019S found in 11 patients (9.7%); all heterozygous; Not present in controls	Mean AAO was 55.3 ± 5.4 years, similar to non-carriers. G2019S was associated with a higher degree of motor effect but does not seem to affect mentation or behavioural aspects of the disease	Hashad et al., 2011
Morocco	1 proband; 96 controls	Genome-wide copy number variation (chromosomal microarray analysis); LRRK2 (exon 41); Sanger sequencing PINK1 (all 8 exons) Sanger sequencing	PINK1 homozygous L539F mutation found in one affected patient; Not present in controls	AAO 54 years; patient presented with right akinetic-rigid syndrome with slight tremor in the hand. He also had neck pain and rapid eye movement behaviour disorder. Rapid progression and early cognitive impairment	Ben El Haj et al., 2016
	1 multiplex family	WES	PINK1 homozygous A217D mutation found in two affected siblings	Early-onset disease (AAO 27 and 29 years), relatively mild and slowly progressive PD, early lower-limb symptoms and gait disturbance with asymmetrical onset	Norman et al., 2017
Tunisia	1 multiplex family	PRKN (all 12 exons) Sanger sequencing	PRKN homozygous two-base AG deletion in exon 2 found in 3 affected siblings	AAO 21, 24, 34 years, clinical features included rest tremor, bradykinesia and rigidity, levopoda responsive	Gouider-Khouja et al., 2003
	91 families	LRRK2 G2019S Modified single base chain extension assay	G2019S found in 38 patients (42%); 23 heterozygous and 15 homozygous	G2019S carriers had an older AAO but had typical clinical features of PD	Ishihara et al., 2007
	91 families (200 PD patients)	LRRK2 G2019S Method not specified	G2019S found in 38 patients (42%)	Mean age at onset for affected individuals was 64 ± 13 years for individuals with G2019S homozygous mutations, and was 68 ± 12 years for individuals with heterozygous mutations, which was similar to individuals without G2019S mutations	Warren et al., 2008
	92 families (76 multiplex families comprised of 208 patients and 16 singleton families)	PINK1 (all 8 exons); Sanger sequencing and exon dosage LRRK2 (all 51 exons) Saner sequencing	Four PINK1 mutations found in 14 families (Q129X, Q129fsX157, G440E, and Q456X); all homozygous	Younger AAO (36 ± 12 years) and longer disease duration, patients more likely to develop akinetic-rigid parkinsonism and had a slow progression	Ishihara-Paul et al., 2008
	238 patients (sporadic PD) 371 controls	LRRK2 G2019 Taqman assay	G2019S found in 72 patients (30%); 60 heterozygous and 12 homozygous; G2019S found in 7 controls (2%)	Clinical features and mean AAO (58 ± 10.7) of G2019S carriers were indistinguishable from noncarriers, and the distribution of akinetic-rigid, mixed, and tremor-dominant phenotypes was similar between the two groups	Hulihan et al., 2008
	89 families (76 multiplex families comprised of 208 patients and 13 singleton families)	ATP13A2 Sanger sequencing (all 29 exons)	No mutations detected		Vilariño-Güell et al., 2009

33 probands	GBA (all 11 exons); Sanger sequencing GBA N370S screened in 395 patients and 372 controls by Taqman Assay	N370S found in one patient and 3 controls	No details provided	Nishioka et al., 2010 Neurosci Lett
231 patients from 90 families	LRRK2 G2019S (exon 41) TaqMan assay PINK1 (all 8 exons) Sanger sequencing and exon dosage PRKN (all 12 exons) Sanger sequencing and exon dosage	LRRK2: 73 G2019S carriers (20 homozygous) PINK1: 42 mutation carriers PRKN: 9 mutation carriers	AAO and mean disease onset in LRRK2 carriers (60 years) were similar to idiopathic PD but they had a more severe motor phenotype, PINK1 carriers had younger mean AAO (35 years) and longer disease duration	Nishioka et al., 2010 J Neurol Neurosurg
250 patients; 218 controls	LRRK2 G2019S; KASP assay	G2019S found in 85 patients (33.6%); 76 heterozygous and 8 homozygous; G2019S found in 3 controls (1.3%); all heterozygous	The mean AAO was 64.1 ± 11.5 years; patients had typical PD	Landoulsi et al., 2017
1 multiplex family	22 candidate genes; next-generation sequencing gene panel	SYNJ1 heterozygous Leu-1406Phefs*42 and Lys1321Glu found in two affected siblings	AAO at 16 and 21 years; one patient had generalized tonic-clonic seizures, moderate cognitive impairment, good response to levodopa	Ben Romdhan et al., 2018

Table 2. Genotype-phenotype summary for monogenic forms of Parkinson's disease in AfrAbia

Gene	Mode of Inheritance	Frequency	Ethnic Population Distribution	Types of Mutations	Clinical Phenotype	Response to PD Medication	Response to DBS	Pathological Findings
LRRK2	AD	1% of PD but higher in North African Berber Arab and Ashkenazi Jewish populations	The p.G2019S mutation found in Europeans with high prevalence in North African Berbers and Ashkenazi Jews	7 missense variants described	Resembles idiopathic PD	Vast majority show a good response to levodopa [Over et al., 2021]	DBS is effective [Leaver et al., 2021]	Most patients with the p.G2019S mutation show LB pathology, whereas this finding is rare for other mutations
PINK1	AR	Second most common cause of EOPD, 1.9% of recessive PD [Lesage et al., 2020]	European, Asian, maybe frequent in Arab Berber and Polynesian populations [Lesage et al., 2020; Kasten et al., 2018; Patel et al., 2021]	Missense mutations, nonsense mutations, structural variants	EOPD, typical PD, dyskinesias, dystonia, and motor fluctuations can occur	Vast majority show a good outcome [Over et al., 2021]	Good or moderate [Over et al., 2021]	LB pathology may or may not be present in the handful of autopsy cases reported
DNAJC6	AR	Rare	Mainly found in Middle Eastern populations	5 different homozygous mutations, largest family carries nonsense mutation [Wittke et al., 2021]	Juvenile PD with complicating features, EOPD	Poor	Good outcome [Kurian et al., 1993]	No reports identified
NRXN2 (Neurxin-2)		Rare	Afrikaner Family (South Africa) Sebate et al., (2021)					

EOPD: early-onset Parkinson's disease.

onset (AAO) of 56.6 (SD 10.9) years, had classic PD symptoms, and the homozygous mutant carrier did not show more severe illness than the others [38], even though two patients had severe lower limb dystonia. Patients of African descent may be carriers of additional LRRK2 mutations but identifying them would require sequencing all 51 exons of this gene. In conclusion, genetic studies in AfrAbian populations offer substantial untapped potential to further PD study worldwide.

Most harmful mutations (80-85%) reported to date are exonic [48], making WES the better option when considering NGS for the research of genetic diseases. Compared to WGS, WES is more cost-effective and requires less computing power [49, 50]. Nevertheless, hybridization biases and insufficient target enrichment in WES might lead to skewed coverage, which makes it difficult to identify copy number variation (CNV) [51]. This is a key drawback of WES in PD investigations, since CNVs comprising full exons (in *PRKN, PINK1,* and *DJ-1*) or spanning multiple gene copies (SNCA) are a major cause of PD. Taken as a whole, these considerations suggest that WGS may be superior to other methods for identifying new or uncommon genetic variations, which is especially important in the case of complicated disorders like PD.

LRRK2

PD has been linked to at least seven different missense variations in *LRRK2 (p.N1437H, p.R1441C/G/H, p.Y1699C, p.G2019S, and p.I2020T)* [52]. *LRRK2*-PD is indistinguishable from idiopathic PD at the individual level. However, this population may be seen as less severe [53, 54]. For instance, olfactory impairment, cognitive abnormalities, and REM behaviour sleep disorder are less common in *LRRK2* mutation carriers [54]. Further, certain malignancies may be more likely to develop in *LRRK2*-PD individuals [55-57]. Recent research shows that *LRRK2*-PD is linked to an increased risk of stroke [58]. Penetrance of PD in carriers of pathogenic and risk variants may be lower in those who regularly use non-steroidal anti-inflammatory medicines [59]. The *LRRK2 p.G2019S* mutation is the most prevalent and well understood of all *LRRK2* mutations. This mutation has a varied penetrance that depends on factors including age, environment, and genetics [60]. Different *LRRK2* mutations may be significant for various racial and geographical groups. The *p.R1441C* mutation, for instance, may be more prevalent in Southern Italy and Belgium [53], and it has a founder impact in Basque people. While *p.G2019S* is very uncommon, *p.G2385R* and p.R1628P variations are somewhat prevalent (5-10% in patients, 2-5% in controls) [61-64]. Despite claims that haploinsufficiency is either causal or protective of PD [64], recent results demonstrate that *LRRK2* loss-of-function mutations are not related with the disease.

All the confirmed *LRRK2* mutations are in the kinase domain, which might lead to hyperactivation [52, 65]. The illness mechanism may be a result of *LRRK2's* significant functions in microtubule function and Rab proteins as phosphorylation substrates [66, 67]. *LRRK2* is engaged in a wide variety of cellular biological activities.

PINK1

Tremor, bradykinesia, and stiffness are all hallmarks of *PINK1*, the second most prevalent cause of autosomal recessive PD [68, 69]. The median age of onset is 32. Cognitive impairment and psychosis occur seldom (14% and 9%, respectively) [68], whereas dyskinesias (39%), dystonia (21%), and motor fluctuations (34%) are additional phenotypic characteristics. Despite an increased propensity for levodopa-induced dyskinesias, the condition progresses slowly and responds well to levodopa treatment. Most alterations were missense variations (47.6%), followed by structural variants (19.1%) and nonsense mutations (14.3%) [68]. The missense mutation c.1040T>C (p.Leu347Pro) was the most prevalent kind in this study [68]. Homozygosity is estimated to occur in 1 in 5000 West Polynesians due to the high frequency of this allele (2.8%), indicating it may have a significant role in the development of EOPD in this population [70].

Mitochondrial homeostasis relies on a process called *PINK1/parkin*-mediated mitophagy, which is disrupted by *PRKN* and *PINK1* mutations [71]. *Parkin*, in summary, is an E3 ubiquitin ligase that ubiquinates mitofusin 1 and 2 and other outer mitochondrial membrane proteins

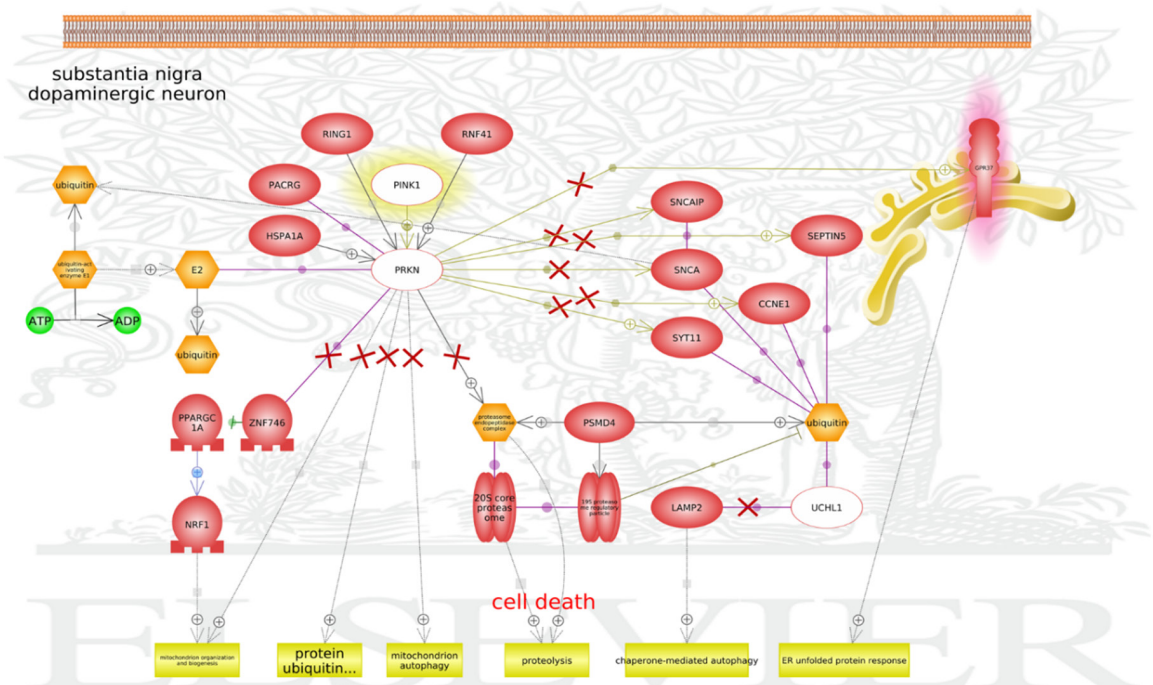

Figure 1. A gene network connecting PINK1 and PRKN was generated with Pathway Studio® (https://mammalcedfx.pathwaystudio.com/). Description on color-coded arrows can be found in the legends located in the bottom-right corner.

[72]. *Parkin* activation is mediated by *PINK1*, which phosphorylates parkin and keeps it stabilised and translocated to mitochondria [66, 72]. **Figure 1** depicts the interconnected pathways that link the *PINK* gene, highlighting their relevant connections and interactions. The expression of *PRKN* (grey arrow) and is indirectly regulated by *PRKN* (dashed arrow).

DNAJC6

Juvenile-onset, atypical parkinsonism is caused by biallelic mutations in *DNAJC6* and is characterised by early-onset symptoms, fast disease progression, and loss of ambulation within 10 years of diagnosis [73, 74]. Patients experience several symptoms, including a lack of response to levodopa treatment, a delay in cognitive development, intellectual impairment, seizures, and movement abnormalities such as dystonia, spasticity, and myoclonus. Early-onset parkinsonism is characterised by the development of symptoms between the ages of 30 and 40 in the absence of other characteristics [75]. In most cases, these people benefit from treatment with levodopa and have a decreased pace of disease development.

Edvardson et al. [73] reported the identification of *DNAJC6*, which was shown to be associated with AR-juvenile parkinsonism in a close-knit Palestinian family. Together with whole-genome sequencing (WES), they also carried out SNP genotyping and homozygosity mapping (HM) analyses [73, 74]. This strategy may allow for more fast disease gene discovery after WES [75]. Using HM analysis, researchers may find extensive patches of homozygosity amongst afflicted family members (where variations related with AR disease genes are expected to be found) [76]. That's why it's possible that HM will help find harmful mutations in AR-PD [47].

Auxilin 1 is a co-chaperone protein involved in clathrin-mediated endocytosis of synaptic vesicles, and it is encoded by the DNAJC6 gene. Animal models have shown that the absence of auxilin disrupts synaptic vesicle endocytosis, which has detrimental effects on synaptic neurotransmission, homeostasis, and signalling [76, 77]. Auxilin deficiency has been linked to dopaminergic neurodegeneration and unusual neurological symptoms, although the specific mechanism by which this occurs is not well understood.

NRXN2 (Neurxin-2)

In 2021, researchers reported the identification of a new PD gene (*NRXN2*) in a South African family [78]. Three afflicted members of an Afrikaner family were studied using whole exome sequencing data. Afrikaners are a South African ethnic group with roots in the Netherlands, Germany, and France.

Discussion and insights

In addition to the rarity of true monogenic PD, there are several factors that can make it difficult to establish a familial PD candidate gene in AfrAbia as pathogenic, including: isolated findings in familial studies; the presence of disease variants in healthy controls; incorrect gene-disease associations; or the presence of complex phenotypes that may lean towards other, diverse parkinsonisms [79]. Pathogenic and rare genetic contributors to PD disease have been identified in *DNAJC6* (PARK19), *DNAJC13* (PARK21), *SYNJ1* (PARK20), *VPS13C* (*PARK23*), and *CHCHD2* (*PARK22*) [75, 80-82]. Additional research is needed to classify the other potential genes as definite PD genes. Novel disease genes need to show "proof of pathogenicity" by having multiple mutations due to AfrAbia consanguinity rates this population is key for those investigations [83, 84]. These requirements seem to need a shift from single-family research to population based NGS investigations, which likewise depend on large cohorts of people, to effectively find uncommon variants. Furthermore, many PD loci may be population-specific, making their identification challenging in preliminary investigations [85]. However, owing to the novelty and the enormous number of variations being revealed using NGS, validation of these potential mutations through functional investigations or by utilising model species remains a difficulty. Therefore, NGS research on PD-affected families is still necessary because of the method's potential to identify putative harmful new genes that are not present in other people but may give mechanistic insight into PD pathobiology. Laboratory-based functional studies of candidate genes are helpful for elucidating disease aetiology, as evidenced with the finding of NUS1 by knockout RNAi studies on Drosophila revealing PD symptoms [86]. Since it is unclear whether the gene is pathogenic, many researchers avoid doing functional analysis in the lab [87].

Alternatively, phenotypic relationships, the determination of gene or protein interaction networks, and the establishment of functional similarities with known PD genes may all be used in conjunction with computational approaches to further correlate candidate genes with a disease of interest [88]. To identify protein or gene interactions between putative and established disease genes, a growing number of machine learning methods are incorporating data from established databases that provide functional annotations (such as Gene Ontology), tissue expression data (such as Human Protein Atlas), and metabolic/signalling pathways (such as Kyoto Encyclopaedia of Genes and Genomes) [89]. Recent research has outlined a comprehensive PD gene database (GENE4PD), and it has been found that simulating a functional correlation network between "high confidence" and "suggestive" PD-associated genes in PD pathways leads to significant associations, such as those seen with RIC3 and CHCHD2, the latter of which is significantly linked to *SNCA, PINK1, LRRK2, PARK7, and VPS35*, suggesting a possible opportunity for elucidating the architecture. Furthermore, owing to the overlap of disease pathways across different parkinsonism diseases, it is challenging to characterise a gene as being just PD-associated [90, 91].

Genetic, archaeological, and anthropological evidence all point to AfrAbia as the birthplace of modern humans about 200,000 years ago [92]. Linguistic, genomic, and archaeological evidence all point to a high degree of genetic diversity over much of AfrAbia, with more private alleles present in AfrAbia than everywhere else. Therefore, there are substantial racial and ethnic distinctions between AfrAbia and European populations. Furthermore, because of high environmental variability, AfrAbia groups have a wide range of cultural and phenotypic variances, making these people intriguing for studying gene-environment interactions. This might significantly advance the field of biological study by illuminating previously unknown connections between genes and between genes and their environments.

There is a notable lack of high-quality research on the prevalence of PD in AfrAbia, both in terms of the number of studies and the breadth of their coverage. Cooperation amongst AfrAbia countries is necessary to pool resources

and patient samples to ensure enough AfrAbia patients are recruited for genetic research. Creating a centralized mutation screening facility for AfrAbia PD patients would significantly contribute to the development of genetics research in Africa. Additionally, locating AfrAbia PD families amenable to whole exome sequencing investigation may aid in the identification of additional PD genes. To train more neurologists and specialists in movement disorders in AfrAbia, substantial time and resources would be needed.

The current study shows how important it is to provide more authority to local researchers to foster long-term variety in genomics studies. This might be achieved through collaboration with countries that have a higher per capita income or through the creation of regional development plans with centralized hubs. International organizations serve a critical role in connecting economically poor nations with economically more developed ones via regional companies and partnerships. Journals and editors should be conscious of the need to properly represent society through increased diversity on editorial boards. It's possible that proposals for URP-centric editions with stringent criteria for inclusion will be made. Finally, if peer review is to be a constructive, successful process that promotes inclusiveness for all participants, it must be conducted with care.

The enormous genetic heterogeneity reported in PD patients, who are all genetically and physiologically unique and carry diverse genetic combinations of common and uncommon variation not shared by most PD patients, may make it very challenging to interpret the genetic data. Nevertheless, future genetic research should test novel approaches in a broader sample of PD patients and controls. Using this method, we should be able to determine the frequency of rare variations in the panel of potential genes for each individual and, hence, identify individuals at increased risk for PD. This will complement GWAS and conventional co-segregation analyses of NGS data for finding variants associated with sporadic PD, drawing attention to the importance of rare variants in the genetics of the disease.

Conclusions

An opportunity to study the underlying genetics of PD in AfrAbian groups has arisen just once in human history. Some data suggest that there may be ethnic differences in the number of alleles that influence disease susceptibility or therapeutic response. To identify the precise genetic variant responsible for a trait, fine-structure mapping may benefit from exploring populations (such as the Yorubans in Nigeria) which harbour shorter-range linkage disequilibrium blocks and greater haplotype diversity [93, 94]. Therefore, studying the molecular epidemiology of PD in AfrAbia is crucial. Furthermore, the genetics of PD in African Americans need greater study [95, 96], and in this regard, recent initiatives such as the Black and African American Connections to PD Study (BLAAC PD) seek to dramatically expand our current understanding of PD etiology in these populations.

No case-control or cohort studies have been conducted on PD in AfrAbia, therefore nothing is known about the environmental and genetic risk factors that contribute to the disease in this population. AfrAbian PD and other movement disorders patients have the same healthcare needs as those in industrialized countries. Data on medication response, quality of life, survival, and other aspects of the social and economic effects of PD in AfrAbia are scarce. Answers to these issues might improve health care planning for Africans and people everywhere by illuminating the root causes of PD. International collaboration might help researchers in AfrAbia overcome the enormous challenges they confront owing to a lack of resources (including money, human resources, and supplies).

The study of monogenic PD has made significant strides in recent years. Multiple PD genes have been identified; however, we stress the need for unbiased confirmation of these results. The genetic findings have been converted into a better knowledge of the pathophysiological process causing PD, and there has been increased insight into genotype-phenotype connections because of laboratory investigations. It has been clear that there are substantial variations in the prevalence of PD gene variants across different ethnic and geographical groups. More information is now available on the impact of harbouring mutations in both LRRK2 and GBA, as well as the involvement of heterozygous carriers in autosomal recessive PD genes. The illness history and the responsiveness to levodopa and DBS may also be

affected by the underlying monogenic aetiology. Genetic testing for PD is becoming more widely available via both clinical and research channels, because to advancements in genomic technology. Utilising this genetic data will need international cooperation. Global studies may pool many patients, making it possible to search for unusual genetic origins of PD and to try to duplicate key genetic findings. They also provide a more accurate portrayal of minorities of various backgrounds and places. The International Parkinson Disease Genomics Consortium (IPDGC) [85], the worldwide Parkinson's Disease Genetics Programme (GP2) [97], and AfrAbia Parkinson's Disease Genomic Consortium (AA-PD-GC) [98] are among the many large-scale worldwide programmes aiming to discover novel disease genes in PD. PD is presently incurable, however research into its genetics might provide light on its pathogenesis and aid in the development of tailored therapeutics.

Perspectives

The intricacy of multi-mapping reads between GBA and GBAP1 and the dearth of well-powered and African-specific RNA sequencing datasets underscore the pressing need for more research. Despite the significant advancement represented by this research, much more work must be done to fully characterize the genetic risk factors for PD. The impact of single-gene mutations on PD-related cognitive decline should be investigated in future research. Here, we provide important insights into the possible unique pathogenic pathways underpinning the genesis of PD and the targeted development of AfrAbian haplotypes. There is no doubting the value of genetically categorizing AfrAbian populations. This research shows how using diverse populations may improve our knowledge of complicated illnesses and highlights the significance of haplotype substructure findings for future fine-mapping efforts. Overall, our work is a useful tool for finding and monitoring certain key monogenic variations that may be relevant for enrolment in target-specific PD clinical trials, since it addresses the genetic complexity underlying these underrepresented groups. Testing for GBA1 in Africans may improve the design of a study so that it is more likely to provide useful information. We expect these findings to be important in elucidating the molecular pathways behind the illness process, which in turn may facilitate the development of novel treatment approaches soon. This would be useful for examining population-specific connections and improving our granularity in association testing via the inclusion of omics data.

Because of their high levels of within-population genetic variability, shorter linkage disequilibrium (LD) blocks, and abundance of alleles that are unique to these populations, AfrAbian populations present exceptional opportunities for studying the genetics of both monogenic and complex diseases [99]. Replication studies may delve into the robustness and applicability of results reported from different populations, and varied representation promotes scientific equality to address health inequities. In addition, it may help us learn more about the pathological and pathogenetic disease pathways in PD by identifying new or unique loci and exploring genotype-phenotype connections.

Disclosure of conflict of interest

None.

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