# Common *GBA* Variants in Parkinson's Disease and Lewy Body Dementia Patients

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## Abstract

Parkinson's disease (PD) and Lewy Body Dementias (LBD) are two distinct synucleinopathies with a great amount of symptomatic and genetic overlap. This overlap can often lead to misdiagnosis. Misdiagnosis can result in improper therapy and therefore a poorer prognosis. LBD is a neuropath diagnosis with subcategories, but for the purpose of this project we discuss LBD as a whole. *GBA* is a gene common to both diseases with different effect sizes in each, although increasing severity of disease for both. Common is defined as a presence greater than 1% in healthy controls. *GBA* is found in 2-37% of Parkinson cases worldwide, with Ashkenazi Jews having the highest frequency of mutation. Our PD cohort is a clinical series, whereas our LBD cohort is a pathological series. A clinical LBD series can skew results as they are often misdiagnosed, so there is more certainty behind a pathological series. Here, we screened ~200 samples for E365K and T408M, two common *GBA* variants. We have reviewed the clinical implications of being a *GBA* carrier for both diseases and have identified differences. We have genotyped ~1200 LBD samples for these two common variants. Now that we know *GBA* plays a role in each disease, we can better understand the mechanism of pathogenesis and can identify potential therapy targets for *GBA* carriers. These therapeutic targets could be a gateway to cures and therapies for an otherwise incurable condition.

## Methods

### PD Samples

Two tubes of blood samples are collected per patient. 5 mL of each sample is transferred to Autogen FlexSTAR sample tubes. The samples are placed in the Autogen FlexSTAR and a simple whole blood DNA extraction is performed. The samples are transferred to 1.5 mL tubes and the concentrations of the samples are recorded in ng/µL using the NanoDrop 2000. The DNA is plated at 20µL per sample and is diluted to 50 ng/µL. A 5µL Taqman PCR is run using primers for each variant. Genotypic results are analyzed using QuantStudio™ 12K Flex Real-Time PCR System with OpenArray® Block.

### LBD Samples

Brain samples from the brain bank that are LBD confirmed are chipped. Two samples are cut per brain and placed in 1.5 mL tubes. Reagents from the QIAamp Fast DNA Tissue Kit are used to digest the tissue. The samples are then placed on a heat block at 55° C until tissues reach full digestion. The samples are then placed in the Autogen FlexSTAR and a tissue DNA extraction is performed. The DNA is then prepped for genotypic analysis the same as the blood samples

## Figure 1: *GBA* Proposed Mechanism

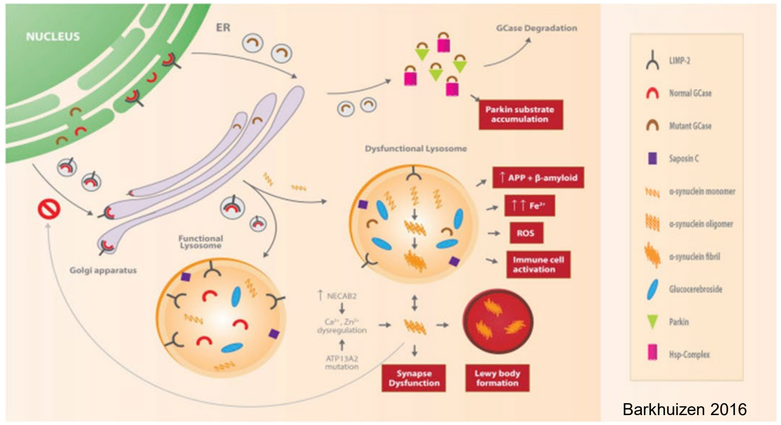


Figure 1. *GBA* codes for a lysosomal storage enzyme known as GCase. Mutant GCase results in aggregation of α-synuclein, the primary component of the Lewy bodies that result in these diseases. Normal GCase leaves the ER and enters a lysosome. The lysosome is functional and produces α-synuclein monomers. Mutant GCase leaves the ER and enters a lysosome. The lysosome is dysfunctional and the α-synuclein monomers begin to oligomerize and aggregate. Some mutant GCase is degraded. Exact mechanism of aggregation is unknown.

## Figure 2: Overlapping Symptoms of PD and LBD

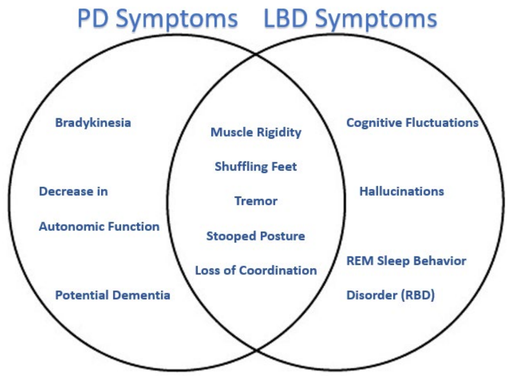


Figure 2. Many symptoms of PD and LBD overlap. To be diagnosed with LBD, the three LBD symptoms are required along with one of the overlapping symptoms.

## Table 1: Demographics of GBA Carrying Patients

| | n=(% of LBD Series) | Gender (%F) | Mean Age ± Standard Dev. |
|---|---|---|---|
| LBD Series | 1298 | 39% | 78.6±8.9 |
| LBD High | 554 (42.6%) | 35% | 77.5±8.0 |
| LBD Intermediate | 386 (29.7%) | 38% | 79.3±8.6 |
| LBD Low | 358 (27.6%) | 47% | 79.7±10.3 |
| Familial PD | 455 | 41% | 68.1±12.6 |
| Controls | 885 | 51% | 57.5±15.2 |

## Table 2: Genotypic Results of E365K and T408M

| GBA E365K | LBD Series | LBD High | LBD Inter. | LBD Low | Fam. PD | Controls |
|---|---|---|---|---|---|---|
| Wild Type | 1178 | 492 | 360 | 326 | 436 | 863 |
| Heterozygous | 72 | 41 | 15 | 16 | 19 | 22 |
| Homozygous | 4 | 2 | 1 | 1 | 0 | 0 |
| Total | 1254 | 535 | 376 | 343 | 455 | 885 |
| MAF | 3.190% | 4.206% | 2.261% | 2.624% | 2.088% | 1.243% |
| Call Rate | 99.2% | 99.8% | 99.2% | 98.3% | 100% | 100% |
| OR [95%CI] | 2.66 [1.66-4.29] | 3.59 [2.14-6.01] | 1.85 [0.98-3.51] | 2.17 [1.15-4.06] | 3.42 [2.01-5.82] | |
| p-value | **1.30E-05** | **4.33E-07** | 0.064 | 0.019 | 0.093 | |

| GBA T408M | LBD Series | LBD High | LBD Inter. | LBD Low | Fam. PD | Controls |
|---|---|---|---|---|---|---|
| Wild Type | 1217 | 518 | 365 | 334 | 444 | 869 |
| Heterozygous | 30 | 12 | 12 | 6 | 11 | 16 |
| Homozygous | 1 | 1 | 0 | 0 | 0 | 0 |
| Total | 1248 | 531 | 377 | 340 | 455 | 885 |
| MAF | 1.282% | 1.318% | 1.592% | 0.882% | 1.209% | 0.904% |
| Call Rate | 98.7% | 99.1% | 99.5% | 97.4% | 100% | 100% |
| OR [95%CI] | 1.43 [0.78-2.61] | 1.47 [0.71-3.02] | 1.79 [0.84-3.79] | 0.98 [0.38-2.50] | 1.35 [0.62-2.91] | |
| p-value | 0.239 | 0.300 | 0.139 | 0.959 | 0.456 | |

## Conclusions and Future Directions

- The only significant associations were found between the E365K variant and the LBD series and LBD high group. The LBD high group is the driving force for the significance of the LBD series. This may be because *GBA* causes a more severe disease and therefore resulting in a LBD high pathology.
- *GBA* is a risk modifier for PD and is not causative. Numbers could be even higher if sporadic PD was included, as only familial exomes were used.
- *GBA* has a stronger effect size in LBD than PD as reflected in Table 2.

## References

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