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Review Article

Prevalence of ten *LRRK2* variants in Parkinson's disease: A comprehensive review

Christopher Simpson [a], Lisa Vinikoor-Imler [b,1], Feiby L. Nassan [b], Julia Shirvan [b], Cathy Lally [a], Tien Dam [b], Nancy Maserejian [b,*]

[a] *Epidemiology Research and Methods LLC, Atlanta, GA, USA*
[b] *Biogen, Cambridge, MA, USA*

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ABSTRACT

Introduction: Variants in the leucine-rich repeat kinase 2 gene (*LRRK2*) are risk factors for Parkinson's disease (PD), but their prevalence varies geographically, reflecting the locations of founder events and dispersion of founders' descendants.

Methods: A comprehensive literature review was conducted to identify studies providing prevalence estimates for any of ten variants in *LRRK2* (G2019S, R1441C, R1441G, R1441H, I2020T, N1437H, Y1699C, S1761R, G2385R, R1628P) among individuals with PD globally. We calculated crude country-specific variant prevalence estimates and, when possible, adjusted estimates for ethno-racial composition. For clinic-based studies, probands were used over other familial cases, whereas for population-based studies, all PD cases were used.

Results: The analysis included 161 articles from 52 countries yielding 581 prevalence estimates across the ten variants. G2019S was the most common variant, exceeding 1.0% in 26 of 51 countries with estimates. The other variants were far less common. G2385R and R1628P were observed almost exclusively in East Asian countries, where they were found in ~5–10% of cases. All prevalence estimates adjusted for ethno-racial composition were lower than their unadjusted counterparts, although data permitting this adjustment was only available for six countries.

Conclusions: Except for G2019S, the *LRRK2* variants covered in this review were uncommon in most countries studied. However, there were countries with higher prevalence for some variants, reflecting the uneven geographic distribution of *LRRK2* variants. The fact that ethno-racial group–adjusted estimates were lower than crude estimates suggests that estimates derived largely from clinic-based studies may overstate the true prevalence of some *LRRK2* variants in PD.

1. Introduction

Variants in the leucine-rich repeat kinase 2 gene (*LRRK2*) have been found to be associated with higher risk for developing Parkinson's disease (PD). Many variants (such as G2019S, R1441 C/G/H, I2020T, N1437H, and Y1699C) meet criteria for the highest tier of clinical risk according to contemporary guidelines and are therefore considered "pathogenic" variants [1], while others (such as G2385R, R1682P, and S1761R) only meet criteria for less stringent risk tiers and therefore may be considered "likely pathogenic" or "uncertain significance." Reflecting this heterogeneity in the pathogenicity of *LRRK2* variants, a 2019 meta-analysis found that, compared with controls, cases had more than tenfold odds of carrying the pathogenic variant G2019S (odds ratio [OR] 13.16; 95% confidence interval [CI] 10.16, 17.04), but only approximately twice the odds of carrying the variant G2385R (OR 2.27; 95% CI 2.03, 2.53) [2]. The most common pathogenic variant, G2019S, as well as others for which sufficient data are available, exhibit incomplete penetrance, indicating that some but not all carriers will develop Parkinson's disease [3,4].

There is significant heterogeneity in the estimates of the prevalence

* Corresponding author. Biogen, 225 Binney St, Cambridge, MA, 02142, USA.
E-mail addresses: chris.simpson@gmail.com (C. Simpson), vinikoor@hotmail.com (L. Vinikoor-Imler), feiby.nassantawadros@biogen.com (F.L. Nassan), Julia.shirvan@biogen.com (J. Shirvan), cathy.lally@epidemiologymethods.com (C. Lally), tien.dam@biogen.com (T. Dam), nancy.maserejian@biogen.com (N. Maserejian).
[1] Affiliation at the time of these analyses.

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of *LRRK2* variants across ethno-racial groups. For instance, G2019S occurs particularly frequently in Ashkenazi Jews [5] and North African Berber Arabs [6,7], whereas it has been observed only infrequently in East Asian populations [8]. R1441G occurs particularly frequently in people with Basque ancestry [9]. Distinct haplotypes of R1441C have been observed in Belgians [10] and in Southern Italians [11]. This variant may be particularly prevalent in at least parts of Belgium and Italy. Meanwhile, G2385R and R1628P occur frequently among East Asians with PD (one meta-analysis [2] estimated 9.19% and 5.78%, respectively), whereas they are mostly absent among West Asians, Europeans, Hispanics, and Africans [2].

The *LRRK2* variants implicated in PD follow an autosomal dominant mode of inheritance, and founder events have been estimated for several variants with considerable precision as to time and place [12–14]. A 2018 meta-analysis [15] found that individuals with PD who carried G2019S were more likely to have a family history of PD than non-carriers (OR 2.62; 95% CI 2.25, 3.06). The same was true for carriers of G2385R (OR 2.10; 95% CI 1.22, 3.59) [15].

Our objective was to estimate the prevalence of ten *LRRK2* variants (G2019S, R1441C, R1441G, R1441H, I2020T, N1437H, Y1699C, S1761R, G2385R, and R1628P) among individuals with PD to obtain country-specific prevalence estimates. An improved understanding of the prevalence of *LRRK2* variants among the PD population by geography is needed to help plan clinical trials and the delivery of potential targeted therapies that are currently in development [16]. Earlier reviews focused on a single variant (such as the 2010 review of G2019S prevalence by Correia Guedes et al. [8]) or, if focused on multiple variants, were primarily concerned with the strength of association between variants and PD, and thus required studies to have controls, which resulted in the exclusion of articles pertinent to the determination of variant prevalence [2,17]. In the current study, we expand on and refine results of earlier studies of *LRRK2* variant prevalence by considering a wide range of variants, drawing from an updated literature base, and employing methods (such as adjustment for the ethno-racial composition of study samples and the inclusion of implicitly reported zeroes) that aimed to increase the accuracy of the prevalence estimates for individual countries.

2. Methods

2.1. Search strategy overview

A stepwise search strategy was implemented to obtain a comprehensive literature review of studies reporting the prevalence of any of the ten variants of interest among persons with PD globally (Fig. 1). First, we identified a set of systematic reviews or meta-analyses, which, together, provided coverage of the variants of interest, ranged over a wide geographic area and examined primary sources with publication

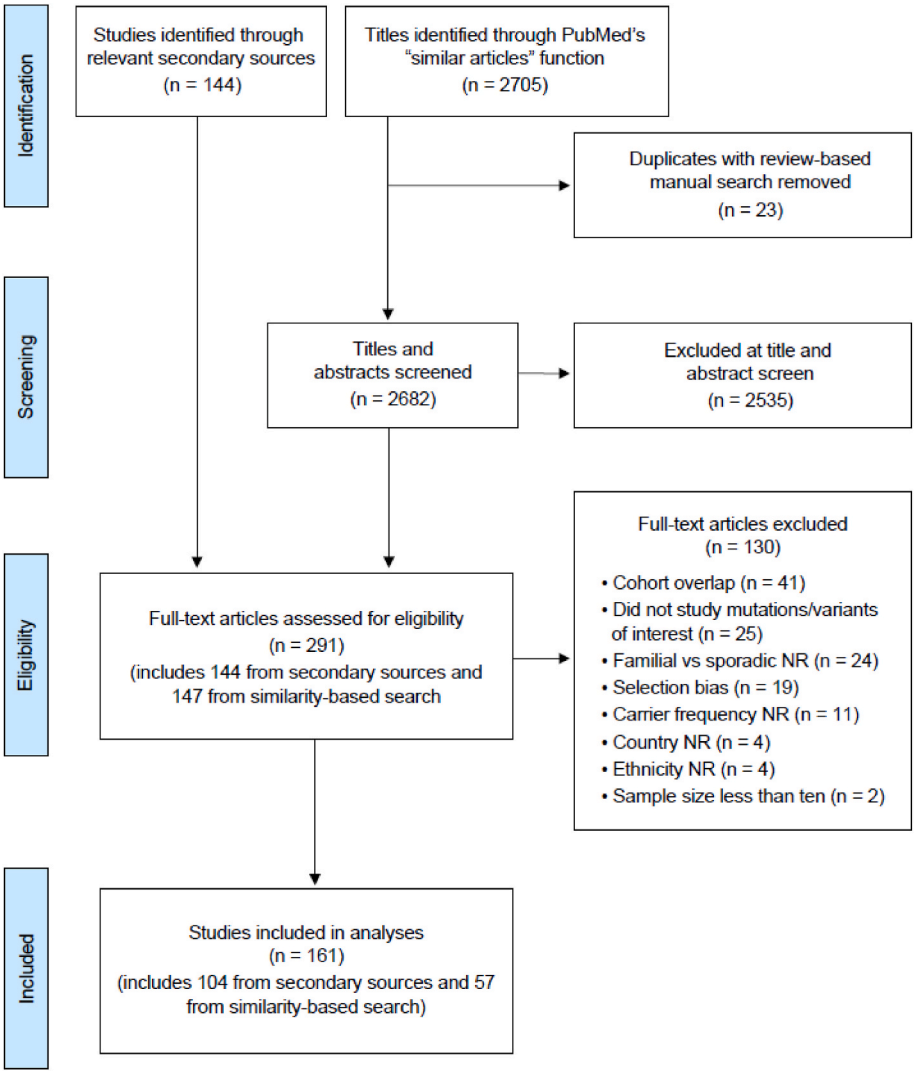

Fig. 1. PRISMA flow diagram of literature search. Abbreviation: NR, not reported.

dates spanning 2004 (first discovery of *LRRK2* variants) to the search date (September 23, 2020). A total of 12 systematic reviews were identified, which collectively included data from 144 studies. Next, to identify additional articles, we applied PubMed's function, "see all similar articles," to each of the aforementioned 144 primary sources and to the 12 reviews/meta-analyses from which they were identified. This step resulted in 2,705 abstracts, of which 2,682 were unique abstracts. From these 2,682 abstracts, 147 full text articles were retrieved for review. In all, we reviewed the full text of 291 articles from our two step search strategy (144 articles retrieved from step 1, and 147 articles from step 2). Systematic reviews were used only to identify the primary sources; all data extraction was performed using the original studies as primary sources. The literature review was completed by one researcher (C.S.) and all extracted data were reviewed by a second researcher for quality control. Additional details on the search strategy are provided in Supplementary Methods.

2.2. Inclusion criteria for variant prevalence estimates

Studies that met the following criteria after full text review were included:

- Clinical diagnostic criteria for PD were clearly stated.
- Ten or more cases were genotyped for the variant of interest.
- Cases had a similar ethno-racial background. A sample was considered ethno-racially similar if $\geq$ 90% of the sample was from the same ethno-racial group, consistent with the methods of an earlier review of G2019S prevalence in PD [8].
- The country from which the cases arose was clearly stated so that the estimate could contribute to some country-specific estimates (relevant, for instance, in multinational studies, which might pool results across countries). An exception to this criterion was made for two studies [7,18] that informed the country-level G2019S prevalence estimates for Algeria and Libya (see Supplementary Material for justification of this exception).
- The same cases were not already included in another estimate for the same variant. This problem of "cohort overlap" was addressed by grouping publications according to the institutions at which their cases were ascertained and then confirming from the texts that each estimate that was included represented distinct PD cases or, if they represented the same cases, studied different variants. If there was a choice to be made between multiple publications that studied some of the same PD cases (e.g., as a cohort grew over time), then the publication with the largest sample size was chosen.
- The numbers of familial vs. apparently sporadic cases and how many of each carried the variant of interest were reported, with exceptions allowed as follows:
  - o Estimates from studies that drew cases primarily from community-based settings or that used population-based sampling methods
  - o Estimates from countries for which the only available estimate(s) did not meet this standard.
- Selection bias was not clearly evident in the PD case ascertainment method. Examples of unacceptable study methods that are potentially susceptible to selection bias: recruiting cases through family members of known *LRRK2* variant carriers; excluding cases with G2019S or other *LRRK2* variants; applying exclusion criteria that broadly affect the phenotypic and genotypic representativeness of the cohort (e.g. excluding all individuals with any history of neurologic or psychiatric conditions other than PD, or requiring a particular history of response to PD treatments).

2.3. Data extraction

The following information, when available, was extracted from each primary source that provided at least one includable prevalence estimate:

- The country or countries studied.
- Methods and settings of PD case ascertainment. Setting was extracted as whether the location(s) from which cases were drawn were primarily tertiary referral centers, more general clinical care, or community settings.
- How family history of PD was defined. If a study provided prevalence estimates for multiple definitions of family history, then the most inclusive definition was used for data extraction, which allowed a more harmonized definition of family history across studies.
- For each variant of interest studied:
  - o How many apparently sporadic cases were genotyped and, of those, how many were carriers. If the number of apparently sporadic cases was not explicitly stated, but the number of familial cases was, then all cases that were not familial were recorded as apparently sporadic.
  - o How many familial probands were genotyped and, of those, how many were carriers. For studies that did not provide information on familial probands, but which did provide information on familial cases generally (i.e., including non-probands), this information was extracted, and it was noted that family members were included in the sample. When studies were unclear as to whether familial cases were probands or not, this was noted.
  - o For studies that provided the above information for different ethno-racial subgroups, this information was extracted for each subgroup.

All information was extracted from the published studies. Authors of the published studies were not attempted to be contacted.

It was anticipated that some studies would omit reports of negative findings. That is, studies may have screened the whole *LRRK2* gene for all known variants, or screened exons containing multiple variants of interest, but only reported by name the ones that were positively identified in the sample. Although this omission of explicit reports of negative findings is standard practice in the literature, to exclude these implicitly reported zeroes from the analysis could easily distort the estimated prevalence of variants, especially for those that occur rarely in at least some geographic regions or ethno-racial groups. Therefore, such zeroes were included and noted in Supplementary Table 1.

2.4. Computation of country-level variant prevalence estimates

A country-specific crude prevalence estimate for each variant was calculated by pooling together all individual estimates by country and variant. Specifically, the country-specific prevalence for a variant among PD cases was calculated as the total number of PD cases with a specific variant in a country, divided by the total number of PD cases genotyped for that variant in that country. In clinic-based studies, to address the general overrepresentation of familial cases, only probands were included where possible. If probands were not reported separately, then we included all PD cases (i.e., possibly including familial non-probands). Conversely, for population-based studies, all PD cases were included.

To evaluate the effect of the ethno-racial distribution, a sensitivity analysis of the estimated ethno-racially adjusted prevalence (crude) was completed. The goal of this adjustment was to estimate the variant prevalence that would have been observed in a country if the studies from that country had recruited individuals from different ethno-racial groups in proportion to those groups' representation in the overall national population. Specifically, the ethno-racial distribution–adjusted prevalence is calculated as the weighted average of the individual ethno-racial group–specific prevalence estimates (for a given variant, in a particular country), weighted by the relative sizes of those ethno-racial groups according to reliable national population statistics.

3. Results

3.1. Literature search

Results of the literature search are depicted in Fig. 1. The 12 earlier systematic reviews and meta-analyses yielded 144 primary sources for full text review, and an additional 147 primary sources (not analyzed by the 12 secondary sources) were identified through the similarity-based search method. Of the 291 primary sources examined, 161 were included in the analysis (i.e., they provided at least one estimate of variant prevalence for at least one ethno-racially similar study sample). Sufficient reasons for the exclusion of articles that were reviewed but not included are presented in Fig. 1. Four articles were excluded for not presenting results on ethno-racially similar samples. The most common reason for exclusion, affecting 41 articles, was repetitive reporting on the same cases, usually in the context of a growing cohort. In total, 581 estimates of variant prevalence across 52 countries were included.

Eight [19–26] of the 161 included studies drew cases primarily from community-based settings, whereas the majority of the remaining studies drew cases primarily (and usually exclusively) from tertiary referral centers, often university hospitals..

3.2. Prevalence estimates

Country-specific crude prevalence estimates for the four most common pathogenic variants—G2019S, R1441C, R1441G, and R1441H—are shown in Table 1. The corresponding estimates for variants G2385R and R1628P are shown in Table 2. The other four variants are described in the text alone. Detailed information on all 581 individual prevalence estimates upon which the country-specific estimates are based is provided in Supplementary Table 1.

3.2.1. G2019S

Overall, 122 studies provided estimates of the prevalence of the G2019S variant in 42,713 PD cases across 51 countries (Table 1). A visualization of the global geographic distribution of G2019S in PD is depicted in Fig. 2. Among the pathogenic variants of interest, G2019S was found to be the most common. Prevalence estimates were non-zero in 37 of 51 countries, >1.0% in 26 countries (24 after ethno-racial composition adjustment), and >5.0% in nine countries (Spain, 6.1%; Portugal, 6.2%; France, 6.8%; Egypt, 9.7%; Israel, 11.8% [7.0% after ethno-racial composition adjustment]; Tunisia, 33.0%; Algeria and Libya, 35.9%; and Morocco, 41.0%) (Table 1). The prevalence estimate for the United States was 2.1% (1.5% after ethno-racial composition adjustment).

The studies identified in this review confirm prior findings of especially high prevalence of the G2019S variant among patients with PD who are Ashkenazi Jewish (14.8%, based on estimates from the United States [5,27–29] and Israel [30,31]) and Berber Arab (35.9%, based on estimates from two studies [7,18] spanning Morocco, Tunisia, Algeria, Libya, and France).

3.2.2. R1441C/G/H

There were 66, 68, and 58 studies that provided estimates of the prevalence of the R1441C, R1441G, and R1441H variants, respectively (Table 1). These studies were conducted across 34 countries and 20,495 PD cases for R1441C, across 36 countries and 19,680 PD cases for R1441G, and across 32 countries and 19,234 PD cases for R1441H (Table 1). R1441H did not exceed 1.0% prevalence in any country, whereas R1441C and R1441G exceeded 1.0% prevalence in one country each: in Belgium, the estimated prevalence of R1441C was 2.0% based on a single study of 304 PD cases [10]; and in Spain, the estimated prevalence of R1441G was 5.1% (2.5% after adjustment for oversampling of ethnic Basques) based on ten studies [9,14,32–39] including a total of 1,933 PD cases. While the estimated R1441C prevalence in all of Italy was narrowly under 1% (0.96%, based on six studies [40–45] including a total of 2,194 PD cases), data from Southern Italy showed a higher prevalence (2.2% based on two studies [40,43] including a total of 602 PD cases). The prevalence estimates for R1441C, R1441G, and R1441H in the United States were 0.03%, 0.04%, and 0.04%, respectively.

3.2.3. I2020T, N1437H, Y1699C, and S1761R

The I2020T variant was detected in seven out of 18,919 (0.037%) PD cases genotyped in 54 studies spanning 31 countries. There were four carriers in Japan among 1,998 (0.20%) cases [46–48]; two in Germany among 434 (0.46%) cases [49,50]; and one in Italy among 2,989 (0.033%) cases [40,41,43–45]. All I2020T carriers reported a family history of PD. No carriers were identified in China among 1,499 PD cases genotyped [51–55].

Six studies (from China [52], Greece [56], Kazakhstan [57], Norway [58], Sweden [19], and Zambia [59]) sought to identify the N1437H variant in 3,368 PD cases, including 137 PD cases in China. Only one individual, in Norway, carried it. The N1437H carrier prevalence was one out of 692 (~0.14%) PD cases in the Norwegian study and one out of 3,368 (~0.030%) PD cases for all six studies.

The Y1699C variant was not detected (0% prevalence) in 45 studies [10,19,25,27,32,33,40,43,47,49,50,52–57,59–86] spanning 29 countries that collectively genotyped 13,031 PD cases, including 1,278 PD cases in China [52–55].

No studies were identified that explicitly sought to detect the S1761R variant (except for investigations of family members of the individual in whom the variant was first detected, which were excluded).

In the studies conducted in the U.S., there were no PD cases that had any of these four variants (I2020T, N1437H, Y1699C, or S1761R), suggesting a very low prevalence of these variants in the US PD population.

3.2.4. G2385R and R1628P

The variant G2835R appeared endemic to East Asia, particularly to people of Han Chinese ethnicity and people of Japanese ancestry. The variant R1628P followed a similar ethnic distribution, except for its noteworthy absence in people of Japanese ancestry.

Thirty-two studies provided estimates of the prevalence of G2385R in 14,454 PD cases across 15 countries (Table 2). The results were bimodal. Studies from nine countries (Austria, Greece, Hungary, India, Iran, Israel, Mexico, Slovakia, and the United States) reported zero G2385R carriers from a total sample of 1,367 PD cases [62,64,68,78,79,81,87–89]. Studies from the other six countries yielded pooled prevalence estimates of 11.2% (Japan), 10.3% (China), 9.9% (South Korea), 9.7% (Taiwan), 5.9% (Singapore), and 1.2% (Kazakhstan) from a total sample of 13,087 PD cases [46–48,57,63,90–107].

Nineteen studies provided estimates of the prevalence of R1628P in 7,920 PD cases across 11 countries (Table 2). The results for R1628P were also bimodal. Studies from seven countries (Hungary, Iran, Israel, Japan, Kazakhstan, Slovakia, and the United States) reported zero R1628P carriers from a total sample of 1,656 PD cases [48,57,62,64,78,81,87,108]. Studies from the other four countries yielded pooled prevalence estimates of 11.1% (Thailand), 7.5% (Taiwan), 5.4% (Singapore), and 5.3% (China) from a total sample of 6,264 PD cases [55,63,91,95,102,104,109–113].

3.2.5. Sensitivity analysis: Adjustment for ethno-racial composition

Sufficient data were available to calculate ethno-racial composition–adjusted prevalence estimates for G2019S in five countries (Argentina, Australia, Israel, US and South Africa) and for R1441G in Spain. All six adjusted prevalence estimates were lower than their unadjusted counterparts. In the United States, based on 12 studies including a total 5,248 PD cases, the estimated prevalence of G2019S dropped from 2.1% to 1.5% after adjustment for oversampling of Ashkenazi Jews. In Israel, based on six studies including a total 1,297 cases, the G2019S prevalence changed from 11.8% to 7.0% after the

Table 1
Crude prevalence of pathogenic variants G2019S and R1441 C/G/H among PD cases in 51[a] countries.

Country	%G2019S (n)	%R1441C (n)	%R1441G (n)	%R1441H (n)	Country	%G2019S (n)	%R1441C (n)	%R1441G (n)	%R1441H (n)
Algeria	35.90% (195) [7,18]	–	–	–	Libya	35.90% (195) [7,18]	–	–	–
Argentina	3.75% [2.54%[b]] (240) [66,114]	0.00% (236) [66,114]	0.00% (236) [66,114]	0.00% (236) [66,114]	Malta	3.39% (118) [115]	–	0.00% (118) [115]	–
Australia	1.11% [0.91%[b]] (904) [116,117]	0.00% (830) [116]	0.00% (830) [116]	0.24% (830) [116]	Mexico	0.64% (472) [84,88]	0.00% (299) [84]	0.33% (299) [84]	0.33% (299) [84]
Austria	0.00% (162) [68]	0.00% (162) [68]	0.00% (162) [68]	0.00% (162) [68]	Morocco	41.00% (100) [118]	–	–	–
Belgium	0.00% (304) [10]	1.97% (304) [10]	0.00% (304) [10]	0.00% (304) [10]	Nigeria	0.00% (183) [119,120]	–	–	–
Brazil	2.65% (528) [121–124]	0.00% (154) [125]	0.00% (154) [125]	–	Norway	2.07% (435) [60]	0.00% (435) [60]	0.00% (435) [60]	0.00% (435) [60]
Canada	1.01% (495) [47,67,126,127]	0.00% (374) [47,67,127]	0.00% (374) [47,67,127]	0.00% (374) [47,67,127]	Peru	0.42% (240) [128]	0.00% (240) [128]	0.00% (240) [128]	0.00% (240) [128]
Chile	3.01% (166) [129]	–	0.00% (166) [129]	–	Poland	0.00% (174) [130]	–	–	–
China	0.07% (1538) [51–53,55,97,131]	0.17% (1811) [51–55,131]	0.00% (1499) [51–55]	0.07% (1499) [51–55]	Portugal	6.19% (436) [132,133]	0.00% (138) [134]	0.00% (262) [132,134]	0.64% (312) [133]
Colombia	1.30% (154) [135]	–	–	–	Russia	1.41% (1066) [136,137]	–	–	–
Czech Republic	2.50% (49) [138]	–	–	–	Serbia	0.21% (486) [70]	0.00% (486) [70]	0.00% (486) [70]	0.00% (486) [70]
Denmark (Faroe Islands)	1.10% (91) [77]	0.00% (91) [77]	0.00% (91) [77]	0.00% (91) [77]	Singapore	0.00% (675) [139]	0.26% (384) [82]	0.00% (384) [82]	0.00% (384) [82]
Ecuador	1.18% (85) [114]	0.00% (85) [114]	0.00% (85) [114]	0.00% (85) [114]	Slovakia	0.00% (216) [62]	0.00% (216) [62]	0.00% (216) [62]	–
Egypt	9.73% (113) [140]	–	–	–	South Africa	1.22% [0.34%[b]] (658) [141,142]	–	–	–
Estonia	0.00% (189) [25]	0.00% (189) [25]	0.00% (189) [25]	0.00% (189) [25]	South Korea	0.00% (949) [143,144]	–	–	–
France	6.83% (2093) [145,146]	–	–	–	Spain	6.11% (2062) [9,32–38,147,148]	0.31% (954) [32–36,38]	5.12% [2.46%[b]] (1933) [9,14,32–39]	0.00% (807) [32–36]
Germany	0.51% (1559) [50,149,150]	0.07% (1483) [49,50,149]	0.00% (1049) [149]	0.00% (1049) [149]	Sweden	0.54% (2206) [19]	0.00% (284) [21]	0.00% (284) [21]	0.00% (2206) [19]
Greece	0.15% (652) [56,89,151,152]	0.00% (472) [56,89,152]	0.00% (338) [56,152]	0.00% (338) [56,152]	Taiwan	0.00% (1538) [153–155]	0.00% (626) [83]	0.00% (626) [83]	0.17% (1197) [83,154]
Hungary	0.00% (142) [69]	0.00% (142) [69]	0.00% (142) [69]	0.00% (142) [69]	The Netherlands	0.00% (187) [75]	0.00% (187) [75]	0.00% (187) [75]	0.00% (187) [75]
India	0.09% (2293) [74,79,80,156–159]	0.00% (1448) [74,79,80,156]	0.00% (1448) [74,79,80,156]	0.00% (1448) [74,79,80,156]	Tunisia	32.96% (807) [6,24,160,161]	0.00% (92) [71]	0.00% (92) [71]	0.00% (92) [71]
Iran	0.00% (205) [81]	0.49% (205) [81]	0.00% (205) [81]	0.00% (205) [81]	Turkey	1.10% (91) [73]	0.00% (91) [73]	0.00% (91) [73]	0.00% (91) [73]
Ireland	0.74% (271) [23]	–	–	–	United Kingdom	0.76% (2747) [20,22,162]	–	–	–
Israel	11.80% [7.01%[b]] (1297) [26,30,31,64,163,164]	0.00% (530) [64,164]	0.00% (530) [64,164]	0.00% (530) [64,164]	Uruguay	4.00% (125) [128]	0.00% (125) [128]	0.80% (125) [128]	0.00% (125) [128]
Italy	1.61% (5292) [40–43,45,165–170]	0.96% (2194) [40–45]	0.00% (2194) [40–45]	0.05% (2144) [40–43,45]	United States	2.08% [1.54%[b]] (5248) [5,6,27–29,61,65,72,76,78,171,172]	0.03% (3192) [27,28,61,65,72,76,78,85]	0.04% (2501) [28,61,65,72,76,78,85]	0.04% (2501) [28,61,65,72,76,78,85]
Japan	0.40% (1998) [46–48]	0.00% (1998) [46–48]	0.15% (1367) [46,47]	0.10% (1998) [46–48]	Zambia	0.00% (38) [59]	0.00% (38) [59]	0.00% (38) [59]	–
Kazakhstan	0.00% (246) [57]	–	–	0.00% (246) [57]					

[a] One country, Thailand, did not have a G2019S prevalence estimate, but did have an estimate for another variant of interest (R1628P), which accounts for the discrepancy between the 52 countries included overall and the 51 countries listed in this table.
[b] Prevalence estimates adjusted for ethno-racial composition.

Table 2
Crude prevalence of variants G2385R and R1628P among Parkinson's disease cases in 16 countries.

	%G2385R (n)	%R1628P (n)
Predominantly East Asian countries		
China	10.32% (5184)	5.34% (4492)
Japan	11.17% (2883)	0.00% (782)
Singapore	5.92% (659)	5.40% (438)
South Korea	9.88% (1032)	–
Taiwan	9.70% (3083)	7.54% (849)
Thailand	–	11.13% (485)
Other countries		
Austria	0.00% (162)	–
Greece	0.00% (134)	–
Hungary	0.00% (124)	0.00% (124)
India	0.00% (270)	–
Iran	0.00% (205)	0.00% (205)
Israel	0.00% (61)	0.00% (61)
Kazakhstan	1.22% (246)	0.00% (246)
Mexico	0.00% (173)	–
Slovakia	0.00% (216)	0.00% (216)
United States	0.00% (22)	0.00% (22)

same adjustment. In Australia, based on two studies including a total 904 cases, the change was from 1.1% to 0.9% after adjustment for oversampling of European Caucasians. In South Africa, based on two studies including a total 658 cases, the change was from 1.2% to 0.3% after adjustment for oversampling of people of European and mixed European/African descent and undersampling of Black African and Asian/Indian people. In Argentina, based on two studies of 240 cases, the change was from 3.8% to 2.5% after adjustment for oversampling of Ashkenazi Jews. Finally, in Spain, based on ten studies of 1,933 cases, the estimated prevalence of R1441G dropped from 5.1% to 2.5% after adjustment for oversampling of Basques.

4. Discussion

This comprehensive literature review examined 291 articles for their potential to contribute to prevalence estimates for ten variants in *LRRK2* among patients with PD in a wide range of countries. Ultimately, 161 articles yielded a total of 581 prevalence estimates across 52 countries. The prevalence of G2019S, R1441 C/G/H, G2385R, and R1628P varied geographically, which is likely owing in part to the variability in prevalence between ethno-racial groups. Although adjustment for the ethno-racial composition of PD cases was only possible for six country-level prevalence estimates (across six countries), all adjusted estimates were lower, suggesting that the crude variant prevalence estimates as reported in this and other reviews may, to some degree, be overstatements. Nevertheless, considering that the crude prevalence estimates for G2019S exceeded 1.0% in approximately half of the 51 countries studied and exceeded 5.0% in nine countries, it is clear that G2019S meaningfully contributes to PD risk at a population level in several countries.

Strengths of this work include the methods used to reduce the potential for bias in prevalence estimates, such as the inclusion of implicitly reported zeroes and adjustment for the ethno-racial composition of study samples. Indeed, the results of sensitivity analyses indicate that the adjustment for ethno-racial composition was important to address the issue that PD patients who participated in *LRRK2* genotyping studies may have had a different ethno-racial distribution compared to the general PD patient population of that country. Without this adjustment, some country-level estimates would likely overestimate the prevalence of a LRRK2 variant. Ideally, to perform this adjustment, we would have applied information on the ethno-racial distribution of the general PD population in a country. However, ethno-racial data on the general PD population in a country were not available from representative data sources, so we instead applied information on the ethno-racial distribution of adults aged ≥40 years when possible, given that general survival into the older adult ages (when PD is most commonly diagnosed) may vary by race or ethnicity. Nonetheless, residual biases cannot be excluded.

Publication biases may also affect our results, since it is conceivable that studies finding no variant carriers are less likely to be published. This concern is mitigated by the fact that many of included studies tested simultaneously for many or all of the variants of interest, which allowed us to capture findings of zero prevalence in many variants incidentally. Another potential bias concerns the possible over- or under-representation of familial versus apparently sporadic cases in the included study samples. To help assuage this concern, we performed a second sensitivity analysis where we recalculated the crude prevalence estimates supposing that 20% of all cases in each country were familial cases and 80% were sporadic, consistent with the distribution of familial and sporadic cases observed in two population-based studies [19,20]. The recalculated estimates did not meaningfully differ from the crude estimates (data not shown). Thus, despite the possibility that familial cases are over-represented in studies conducted at tertiary referral centers, our method to preferentially use data on probands, rather than data on all familial cases, seems to have provided robust results on the prevalence of these *LRRK2* variants in PD.

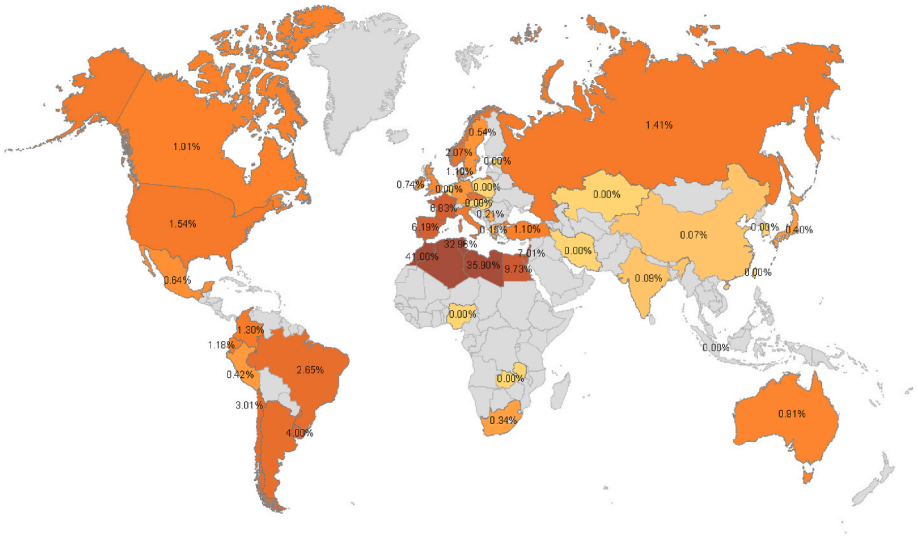

Fig. 2. Estimates of G2019S prevalence among patients with Parkinson's disease, adjusted for ethno-racial composition when possible.

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Author roles

Concept and design: Christopher Simpson, Nancy Maserejian, Julia Shirvan, Cathy Lally, Tien Dam, Lisa Vinikoor-Imler. Acquisition and analysis of data: Christopher Simpson, Lisa Vinikoor-Imler, Cathy Lally. Interpretation of data: all authors. Drafting of the manuscript: Christopher Simpson, Lisa Vinikoor-Imler, Feiby Nassan, Nancy Maserejian, Cathy Lally. Critical revision of the manuscript for important intellectual content: all authors. Approval of the final article for submission: all authors.

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C.S. and C.L. are employees of Epidemiologic Research and Methods LLC (ERM) and consultants for Biogen. L.V.I. is a stockholder in Biogen and was an employee of Biogen at the time of the study. F.L.N., J.S., T.D., and N.M. are employees of and stockholders in Biogen.

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Appendix A. Supplementary data

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