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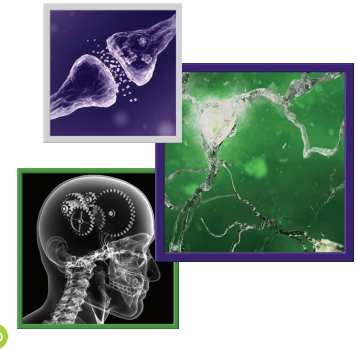

An overview of the worldwide distribution of *LRRK2* mutations in Parkinson's disease

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Practice points

Genetic landscape of *LRRK2*-related Parkinson's disease

- Parkinson's disease (PD) is associated with mutations in the *LRRK2* gene, with the G2019S mutation being the most prevalent and a major cause of autosomal-dominant PD.
- Penetrance of *LRRK2* pathogenic variants is influenced by age and ethnic background.

Phenotype & therapeutic approaches

- Clinical features of *LRRK2*-PD are generally similar to idiopathic PD, with some distinctions, such as higher rates of depression and better olfactory function.
- *LRRK2* mutation carriers tend to have a slower disease progression and are more prone to experience dyskinesias.
- Deep brain stimulation is particularly effective for G2019S mutation carriers.
- The upregulation of *LRRK2* kinase activity in the G2019S mutation suggests the potential of kinase inhibitors as a therapeutic option.

Worldwide distribution of *LRRK2* mutations

- The G2019S mutation is most prevalent in north African countries, particularly Tunisia, Morocco and Algeria. The Ashkenazi–Jewish population in Israel also shows a relatively higher prevalence of the G2019S mutation.
- Prevalence of G2019S mutation decreases as one moves away from northwest Africa, creating a geographical gradient.
- Other regions like north America, south America, Asia, Russia and Australia report lower prevalence rates of the G2019S mutation.
- Other pathogenic *LRRK2* mutations exhibit varying prevalence rates globally, with some regions showing very low occurrences or being entirely absent.

Founder effect of G2019S mutation

- The founder effect is observed in the concentration of the G2019S mutation in northwest Africa, suggesting a shared common ancestor with the Berber ethnicity at least 5000 years ago.
- This mutation is not commonly found in Asian populations, except for unique variations like R1628P and G2385R in southeast Asia.

Age of onset in *LRRK2* mutations

- The age of onset for individuals with *LRRK2* mutations, like G2019S, closely mirrors the general age of onset for PD patients in the studies we examined.
- Our finding highlights the potential influence of participant selection biases favoring younger individuals in PD research and underscores the importance of addressing these biases in future studies.

Parkinson's disease (PD) is a neurodegenerative disorder with significant genetic influence. The *LRRK2* gene is a major genetic contributor, particularly the Gly2019Ser mutation. This focused review investigates the global distribution of *LRRK2* mutations, with emphasis on Gly2019Ser and other pathogenic variants. Prevalence rates of Gly2019Ser are highest in north Africa and the Ashkenazi–Jewish population, indicating a potential common ancestor and founder effect. Other *LRRK2* mutations, including Asn1437His, Arg1441Gly/Cys/His, Tyr1699Cys and Ile2020Thr, exhibit varying global prevalences. Understanding these distributions enhances our knowledge of PD genetics and aids personalized

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medicine. Further research is crucial to unravel clinical implications and develop targeted therapies for *LRRK2* mutation carriers.

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra *pars compacta*, which manifests as motor symptoms including rest tremors, bradykinesia and rigidity [1]. While the majority of PD cases are considered idiopathic, recent advancements in genetic research have revealed a significant contribution of genetic factors to the development of the disease. Among the known genetic variants associated with PD, mutations in the *LRRK2* or *PARK8* genes have garnered considerable attention. *LRRK2* mutations have been found to be one of the most prevalent genetic causes of both familial and sporadic forms of PD [2]. A growing body of research shows that *LRRK2* plays a fundamental role in inflammation regulation within the central and peripheral immune systems [3,4].

It dates back to 2004 when Paisan-Ruiz *et al.* [5] and Zimprich *et al.* [6] identified *LRRK2* mutations among families with autosomal-dominant PD. One year later, several studies reported a specific mutation in this gene, called G2019S, responsible for PD in both familial and sporadic cases [7,8]. This mutation in *LRRK2* is, on its own, responsible for the majority of the autosomal dominant forms of PD. However, since 2004, over 100 to 200 variants in the *LRRK2* gene have been reported, including both missense and loss of function mutations [9].

In this focused review, we provide an overview of the worldwide distribution of *LRRK2* mutations, focusing on the Gly2019Ser mutation and other pathogenic variants, including Asn1437His, Arg1441Gly/Cys/His, Tyr1699Cys and Ile2020Thr. We will also give some relevant clinical and future therapeutic implications of these mutations in PD.

Penetrance of *LRRK2* mutations

LRRK2-associated PD follows an autosomal dominant inheritance pattern [10]. However, despite its autosomal dominant nature, the condition exhibits reduced penetrance, which contributes to a significant number of affected individuals having unaffected parents [11]. Each child of an individual with *LRRK2*-PD has a 50% chance of inheriting the pathogenic variant. Still, the risk of developing the disease is lower than 50% due to age-related reduced penetrance, which means that not everyone carrying the pathogenic variant will manifest the disease. Penetrance of *LRRK2* G2019S is age-dependent and can vary based on the type of pathogenic variant and the population's ethnicity, including country of origin and ancestral background [11,12]. In Ashkenazi Jews carrying G2019S variant, penetrance is estimated at approximately 26% up to age 80 [13], and in non-Jewish individuals, the penetrance associated with G2019S is estimated to be around 42% by age 80 [14]. In addition, north African population have a higher estimated lifetime penetrance of around 45% [15]. Higher penetrance has been reported for other rarer pathogenic *LRRK2* variants. For example, the Arg1441Cys variant is associated with an estimated penetrance of 95% by age 75 in one study [16] and 80% by age 80 in another, primarily in familial cases [17]. The Ile2020Thr variant, found in the original *LRRK2*-linked family, was estimated to have a 70% penetrance by age 70 [18]. These variations in penetrance highlight the complex nature of *LRRK2*-PD and the influence of specific pathogenic variants on disease risk.

Phenotype & therapeutic approach for *LRRK2*-related Parkinson's disease

While the basic clinical features of *LRRK2*-associated PD are similar to those of idiopathic PD, there are some notable differences. Individuals with *LRRK2* mutations tend to experience a higher prevalence of depression, impaired color vision discrimination and postural instability gait disorder phenotype. However, they also tend to preserve better olfactory function compared with those with idiopathic PD [19,20]. Additionally, *LRRK2* mutation carriers seem to have a slower disease progression and a higher likelihood of experiencing dyskinesias [21,22]. Individuals with R1441G, R1441C and R1441H pathogenic variants experience more frequent motor fluctuations compared with those with the G2019S. In terms of therapeutic approaches, it has been observed that patients with the G2019S mutation demonstrate a greater improvement in motor symptoms following bilateral subthalamic nucleus deep brain stimulation - a surgical intervention commonly utilized for advanced PD management. This improvement

is particularly evident when compared with patients with idiopathic PD [23]. However, there is a lack of scientific literature evaluating the efficacy and safety of DBS in patients with other *LRRK2* mutations.

The upregulation of *LRRK2* kinase activity associated with the G2019S mutation suggests that the development of kinase inhibitors could be a potential therapeutic strategy for patients harboring this specific mutation. Several small-molecule kinase inhibitors have been studied as potential therapeutics for LRRK2-related PD [24]. For instance, compounds like staurosporine, indirubin-3′-monooxime, sorafenib, GW5074 [25], sunitinib, H-1152 [26], CZC-25146, CZC-54252 and LRRK2-IN-1 [27,28] have shown promising results in *in vitro* and *in vivo* models. These compounds inhibit *LRRK2* autophosphorylation or its phosphorylation of other proteins involved in PD pathology. In addition to kinase inhibition, modulation of *LRRK2* GTPase activity is another possible therapeutic target. Mutated forms of LRRK2 have lower GTPase activity, which is associated with the disease [29]. By either blocking the GTP-binding pocket of *LRRK2* or stimulating GTPase activity, it may be possible to limit the pathological interactions involving *LRRK2* in PD pathology and provide a therapeutic benefit. Furthermore, studies have explored synthetic compounds such as diapocynin, which have shown neuroprotective effects in animal models of *LRRK2*-related PD [30]. This compound has demonstrated the potential to prevent early PD symptoms and improve neurobehavioral function [30]. As well, antisense oligonucleotides (ASOs) are a type of therapeutic molecules that can modulate gene expression by targeting specific RNA sequences involved in pre-mRNA splicing. In the context of *LRRK2*, ASOs can be designed to target and alter the splicing pattern of *LRRK2* mRNA [31].

It is important to consider the selectivity of kinase inhibitors, as many of them can inhibit other kinases in addition to *LRRK2*. However, compounds like LRRK2-IN-1 [27] and CZC-25146 [28] have shown better selectivity for *LRRK2*. These inhibitors have been effective in reversing *LRRK2*-induced toxicity in neuronal cells and rescuing behavioral deficits in animal models. While progress has been made in identifying potential therapeutic targets and developing compounds to modulate *LRRK2* activity, there are still unanswered questions. The exact functional effects of *LRRK2* mutations on neurons and the sensitivity of dopaminergic neurons to *LRRK2* mutations remain unclear. Further research is needed to fully understand the underlying mechanisms of *LRRK2*-related PD and optimize therapeutic interventions.

Worldwide distribution of *LRRK2* Gly2019Ser mutation

The distribution of *LRRK2* mutations worldwide exhibits intriguing patterns, indicating significant geographic variations. The highest prevalence rates of the G2019S mutation have been consistently reported in north African countries [32], particularly Tunisia, Morocco and Algeria, with prevalence rates ranging from 30 to 42% among individuals with PD [15,33–36]. Notably, the Ashkenazi Jewish population in Israel demonstrates a relatively higher prevalence of this mutation, ranging from 10.3 to 18.3% among PD cases [37–39]. The close relationship between the Ashkenazi Jewish population and north African regions [40] suggests the possibility of a shared common ancestor with the G2019S mutation among these populations. In addition, other African nations, including Egypt [41,42] and South Africa [43,44], have reported the presence of these mutations, while Ghana [45], Nigeria [46] and Zambia [47] have not detected the G2019S mutation.

Furthermore, studies from France, Portugal and Spain have reported moderate prevalence rates of *LRRK2* mutations, ranging from 6 to 7% [48–51]. However, it's noteworthy that concurrent investigations in Spain and France have shown lower prevalence for these mutations [52–56]. Additionally, other European countries such as Germany [57], Greece [58], Italy [59–64], Ireland [65], Norway [66], Sweden [67,68] and the UK [69] have reported the presence of these mutations, albeit with lower prevalence rates ranging from 0.3 to 2.7%. As one moves further away from northwest Africa, the prevalence of G2019S mutations decreases from north to south, indicating a geographical gradient. Figure 1 shows the worldwide distribution of the G2019S mutation.

The G2019S mutation in north America exhibits low prevalence rates in the USA [70–72], ranging between 0.01 and 1.46% [72,73], and is not detected in Canada [73]. South America shows a similar trend, with Argentina [74], Brazil [75], Chile [76], Colombia [77], Mexico [78], Peru [79] and Uruguay [79] reporting prevalence rates ranging from 0.4 to 5.45% [74–76,79]. Asian countries, such as Japan and Taiwan, report prevalence rates below 1% [80–82], while Russia and Australia show rates of 1.44 and 0.96%, respectively [83,84]. However, countries including India [85,86], Iran [87], Kazakhstan [88], Korea [89,90], Saudia Arabia [91] and Taiwan [82,92]. Overall, the data in Tables 1 & 2 highlight the geographical variability in the prevalence of the G2019S mutation in PD across the world. These variations may be attributed to increased population migration from subpopulations where the mutation originated, resulting in founder effects in different regions.

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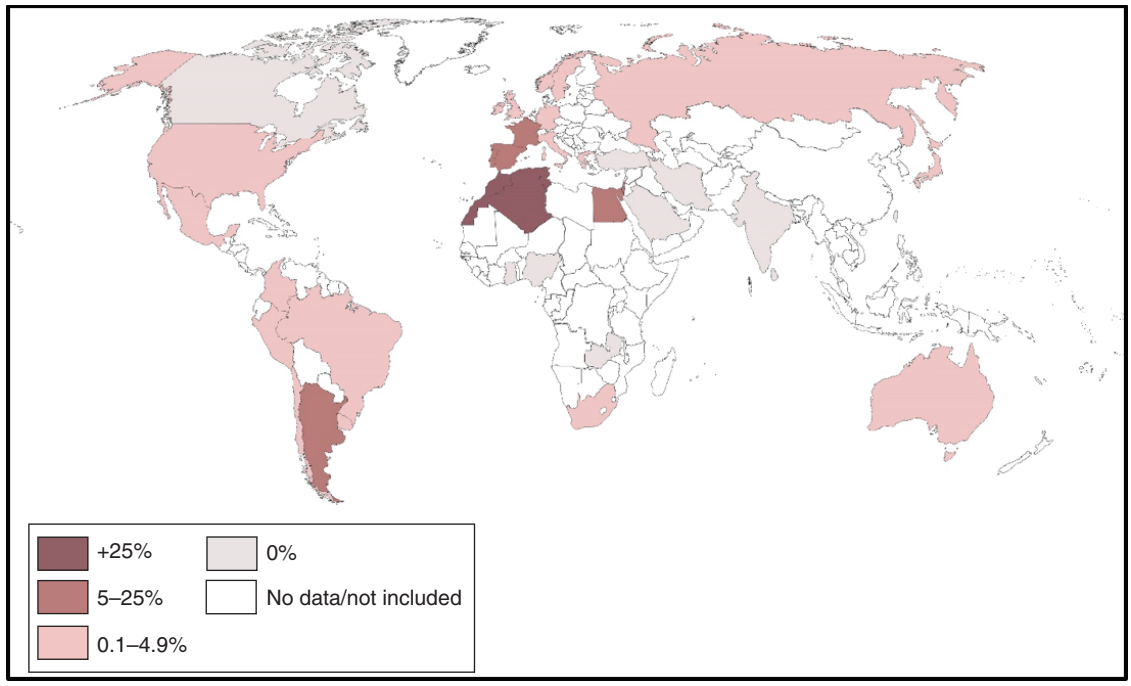

Figure 1. The worldwide distribution of Gly2019Ser mutation in Parkinson's disease.

In our 65 included studies specifically focused on the G2019S mutation, we observed a significant variation in study designs and patient recruitment strategies. Among these studies, 12 were monocentric, 25 adopted a multicentric approach and 4 were conducted in national or reference centers, reflecting the diversity in patient recruitment. Furthermore, 15 studies were conducted within university hospital settings, and five utilized genetic databases or PD patient registries. Interestingly, three of the 65 studies were centered on the Ashkenazi Jewish population, given the higher prevalence of the G2019S mutation within this group. Only one study did not provide clear information regarding its patients' recruitment strategy. The scarcity of studies explicitly targeting other specific areas with high prevalence like north Africa highlights a gap in the existing research landscape. However, it's important to note that certain variants may exist but were not included in the patient series studied. This also highlights the possibility of unreported variants, even in larger-scale studies.

Founder effect of G2019S mutation

The founder effect refers to the phenomenon where a population that descends from a small group of individuals carries a specific genetic mutation or trait at a higher frequency compared with the general population [96]. In the context of *LRRK2* mutations, it suggests that migration or dispersal of individuals carrying the *LRRK2* mutation from a specific ancestral population has led to the establishment of new populations in different regions with a higher prevalence of that mutation. Notably, a study provided evidence of this effect, demonstrating the presence of three distinct haplotypes associated with *LRRK2* mutations dating back to 4000 years ago [97].

The presence of a founder effect for the G2019S mutation in northwest Africa (Maghreb region) is supported by multiple lines of evidence [98]. The higher prevalence of this mutation in northwest Africa suggests that the first patient carrying the G2019S mutation lived in this region at least 5000 years ago, possibly belonging to the Berber ethnicity. Further studies exploring the ancestral origins, migration patterns, and genetic diversity among G2019S mutation carriers would provide valuable insights into the evolutionary history of this mutation and its impact on PD.

Global prevalence variation of Arg1441Cys/Gly/His, Ile2020Thr, Tyr1699Cys & Asn1437His mutations

In addition to the G2019S mutation, several other *LRRK2* mutations have been identified and validated as pathogenic but with varying prevalence rates globally, as highlighted in Tables 3–5. Starting with the Arg1441Cys mutation, it is obvious that its occurrence is relatively low in many regions. In the Middle East and African countries,

Table 1. Distribution of Gly2019Ser mutation in Parkinson's disease across Africa, Asia, Oceania and south America.

Region	Country	Study	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Africa and Middle East	Algeria	Belarbi *et al.*	2010	106 PD	52.14	57.07	–	Outpatients clinic - monocentric	32	[33]
	Egypt	Hashad *et al.*	2011	113 PD	55.3	56.4	56.3	University Hospital - monocentric	9.7	[42]
		Desoky at al	2015	69 PD	–	–	–	University hospital - monocentric	1.45	[41]
	Ghana	Cilia *et al.*	2012	54 PD	–	–	59.5	Outpatient clinic - multicentric	0	[45]
	Morocco	Bouhouche *et al.*	2017	100 PD	52.15	55.12	53.9	University Hospital - monocentric	41	[34]
		Ait Wahmane *et al.*	2022	14 PD	52.0	64.45	57.83	University Hospital - multicentric	21.4	[93]
	Nigeria	Okubadejo *et al.*	2018	126 PD	–	–	59.0*	University hospital - monocentric	0	[46]
	South Africa	Bardien *et al.*	2010	205 PD	–	–	54.4	Outpatient clinic - multicentric	2	[43]
		du Toit	2019	647 PD	56.6	–	–	Outpatient clinic - multicentric	1.2	[44]
	Tunisia	Ishihara *et al.*	2007	91 PD	58.9	48.6	–	Outpatients clinic - monocentric	42	[35]
		Hulihan *et al.*	2008	238 PD	58	56·8	57	University hospital - monocentric	30	[15]
		Landoulsi *et al.*	2017	250 PD	56.1	59.6	58.5	University hospital - monocentric	33.6	[36]
	Zambia	Yonova-Doing *et al.*	2012	38 PD	–	–	54.9	University hospital - monocentric	0	[47]
South America	Argentina	Gatto *et al.*	2015	55 PD	66.67	58.78	–	Neurology units - multicentric	5.45	[74]
	Brazil	Pimentel *et al.*	2008	154 PD	51.6	–	62.6	University hospitals - multicentric	2	[75]
	Chile	Perez-Pastene *et al.*	2007	166 PD	61.4	–	–	Organization 'Parkinson's Liga'	3.01	[76]
	Colombia	Duque *et al.*	2015	154 PD	50.5	–	–	University hospital - monocentric	1.3	[77]
	Mexico	Yescas *et al.*	2010	319 PD	61	–	52.4	Nacional Institute - monocentric	0.31	[78]
	Peru	Mata *et al.*	2009	240 PD	68	59.0	59.1	Outpatient clinic - multicentric	0.4	[79]
	Uruguay	Mata *et al.*	2009	125 PD	50.2	55.4	55.1	Outpatient clinic - multicentric	4	[79]
Asia and Oceania	Australia	Huang *et al.*	2007	830 PD	61.8	–	59.5	PD DNA banks - multicentric	0.96	[84]
	India	Vijayan *et al.*	2011	186 PD	–	–	51.2	Outpatient clinic - monocentric	0	[86]
		Punia *et al.*	2006	800 PD	–	–	50.48	Ntional institutes - multicentric	0.1	[85]
	Iran	Shojaee *et al.*	2009	205 PD	–	–	48.9	National centers - multicentric	0	[87]
	Israel	Orr-Urtreger *et al.*	2007	472 PD	56.9	59.4	59.05	Jewish PD patients Medical Center - monocentric	12.3	[38]
	Israel: Ashkenazi Jewish	Hassin-Baer *et al.*	2009	155 PD	60.6	61.1	–	Medical center - monocentric	10.3	[37]
		Orr-Urtreger *et al.*	2007	344 PD	57.7	59.2	59.05	Jewish PD patients Medical Center - monocentric	14.8	[38]
		Ozelius *et al.*	2006	120 PD	–	–	–	Ashkenazi Jewish - monocentric	18.3	[39]

AAO: Age at onset; PD: Parkinson's disease.

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Table 1. Distribution of Gly2019Ser mutation in Parkinson's disease across Africa, Asia, Oceania and south America (cont.).

Region	Country	Study	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
	Japan	Zabetian *et al.*	2006	586 PD	62	–	61.5	Medical centers - multicentric	0.34	[80]
		Li *et al.*	2020	1402 PD	54.1	–	48	Peripheral blood samples	0.5	[81]
	Kazakhstan	Kaiyrzhanov *et al.*	2020	246 PD	–	–	55.06	Medical centers - multicentric	0	[88]
	Korea	Cho *et al.*	2009	877 PD	–	–	55.7	University Hospital - monocentric	0	[89]
		Choi *et al.*	2008	72 PD	–	–	38.8	Movement disorders clinics - multicentric	0	[90]
	Russia	Pchelina *et al.*	2006	208 PD	–	–	55.5	University hospital - monocentric	1.44	[83]
	Saudia Arabia	Al-Mubarak at al	2015	98 PD	–	–	–	Outpatient clinic - monocentric	0	[91]
	Taiwan	Fung *et al.*	2006	343 PD	–	–	62.1	Neurology Clinic - monocentric	0	[82]
		Lu *et al.*	2005	624 PD	–	–	–	Referral center - monocentric	0	[92]

AAO: Age at onset; PD: Parkinson's disease.

Iran showed a prevalence of 0.49% in PD patients [87], while Israel and Ghana did not exhibit any cases of this mutation [38,45]. Within Europe, Italy displayed varying prevalence rates, ranging from 0.6 to 4.16%, depending on the studies [59–62]. Other European countries, including Germany [57], Spain [56], Portugal [50], Slovakia [94], Sweden [67] and Turkey [95] reported an absence of such mutation. Countries of the Americas, such as Canada [73], Peru, Uruguay [79] and the USA [70] did not exhibit the Arg1441Cys mutation, except for Japan in Asia, where it was found in 0.16% of PD patients studied [81]. Moving on to the Arg1441Gly mutation, a similar pattern of variation in prevalence emerges. In Table 4, it's highlighted that several European countries, namely France [53], Italy [61,62], Germany [57], Greece [58], Portugal [50], Spain [48,56], Slovakia [94], Sweden [67] and Turkey [95], did not report any cases with this specific mutation. However, in Spain, other findings indicate a prevalence of 13.15% in one study with a sample size of 418 PD patients, and another study reported a prevalence of 0.7% [54,55]. Moving beyond Europe, this mutation was also found in Japan (0.28%) [78,79,81], Mexico (0.31%) and Uruguay (0.8%). On the other hand, no instances of this mutation were found in Argentina [74], Australia [84], Canada [73], Ghana [45], India [85], Israel [38], Peru [79] and the US [99]. It's worth highlighting that a study from the US reported a prevalence of 0.2% for this mutation, with some of the participants being of Ashkenazi Jewish descent [70]. The Arg1441His mutation has been notably absent in several European, American and African countries, as indicated by the findings outlined in Table 5. These countries include Canada [73], Germany [57], Ghana [45], India [85], Iran [87], Israel [38], Italy [61], Kazakhstan [88], Nigeria [100], Portugal [49], Spain [56], Sweden [67], Turkey [95] and the US [67,99]. However, it's important to note that this mutation was identified in Australia [84], Japan [50,78,81,84], Mexico [78] and Portugal [50]. In a study encompassing all of Europe, the Arg1441His mutation was specifically reported in two French families, corresponding to a frequency of 0.13% (2 out of 1530 Europeans) [51]. Table 6 provides data on the prevalence of three mutations, Ile2020Thr, Tyr1699Cys and Asn1437His, in PD across different countries. Norway reported a prevalence of 0.15% for the N1437H mutation in a sample size of 693 PD patients [101]. In Japan, the I2020T mutation was found in 0.5% of the examined PD patients [81]. However, other countries such as Canada [73], Kazakhstan [88], India [85], Italy [61], Israel [38], Slovakia [94], Sweden [68], Taiwan [92], Turkey [95] and the US [99], did not show any cases of these mutations in their respective PD populations. However, *LRRK2* mutations are not commonly found in Asian populations, except for two specific variations called R1628P and G2385R [102–106]. These two variations are unique to the southeast Asian region and are not observed in other parts of Asia. On the other hand, the Y2189C mutation is associated with an increased risk of PD and is predominantly observed in the Berber population [107], which is an ethnic group primarily residing in north Africa. These findings underscore the variability in mutation prevalence and suggest the influence of genetic and environmental factors in different populations.

Table 2. Distribution of Gly2019Ser Mutation in Parkinson's disease across north America and Europe.

Region	Country	Study	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Europe	France	Lesage *et al.*	2005	155 PD	55.3	50.1	50.3	Probands with autosomal dominant PD - multicentric	1.3	[52]
		Lesage *et al.*	2020	1805 PD	51.6	47.3	–	Through the French PD Genetics Network	7.5	[51]
		Funalot *et al.*	2006	103 PD	–	–	65.7	Outpatient clinic - multicentric	1.9	[53]
	Germany	Möller *et al.*	2008	1049 PD	–	–	–	N/A	0.5	[57]
	Greece	Xiromerisiou *et al.*	2007	290 PD	–	–	–	Outpatients clinic - monocentric	0.3	[58]
	Italy	Criscuolo *et al.*	2011	192 PD	–	–	54.0	Movement disorder unit - monocentric	0.52	[59]
		De Rosa *et al.*	2014	513 PD	–	–	–	Medical centers - multicentric	0,78	[60]
		Floris *et al.*	2009	356 PD	64.5	–	62.1	University Hospital - monocentric	1.7	[61]
		Goldwurm *et al.*	2005	629 PD	–	–	52.7	Reference center - monocentric	2.1	[62]
		Goldwurm *et al.*	2006	1092 PD	53	54.28	54.23	DNA Bank of the Parkinson Institute	1.47	[63]
		Marongiu *et al.*	2006	1072 PD	–	–	50.7	Movement disorder units - multicentric	1.9	[64]
	Ireland	Marongiu *et al.*	2006	1072 PD	–	–	50.7	Movement disorder units - multicentric	1.9	[64]
	Norway	Aasly *et al.*	2005	435 PD	59	–	60.3	Outpatient clinic - multicentric	2.7	[66]
	Portugal	Bras *et al.*	2005	124 PD	54.8	–	57.1	University Hospital - monocentric	6	[49]
		Ferreira *et al.*	2007	138 PD	55.9	–	–	Outpatients clinic - monocentric	6.52	[50]
	Slovakia	Bognar *et al.*	2013	216 PD	–	–	59.77	N/A	0	[94]
	Spain	Infante *et al.*	2006	105 PD	68	–	–	University Hospital - monocentric	7.6	[48]
		Gaig *et al.*	2006	302 PD	–	53.7	53.8	Outpatients clinic - monocentric	4.3	[54]
		Gorostidi *et al.*	2008	418 PD	–	64.3	63.8	Movement Disorders Unit - monocentric	3.82	[55]
		Morán *et al.*	2010	96 PD	–	–	–	Outpatients clinic - monocentric	2,08	[56]
	Sweden	Carmine Belin *et al.*	2006	284 PD	58.25	–	59.5	University hospitals - multicentric	1.4	[67]
		Puschmann *et al.*	2019	2,206 PD	54.9	–	60.7	Clinical research centers - multicentric	0.54	[68]
	Turkey	Hanagasi *et al.*	2011	255 PD	–	–	48.6	University hospital - monocentric	0	[95]
	UK	Williams-Gray *et al.*	2006	519 PD	–	–	63	Community based sources / multicentric	0.4	[69]
	All Europe	Lesage *et al.*	2005	174 PD	55.3	50.1	50.3	Probands with autosomal dominant PD - multicentric	2.9	[52]
North America	Canada	Grimes *et al.*	2007	230 PD	–	–	57.7	Clinics – multicentric	0	[73]
	USA	Deng *et al.*	2006	496 PD	56	–	55.1	N/A - (28 were Ashkenazi Jewish PD patients)	1.2	[70]
		Kay *et al.*	2006	1425 PD	53.8	–	58	Movement disorder clinics - multicentric	0.01	[71]
		Paisán-Ruíz *et al.*	2008	272 PD	–	–	–	National Institute - monocentric	1.46	[72]

AAO: Age at onset; N/A: Non applicable; PD: Parkinson's disease.

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Table 3. Arg1441Cys mutation in Parkinson's disease across the world.

Region	Country	Authors	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Africa and Middle East	Ghana	Cilia *et al.*	2012	54 PD	–	–	59.5	Outpatient clinic - multicentric	0	[45]
	Iran	Shojaee *et al.*	2009	205 PD	–	–	48.9	National centers - multicentric	0.49	[87]
	Israel	Orr-Urtreger *et al.*	2007	472 PD	–	–	59.05	Jewish PD patients Medical Center - monocentric	0	[38]
Europe	Germany	Möller *et al.*	2008	1049 PD	–	–	–	N/A	0	[57]
	Italy	De Rosa *et al.*	2014	513 PD	–	–	–	Outpatient clinic - multicentric	2.53	[60]
		Criscuolo *et al.*	2011	192 PD	–	–	54.0	Outpatients clinic - monocentric	4.16	[59]
		Floris *et al.*	2009	356 PD	–	–	62.1	University Hospital - monocentric	0.6	[61]
		Goldwurm *et al.*	2005	629 PD	–	–	52.7	Reference center - monocentric	0.16	[62]
	Portugal	Ferreira *et al.*	2007	138 PD	–	–	–	Outpatients clinic - monocentric	0	[50]
	Slovakia	Bognar *et al.*	2013	216 PD	–	–	59.77	N/A	0	[94]
	Spain	Morán *et al.*	2010	96 PD	–	–	–	Outpatients clinic - monocentric	0	
		Gaig *et al.*	2006	302 PD	–	53.7	53.8	Outpatients clinic - monocentric	0.3	[54]
	Sweden	Carmine Belin *et al.*	2006	284 PD	–	–	59.5	University hospitals - multicentric	0	[67]
	Turkey	Hanagasi *et al.*	2011	255 PD	–	–	48.6	University hospital - monocentric	0	[95]
North America	Canada	Grimes *et al.*	2007	230 PD	–	–	57.7	Clinics – Multicentric	0	[73]
	United State	Deng *et al.*	2006	496 PD	–	–	55.1	N/A - (28 were Ashkenazi Jewish PD patients)	0	[70]
		Pankratz *et al.*	2006	956 PD	52.5	–	61.2	59 Parkinson Study Group sites	0.2	[99]
South America	Peru	Mata *et al.*	2009	240 PD	–	59.0	59.1	Outpatient clinic - multicentric	0	[79]
	Uruguay	Mata *et al.*	2009	125 PD	–	55.4	55.1	Outpatient clinic - multicentric	0	[79]
Asia	Australia	Huang *et al.*	2007	830 PD	–	–	59.5	PD DNA banks - multicentric	0	[84]
	India	Punia *et al.*	2006	800 PD	–	–	50.48	National institutes - multicentric	0	[85]
	Japan	Li *et al.*	2020	1402 PD	–	–	48	Peripheral blood samples	0	[81]

AAO: Age at onset; N/A: Non applicable; PD: Parkinson's disease.

Age of onset & *LRRK2* mutations in Parkinson's disease

We have also investigated the age of onset in PD in relation to specific genetic variants. The average age of onset for all PD patients in these studies was 48.36 years, with a median age of 55.1 years, ranging from 38.8 to 65.7 years. In the case of the G2019S mutation, the mean age of onset was approximately 48.36 years among all PD patients and around 55.76 years when considering only individuals carrying the G2019S mutation. Similarly, for the R1441C mutation, the mean age of onset was approximately 54.52 years, while it was 57.17 years for the R1441G mutation, and 59.96 years for the R1441H mutation. When considering the Ile2020Thr, Tyr1699Cys and Asn1437His mutations together, the mean age of onset was approximately 65.64 years.

It's noteworthy that the mean age of onset for individuals with *LRRK2* mutations, such as G2019S, does not significantly differ from the overall age of onset for PD patients in the studies we examined. This observation is particularly significant because the average age of disease onset in the majority of those studies is notably younger than the general population's average, which typically exceeds 70 years. This underscores the potential impact of

Table 4. Arg1441Gly mutation in Parkinson's disease across the world.

Region	Country	Authors	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Africa and Middle East	Ghana	Cilia *et al.*	2012	54 PD	–	–	59.5	Outpatient clinic - multicentric	0	[45]
	Israel	Orr-Urtreger *et al.*	2007	472 PD	–	–	59.05	Jewish PD patients Medical Center - monocentric	0	[38]
Europe	France	Funalot *et al.*	2006	103 PD	–	–	65.7	Outpatient clinic - multicentric	0	[53]
	Italy	Floris *et al.*	2009	356 PD	–	–	62.1	University Hospital - monocentric	0	[61]
		Goldwurm *et al.*	2005	629 PD	–	–	52.7	Reference center - monocentric	0	[62]
	Portugal	Ferreira *et al.*	2007	138 PD	–	–	–	Outpatients clinic - monocentric	0	[50]
	Germany	Möller *et al.*	2008	1049 PD	–	–	–	N/A	0	[57]
	Greece	Xiromerisiou *et al.*	2007	290 PD	–	–	–	Outpatients clinic - monocentric	0	[58]
	Slovakia	Bognar *et al.*	2013	216 PD	–	–	59.77	N/A	0	[94]
	Spain	Gaig *et al.*	2006	302 PD	–	53.7	53.8	Outpatients clinic - monocentric	0.7	[54]
		Gorostidi *et al.*	2008	418 PD	–	64.3	63.8	Outpatients clinic - monocentric	13.15	[55]
		Infante *et al.*	2006	105 PD	–	–	–	University Hospital - monocentric	0	[48]
		Morán *et al.*	2010	96 PD	–	–	–	Outpatients clinic - monocentric	0	[56]
	Sweden	Carmine Belin *et al.*	2006	284 PD	–	–	59.5	University hospitals - multicentric	0	[67]
	Turkey	Hanagasi *et al.*	2011	255 PD	–	–	48.6	University hospital - monocentric	0	[95]
North America	Canada	Grimes *et al.*	2007	230 PD	–	–	57.7	Clinics – Multicentric	0	[73]
	United State	Deng *et al.*	2006	496 PD	48	–	55.1	N/A - (28 were Ashkenazi Jewish PD patients)	0.2	[70]
		Pankratz *et al.*	2006	956 PD	–	–	61.2	59 Parkinson Study Group sites	0	[99]
South America	Argentina	Gatto *et al.*	2015	55 PD	–	58.78	–	Neurology units - multicentric	0	[74]
	Mexico	Yescas *et al.*	2010	319 PD	56	–	52.4	Nacional Institute - monocentric	0.31	[78]
	Peru	Mata *et al.*	2009	240 PD	–	59.0	59.1	Outpatient clinic - multicentric	0	[79]
	Uruguay	Mata *et al.*	2009	125 PD	50	55.4	55.1	Outpatient clinic - multicentric	0.8	[79]
Asia	Australia	Huang *et al.*	2007	830 PD	–	–	59.5	PD DNA banks - multicentric	0	[84]
	India	Punia *et al.*	2006	800 PD	–	–	50.48	National institutes - multicentric	0	[85]
	Japan	Li *et al.*	2020	1402 PD	45.8	–	48	Peripheral blood samples	0.28	[81]

AAO: Age at onset; N/A: Non applicable; PD: Parkinson's disease.

participant selection biases in these studies, where younger individuals may have a higher likelihood of participating in PD research.

Limitations

In the context of this scientific study, it is imperative to address potential biases that may influence the interpretation of findings reported in the cited studies and the broader implications of *LRRK2* variant epidemiology in PD. One key limitation pertains to the possibility of publication bias, which may skew the reported results, as studies with negative findings might not have been published. Consequently, there is a risk of overestimating the prevalence of

Table 5. Prevalence of the Arg1441His mutation in Parkinson's disease worldwide.

Region	Country	Authors	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Africa and Middle East	Ghana	Cilia *et al.*	2012	54 PD	–	–	59.5	Outpatient clinic - multicentric	0	[45]
	Iran	Shojaee *et al.*	2009	205 PD	–	–	48.9	National centers - multicentric	0	[87]
	Israel	Orr-Urtreger *et al.*	2007	472 PD	–	–	59.05	Jewish PD patients Medical Center - Monocentric	0	[38]
	Nigeria	Rizig *et al.*	2021	92 PD	–	–	62.1	Movement Disorders Clinic - monocentric	0	[100]
Europe	Germany	Möller *et al.*	2008	1049 PD	–	–	–	N/A	0	[57]
	Italy	Floris *et al.*	2009	356 PD	–	–	62.1	University Hospital - monocentric	0	[61]
	Portugal	Ferreira *et al.*	2007	138 PD	68,6	–	–	Outpatients clinic - monocentric	0.72	[50]
		Bras *et al.*	2005	124 PD	–	–	57.1	University Hospital - monocentric	0	[49]
	Spain	Morán *et al.*	2010	96 PD	–	–	–	Outpatients clinic - monocentric	0	[56]
	Sweden	Carmine Belin *et al.*	2006	284 PD	–	–	59.5	University hospitals - multicentric	0	[67]
	Turkey	Hanagasi *et al.*	2011	255 PD	–	–	48.6	University hospital - monocentric	0	[95]
	All Europe	Lesage *et al.*	2020	1530 PD	52.6	51.4	–	Through the French PD Genetics Network	0.13	[51]
America	Canada	Grimes *et al.*	2007	230 PD	–	–	57.7	Clinics – multicentric	0	[73]
	Mexico	Yescas *et al.*	2010	319 PD	43	–	52.4	Nacional Institute - monocentric	0.31	[78]
	USA	Deng *et al.*	2006	496 PD	–	–	55.1	N/A - (28 were Ashkenazi Jewish PD patients)	0	[70]
		Pankratz *et al.*	2006	956 PD	–	–	61.2	59 Parkinson Study Group sites	0	[99]
Asia	Australia	Huang *et al.*	2007	830 PD	52.2	–	59.5	PD DNA banks - multicentric	0.24	[84]
	India	Punia *et al.*	2006	800 PD	–	–	50.48	National institutes - multicentric	0	[85]
	Japan	Li *et al.*	2020	1402 PD	64.2	–	48	Peripheral blood samples	0.35	[81]
	Kazakhstan	Kaiyrzhanov *et al.*	2020	246 PD	–	–	55.06	Medical centers - multicentric	0	[88]

AAO: Age at onset; N/A: Non applicable; PD: Parkinson's disease.

LRRK2 variants in PD. Moreover, a notable bias is the overrepresentation of urban populations from tertiary centers in most published studies, which may not accurately reflect the diversity of global populations. This sampling bias can lead to a lack of generalizability. Another aspect to consider is the age of onset in PD studies, which is typically significantly younger than the average age of PD onset in the general population. This discrepancy can introduce a bias in the reported frequencies of *LRRK2* variants. Furthermore, a participation bias may be at play, as patients with a positive family history of PD might be more inclined to participate in genetic studies, potentially inflating the reported prevalence of *LRRK2* variants. These limitations underscore the necessity for larger and more diverse studies to obtain a more accurate understanding of the true frequency of *LRRK2* variants in international populations. To mitigate those limitations, future research should prioritize collaborative meta-analyses, age-specific and longitudinal analyses.

Table 6. Ile2020Thr, Tyr1699Cys and Asn1437His mutations in Parkinson's disease across different countries.

Region	Country	Mutation code	Authors	Year	Sample size	AAO (carriers)	AAO (no carriers)	AAO (all PD)	Setting	Prevalence (%)	Ref.
Africa and Middle East	Israel	I2020T	Orr-Urtreger *et al.*	2007	472 PD	–	–	59.05	Jewish PD patients Medical Center - monocentric	0	[38]
Europe	Italy	I2020T	Floris *et al.*	2009	356 PD	–	–	62.1	University Hospital - monocentric	0	[61]
	Norway	N1437H	Aasly *et al.*	2010	693 PD	–	–	60.3	Outpatient clinic - multicentric	0.15	[101]
	Slovakia	I2020T	Bognar *et al.*	2013	216 PD	–	–	59.77	N/A	0	[94]
		Y1699C	Bognar *et al.*	2013	216 PD	–	–	59.77	N/A	0	[94]
	Sweden	I2020T	Puschmann *et al.*	2019	2,206 PD	–	–	60.7	clinical research centers - multicentric	0	[68]
		Y1699C	Puschmann *et al.*	2019	2,206 PD	–	–	60.7	clinical research centers - multicentric	0	[68]
		N1437H	Puschmann *et al.*	2019	2,206 PD	–	–	60.7	clinical research centers - multicentric	0	[68]
	Turkey	I2020T	Hanagasi *et al.*	2011	255 PD	–	–	48.6	University hospital - monocentric	0	[95]
North America	Canada	I2020T	Grimes *et al.*	2007	230 PD	–	–	57.7	Clinics – Multicentric	0	[73]
	USA	I2020T	Pankratz *et al.*	2006	956 PD	–	–	61.2	59 Parkinson Study Group sites	0	[99]
		Y1699C	Pankratz *et al.*	2006	956 PD	–	–	61.2	59 Parkinson Study Group sites	0	[99]
Asia	India	I2020T	Punia *et al.*	2006	748 PD	–	–	50.48	National institutes - multicentric	0	[85]
	Japan	I2020T	Li *et al.*	2020	1402 PD	55.9	–	48	Peripheral blood samples	0.5	[81]
	Kazakhstan	I2020T	Kaiyrzhanov *et al.*	2020	246 PD	–	–	55.06	Medical centers - multicentric	0	[88]
		Y1699C	Kaiyrzhanov *et al.*	2020	246 PD	–	–	55.06	Medical centers - multicentric	0	[88]
		N1437H	Kaiyrzhanov *et al.*	2020	246 PD	–	–	55.06	Medical centers - multicentric	0	[88]
	Taiwan	I2020T	Lu *et al.*	2005	624 PD	–	–	–	Referral center - monocentric	0	[92]

AAO: Age at onset; N/A: Non applicable; PD: Parkinson's disease.

Conclusion

Understanding the worldwide distribution of *LRRK2* mutations is of significant importance for unraveling the genetic landscape of PD. The identification of population-specific mutation patterns can provide valuable insights into the genetic and evolutionary factors contributing to PD. Further research is needed to explore the clinical implications of *LRRK2* mutations and to develop targeted therapies for specific mutation carriers. Additionally, investigating the founder effect and conducting comprehensive genetic screenings within specific populations will contribute to our understanding of the geographic distribution and clinical characteristics associated with *LRRK2*-related PD.

Future perspective

In the next decade, the field of *LRRK2*-related PD is expected to witness significant advancements, potentially enabling personalized therapeutic strategies tailored to the specific *LRRK2* mutations carried by patients. This shift toward precision medicine will likely lead to the development of targeted kinase inhibitors aimed at modulating *LRRK2* activity. These inhibitors will likely become the focus of rigorous clinical trials, offering the potential for disease-modifying treatments. International collaborations and extensive population studies are projected to expand, providing a more comprehensive academic understanding of the global distribution and prevalence of

LRRK2 mutations, shedding light on historical and evolutionary aspects. Genetic screening for *LRRK2* mutations is expected to become more accessible, opening avenues for academic investigations into disease prevention and management, even before symptom onset.

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