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Classification of *GBA1* variants in Parkinson's disease; the *GBA1*-PD browser

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Abstract

Background: *GBA1* variants are among the most common genetic risk factors for Parkinson's Disease (PD). *GBA1* variants can be classified into three categories based on their role in Gaucher's Disease (GD) or PD: severe, mild, and risk variant (for PD).

Objectives: This paper aims to generate and share a comprehensive database for *GBA1* variants reported in PD to support future research and clinical trials.

Methods: We performed a literature search for all *GBA1* variants that have been reported in PD. The data has been standardized and complimented with variant classification, Odds Ratio (OR) if available and other data.

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AUTHORS' ROLES

S. Parlar: Execution of the research project. Literature search and review. Collection and organization of data. Making tables and figures, writing, and editing for the manuscript.

Z. Gan-Or: Conception of the research project and supervision in its execution. Review and critique of the manuscript.

C. Blauwendraat, F. P. Grenn, and J. J. Kim: Conception, organization, and execution of the online PD *GBA1* variant searching tool database. Review and critique of the manuscript.

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Results: We found 371 *GBA1* variants reported in PD: 22 mild, 84 severe, 3 risk variants, and 262 of unknown status. We created a browser, containing up-to-date information on these variants (https://pdgenetics.shinyapps.io/GBA1Browser/).

Conclusions: The classification and browser presented in this work should inform and support basic, translational, and clinical research on *GBA1*-PD.

INTRODUCTION

The risk, onset, and progression of PD are influenced by a multitude of factors including aging, environmental exposures, and genetic background.[1] The underlying pathobiological mechanisms influencing PD risk are not fully understood; however, multiple genetic loci for PD risk have been identified in the human genome, as well as genes involved in rare Mendelian forms of PD. Notable genes implicated in PD include: *SNCA*, *LRRK2*, *PRKN*, and *PINK1*, among others.[1] One of the most important genes in PD is *GBA1*, as 5–20% of PD patients in different populations carry variants in this gene.[2]

GBA1 encodes the lysosomal enzyme glucocerebrosidase (GCase), responsible for hydrolyzing glucosylceramide and glucosylsphingosine.[3] Pathogenic biallelic *GBA1* variants cause a lysosomal storage disorder, Gaucher Disease (GD), which can be classified as type I (mild, non-neuronopathic form of GD), type II or type III (severe, neuronopathic forms of GD). Accordingly, *GBA1* variants can be classified as mild or severe, based on the type of GD that they lead to in a homozygous state.[2]

The association between *GBA1* variants and PD originates from clinical observations, reporting that some GD patients had been also displaying clinical signs of PD.[4–6] Genetic studies subsequently showed that *GBA1* variants are common risk factors in PD in various populations[2, 7] and that the type of *GBA1* variants, mild or severe, is associated with differential risk and progression of PD. Carriers of severe *GBA1* variants have higher risk for PD, earlier age at onset[2], and their motor and cognitive decline is faster.[8, 9] However, the majority of *GBA1* variant carriers do not develop PD, as the penetrance of heterozygous *GBA1* variants in most PD populations ranges between 10–30%.[10–12] This is much higher compared to a 6.6% reported life-time risk for PD observed in the overall population,[13–16] yet the mechanism by which *GBA1* variants cause or increase the susceptibly for PD is still unknown.[17]

Since the association was first established between *GBA1* variants and PD, there has been extensive research on genotype-phenotype correlations. The list of *GBA1* variants reported in PD cases has grown overtime, and is not fully overlapping that of GD. Notably, the p.E326K and p.T369M variants, which do not cause GD, are risk factors of PD.[18, 19] Since more and more clinical trials targeting individuals with PD and *GBA1* variants are being performed and planned, it is important to gather data on *GBA1* variants to inform the design of these trials and other clinical and functional studies. For example, since carriers of severe *GBA1* variants are likely to progress faster, it will be important that they will be equally represented in the treatment and placebo arms of trials. Here, we compiled a list of all *GBA1* variants reported in individuals with PD to date. We generated an online browser to mine

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data on these variants, including the severity if known among other important information, and we will continue to update this resource.

METHODS

Literature Search Criteria

For the purposes of creating the *GBA1*-PD browser, we searched for all studies that reported *GBA1* variants in PD populations. An initial search on PubMed was done including the variations of the following keywords: "*GBA*," "*GBA1*," and "glucocerebrosidase," and "Parkinson's," and "parkinsonism." The search included papers published from the year 2004, when *GBA*1 was first suggested as a probable risk factor for PD onset,[20] up to April 2022, when the literature search was conducted. As a result of this initial search, 1128 papers were found. After removing meta-analyses and review papers from the list, the remaining 834 papers were thoroughly screened. The screening then filtered for studies involving case-control or case-only PD populations with data on common and rare *GBA1* variants. The final list after this second screening step consisted of 86 papers in total (Figure 1).

Quality Control

GBA1 variants collected from the final list of literature were then validated based on the sequencing data of the *GBA1* gene in ensemble.org.[21] In addition, variant information was revised according to the Human Genome Variation Society (HGVS) guidelines for variants nomenclature.[22]

Clinical Classification of *GBA1* variants

As mentioned earlier, the classification of *GBA1* variants as mild or severe is based on GD: mild mutations cause GD type I and severe mutations cause GD type II or III. This classification is also important in PD, as carriers of severe *GBA1* variants have a higher risk of PD, earlier AAO,[2] and faster cognitive and motor decline.[8, 9, 23] There are also *GBA1* variants that do not cause GD but are associated with increased risk of PD, such as p.E326K and p.T369M.[18, 19] We therefore performed a literature search for each variant to find if it was reported in GD and if its severity was interpretable. We then classified the variants accordingly as mild (causing GD type I), severe (causing GD type II or III), risk variant (variants that are associated with risk of PD but do not cause GD), and unknown.

In addition, we have also included the American College for Medical Genetics classification (ACMG), which classifies variants to "pathogenic', "likely pathogenic", "variant of unknown significance" (VUS), "likely benign" and "benign".[24] This classification is based on a set of criteria that consider how these variants contributes to GD in general, but it does not consider the specific type of GD the variants are associated with. To collect the data, we used the Clinvar and InterVar datasets.[24, 25]

Construction of browser and data sharing

In order to make the information openly accessible, we built the *GBA1*-PD Browser (https://pdgenetics.shinyapps.io/GBA1Browser/). This browser was built using R Shiny and includes

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specific information pertaining to each variant reported in PD as follows: variant name, full length name, clinical classification (i.e. mild, severe, risk variant, or unknown), rsID, genome base pair position (hg19), exon number, allele frequency in gnomAD,[26] CADD PHRED-scaled score,[27] GERP scores,[28] and the manuscript that reported the variant. The data were generated and compiled before being added into the browser.

RESULTS

Identification and classification of *GBA1* variants

From the 86 studies that reported *GBA1* variants in PD cases, we identified 371 unique variants reported to date (https://pdgenetics.shinyapps.io/GBA1Browser/). Of the 371 variants, 22 (5.9%) were identified as mild (type- I GD causing) variants, 84 (22.6%) were identified as severe (type-II and III GD causing) variants and 3 (0.8%) were identified as non-GD risk variants for PD. The risk variants found were biallelic and heterozygous forms of p.E326K, p.T369M, and p.E388K. The remaining 262 (70.6%) were classified as unknown due to lack of information on their GD pathology and/or PD risk associations. Figure 2 depicts the distribution of *GBA1* variants per exon, and the location of the most common variants associated with PD. Among the 86 studies included in this analysis, 16 reported variant specific odds ratio (OR) data for PD risk (Table 1).

The *GBA1*-PD browser

The *GBA1*-PD browser is a public-facing database created to assist researchers in finding *GBA1* variants relevant to PD risk. The previously described 371 variants can be searched and filtered through using hg19/hg38 position, protein consequence, rsID, clinical classification, and exon number. An interactive plot displays the location of the included variants in *GBA1*, and groups variants by their severity. Additional relevant information including reported allele frequency in gnomAD, CADD score, GERP score, and the reporting manuscript are available for each variant.

DISCUSSION

The *GBA1* browser generated through this work could serve as a valuable resource for researchers, clinicians, and for design of clinical trials. There are notable differences across ancestries as to how common *GBA1* variant carriers are. For instance, the prevalence of *GBA1* variants in the Ashkenazi Jewish PD population is around 20%,[2, 29] whereas for Chinese PD cases it is found at a much lower prevalence rate of around 5.4–8.4%.[30–32] The frequencies of specific *GBA1* variants also differ across populations. The most frequent *GBA1* variants in Ashkenazi Jews with PD is p.N370S, while in European populations it is mostly p.E326K or p.T369M, and in some East and South Asian populations it is p.L444P.[2, 26]

These different variants also represent different categories of variants, classified based on their effect in GD. The p.N370S variant is a mild variant associated with GD type I,[33, 34] p.E326K and p.T369M are risk variants for PD that do not cause GD,[19, 35, 36] and p.L444P is a severe variant associated with the severe form of GD.[37–39] While the odds ratio for PD associated with risk variants (i.e. p.E326K and p.T369M) is below 2,[19, 35] the odds ratio

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of mild *GBA1* variants is above 2, and the odds ratio of severe *GBA* variants may reach above 10.[2] There are cases where different combinations of more than one variant have been reported. These can occur due to recombination event with the *GBA1P* pseudogene, in which case the classification would be "severe" as these recombinations do not lead to a functional protein. They can also occur simply in biallelic variant carriers or two variants that are part of a certain haplotype that is not a result of a recombination with *GBA1P*. In such cases we provided the classification for each variant. For example, p.N370S/p.E326K would be classified as "mild"/"risk factor". Many variants are classified as "unknown", which means that it is unknown if they are severe, mild, risk factors, or have no association with PD. This should not necessarily exclude them from participating in clinical trials for example, especially if they are known to be pathogenic for GD.

Out of the 371 variants in the browser, 262 (70.6%) have the status of "unknown" for the classification based on severity. The reason why so many variants have this classification is that they are rare, and in order for them to be classified they have to appear in either homozygous or compound heterozygous state with a known "severe" variant in a GD patient. When they appear with "mild" variants, the patient will have the mild type 1 of GD, and it will not be possible to determine the severity of the second mutation. The p.R44C mutation, for example, is defined as "unknown", since it is considered as benign or likely benign for GD, and in PD there are contradicting evidence for it being a risk factor, as one study reported an odds ratio of 18 in one study with very large confidence intervals,[40] while in another study it was found more frequently in controls.[41] Another variant of interest is p.K(−27)R, which is found mainly in people of African origin. This variant was initially reported in GD patients,[42] suggesting it is potentially pathogenic. However, it only appeared in patients with three *GBA1* variants, and multiple reports to ClinVar later showed that it was benign (https://www.ncbi.nlm.nih.gov/clinvar/variation/196296/). In PD, it was reported in black PD patients from South Africa,[43] yet in a previous study it had similar frequencies in patients and controls.[44] Therefore, we would suggest at this point not including individuals with these variants in clinical trials for *GBA1*-targeting treatments, or alternatively to include them but perform the endpoint analyses with and without carriers of these variants. For unique cases such as p.R44C and K.(−27R), we added short comments in the *GBA1* browser to address these issues.

The types of variants have been reported to have different effects on PD progression, as motor symptoms and cognition seem to decline faster among carriers of severe *GBA1* variants.[8, 9, 23] These observations could be especially important for clinical trials on *GBA1*-PD. If the treatment and placebo arms of a trial will not be balanced in terms of the composition of severe and mild variants in each arm, it is possible that one arm will progress faster than the other, which may lead to either false positive or negative results for a trial. Furthermore, trials that only include severe *GBA1* variant carriers may require a shorter trial duration and a smaller trial population, while trials that include mild or risk variant carriers may require a longer trial duration and a larger trial population. It is important to note that other forms of mutation classifications, perhaps more accurate, could be based on different biomarkers on top of mutation type, as was recently suggested.[45] As new studies are published with new *GBA1* mutations in PD and/or with new information about mutation classification, the browser will be regularly updated by our team. Additional classification of

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importance that we added to the browser is the ACMG classification. This classification, in the case of *GBA1* variants, only recognizes the contribution for GD, without distinguishing which type of GD is caused by the variant. In addition, this classification may provide classification that is less informative for PD. For example, the p.E326K variant receives the ACMG classification of benign/likely benign, because it does not cause GD, yet it is an important risk factor for PD. Nevertheless, it could be useful for certain analyses, and we therefore added it to the browser. Other forms of classifications could also be added to the browser in the future, including using biomarkers, which will make the *GBA1*-PD browser helpful for designing trials, guiding patient recruitment and patient randomization, and guiding specific research efforts.

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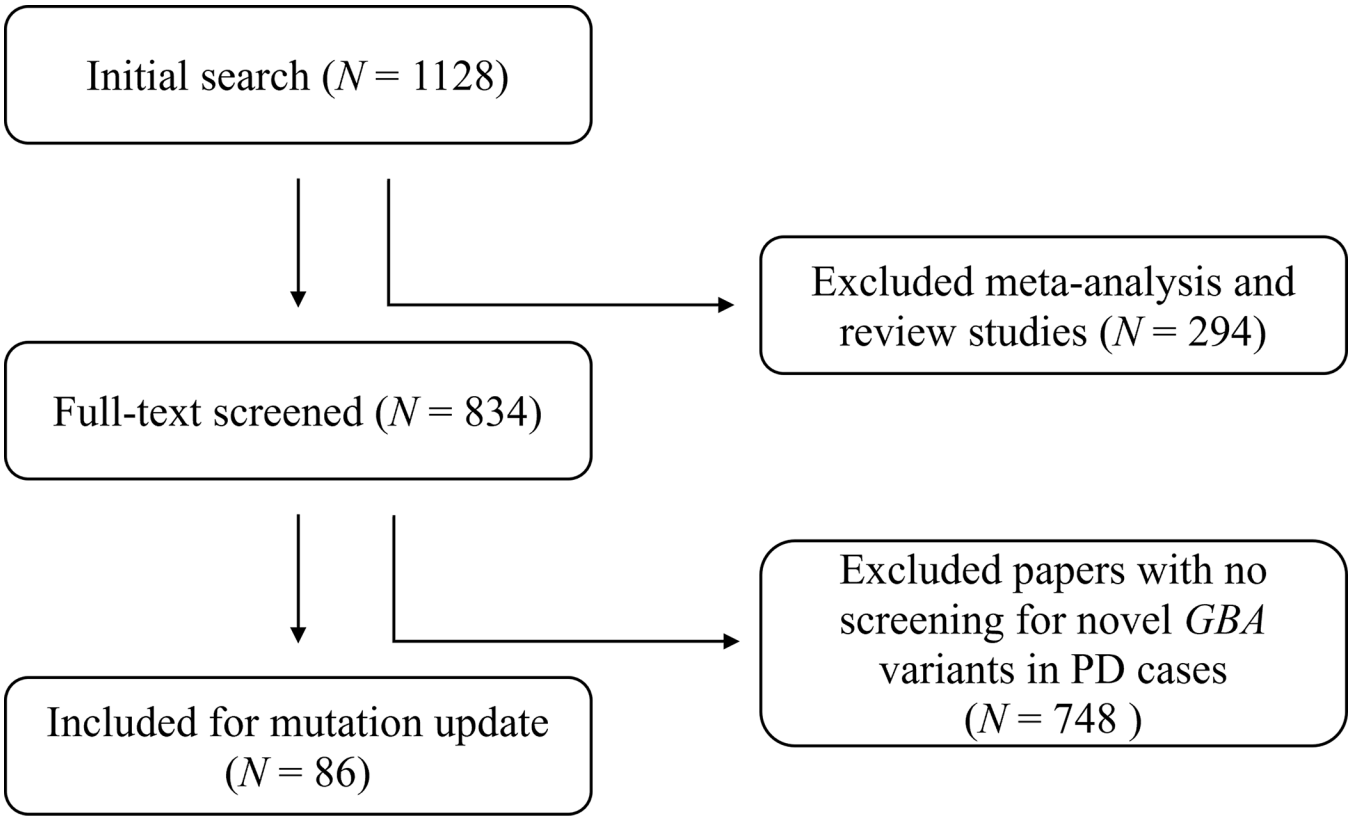

Figure 1. Flow chart of the literature search

Representation of the literature search in flowchart format, involving two sequential steps for screening: the removal of meta-analyses and review papers, and the removal of papers that do not contain novel GBA1 variants in PD patients. N=number of studies

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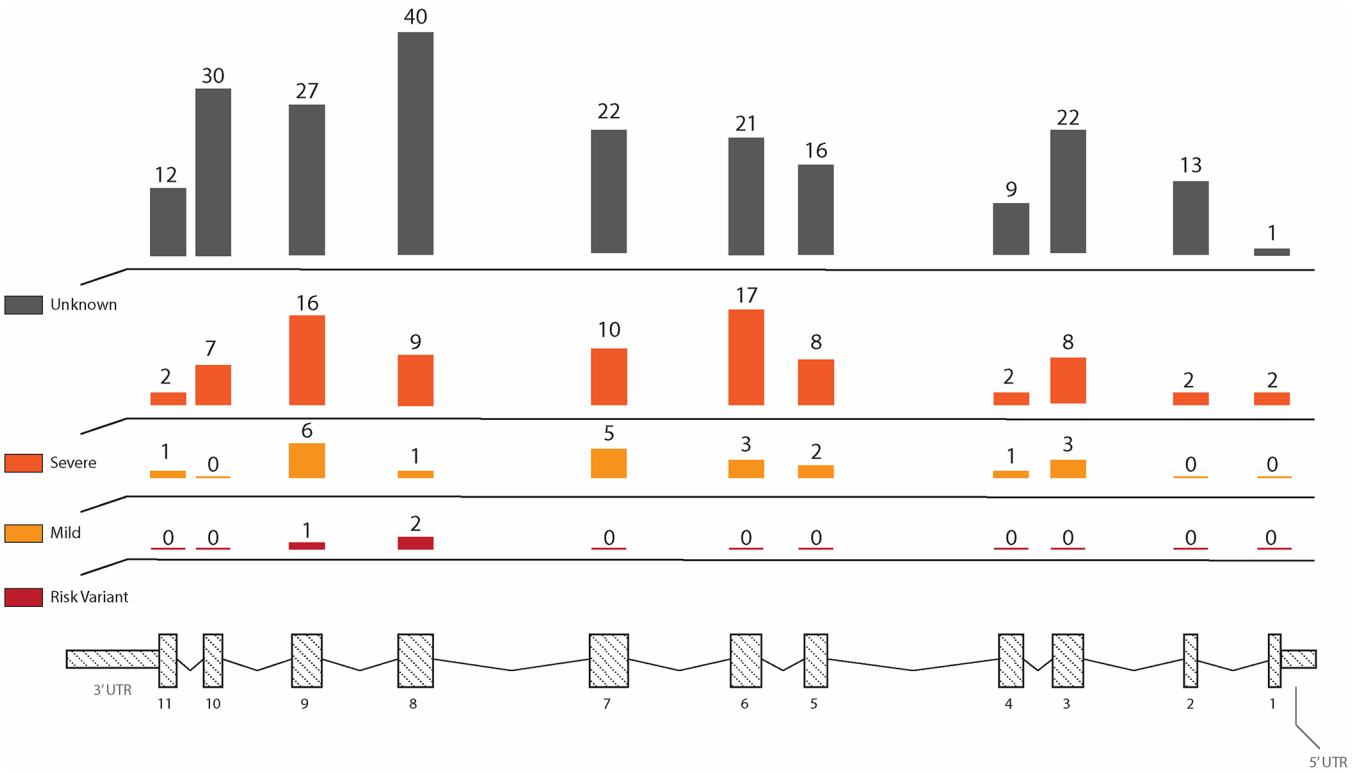

Figure 2. Distribution of *GBA1* variants reported in PD across the gene

Representation of the number of unique reported *GBA1* variants on each exon (numbered 1–11) by clinical classification (Unknown, Severe, Mild, and Risk Variant).

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Table 1.

Odds Ratios of Parkinson's Disease for specific *GBA1* variants

Variant Name	rsID	cDNA	Full-length Protein	Clinical Classification	Range of reported Odds Ratio (OR) in PD	References
IVS2+1G>A	rs104886460	c.115+1G>A	-	Severe	7.96–19.1	2, 46
p.L(−11)Afs*18 (84GG)	rs387906315	c.84dupG	p.Leu29AlafsTer18	Severe	10.1–13.6	2, 41, 46
p.R44C	rs1141812	c.247C>T	p.(Arg83Cys)	Unknown	0.3–18.0	40, 41
p.D140H + p.E326K	rs147138516 + rs2230288	c.[535G>C;1093G>A]	p.[(Asp179His;Glu365Lys)]	Mild + Risk variant	2.01–2.70	47
p.E326K*	rs2230288	c.1093G>A	p.(Glu365Lys)	Risk Variant	1.57–5.50	18, 36, 40, 41, 46–49
p.T369M*	rs75548401	c.1223C>T	p.(Thr408Met)	Risk Variant	1.40–4.98	40, 46, 47, 50
p.N370S*	rs76763715	c.1226A>G	p.(Asn409Ser)	Mild	2.20–7.80	2, 18, 40, 41, 46, 49, 51
p.N370S/N370S	rs76763715	c.[1226A>G;1226A>G]	p.[(Asn409Ser;Asn409Ser)]	Mild/Mild	11.40	2
p.V394L	rs80356769	c.1297G>T	p.(Val433Leu)	Severe	4.85–6.70	2, 46
RecTL	(N/A) + rs1064651 + rs421016 + rs368060 + rs1135675	c.[1263–1317del;1342G>C;1448T>C;1483G>C;1497G>C]	p.[(Asp448His);(Leu483Pro);(Ala495Pro);(Val499Val)]	Severe	12.8–15.3	2, 46
p.L444P	rs421016	c.1448T>C	p.(Leu483Pro)	Severe	6.40–30.4	40, 46, 49, 51–54
RecNCiI	rs421016 + rs368060 + rs1135675	c.[1448T>C;1483G>C;1497G>C]	p.[(Leu483Pro;Ala495Pro;Val499Val)]	Severe	7.30	55
p.R496H	rs75822236	c.1604G>A	p.(Arg535His)	Mild	4.37	46

rsID, reference sequence Identification number; cDNA, coding DNA; OR, odds ratio; PD, Parkinson's disease

*Based on larger sample size studies and GWASs the OR of these variants are likely to be closer to the lower boundaries of the range of ORs reported in this table