# *GBA*-ASSOCIATED PARKINSON'S DISEASE
## INFORMATION FOR HEALTH CARE PROVIDERS

Individuals with one or two *GBA* (glucosylceramidase beta) gene mutations are now known to be at an increased risk of developing Parkinson's disease. While this link was previously suspected, current literature reports large cohorts with increasingly clear risk associations. The associated risk of developing Parkinson's disease has been shown to be both dosage and mutation specific with severe mutations carrying a higher risk than mild mutations. This fact sheet provides an overview of Gaucher disease and Parkinson's disease, information for risk communication, and practical considerations to use in counseling individuals with *GBA* mutations about their associated Parkinson's disease risk.

## Gaucher Disease

Gaucher disease is an autosomal recessive metabolic disorder characterized by reduced enzyme beta-glucocerebrosidase leading to accumulation of glucocerebroside within lysosomes. Symptoms include hepatosplenomegaly, anemia, thrombocytopenia, bone pain, fractures and, in some cases, neurologic abnormalities[24]. There are three recognized types of Gaucher disease ranging in symptoms and severity. Type 1 is the most common, does not typically affect the nervous system, and may have early or late onset. Types 2 and 3 are acute and chronic neuronopathic forms characterized by primary involvement of the central nervous system[20]. Enzyme replacement therapy is used to treat primarily type 1 and may eliminate many of the symptoms of Gaucher disease. However, enzyme replacement therapy may not reverse or prevent progression of neurological complications associated with the more severe types[20].

Gaucher disease is caused by homozygous or compound heterozygous mutations in the *GBA* gene. Carrier frequency is estimated at 1 in 100 or less in the general population and 1 in 18 in individuals with Ashkenazi Jewish ancestry[8,13,16]. Over 300 *GBA* mutations have been identified; these can be characterized as mild or severe depending on their phenotypic consequence[1,6,9]. The *GBA* mutation N370S is most common and comprises about 70% of all reported *GBA* mutations in the Ashkenazi Jewish population.

## Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder, affecting 1% to 3% of the general population by age 80 years[17,20]. Risk of disease increases with age, and males have a higher incidence. The disease is caused by the malfunction and death of dopaminergic neurons in the substantia nigra of the midbrain with inclusions of Lewy bodies in remaining neurons[4,20].

Parkinson's disease can be highly variable; symptoms, age of onset and rate of progression can differ greatly among patients. Diagnosis is made by clinical examination noting the presence of the major symptoms of tremors, bradykinesia, rigidity and postural instability. There may also be non-motor symptoms such as sleep disorders, mood problems, and cognitive changes. Positive response to dopamine therapy is used to support a clinical diagnosis. There is currently no cure for Parkinson's disease nor a treatment that reliably slows the progression; however, there are medications and surgical options that can improve the symptoms[18].

Parkinson's disease is a multifactorial condition with both genetic and environmental contributions. Parkinson's disease is often observed to be sporadic in a family; however, genetic risk factors have been identified in both sporadic and familial Parkinson's disease. Some of the primary genes associated with late-onset Parkinson's disease include the *SNCA* (synuclein alpha) gene that encodes alpha-synuclein, and the *LRRK2* (leucine-rich repeat kinase 2) gene,[10,19,26] and the *GBA* gene[23].

## Association and Penetrance

According to the Gaucher Disease Registry, the estimated risk for Parkinson's disease in patients with Gaucher disease is 5-7% before age 70 and 9-12% by age 80. The risks for individuals carrying a single *GBA* mutation are estimated to be slightly less: 8% by 80 years old[1] and 11% by age 85 in another study[21]. It should be noted that the majority of individuals in these studies were Ashkenazi Jewish, and most carried a N370S mutation. There is a wide range of penetrance risk figures reported for carriers depending on the populations studied, mutations carried, and robustness of study design. These include studies in Europe that observed a 15% risk by 80 years old in the United Kingdom and 29.7% by 80 years old for individuals with familial Parkinson's disease in France (note that sample sizes were limited, reducing the validity of this data)[2,12]. In a meta-analysis utilizing worldwide data, the odds ratio for Parkinson's disease in carriers of mild *GBA* mutations ranged from 3.0 to 4.7, and for severe mutations, 14.6 to 19.3[7].

| POPULATION | PARKINSON'S RISK (BY AGE 80 YEARS) | REFERENCE |
|---|---|---|
| General population | 1-3% | Pastores & Hughes, 2000; Alcalay et al., 2014 |
| *GBA* mutation carriers | 7.7%-11% | Alcalay et al., 2014; Rana et al., 2012 |
| *GBA* "mild" mutation carriers (e.g. N370S) | 6%-9% | Gan-Or et al., 2015; Alcalay et al., 2014 |
| *GBA* "severe" mutation carriers (e.g. 84GG, IVS2+1G>A, L444P) | 17-24% | Gan-Or et al., 2015 |
| Gaucher disease population | 9-12% | Alcalay et al., 2014; Rosenbloom et al., 2011 |

Approximately 7% to 15% of individuals with Parkinson's disease carry a *GBA* mutation, with higher rates in Ashkenazi Jews[24]. Identification of a *GBA* mutation varies depending on the population and type of genetic testing performed (targeted vs. sequencing). All *GBA* pathogenic mutations are associated with an increased risk of developing Parkinson's disease, although the penetrance, age of onset, and severity may vary[24]. Infrequently, variants that are thought to be associated with Parkinson's disease, but not Gaucher disease, have been reported; more research is underway to understand these atypical variants.

## *GBA*-type Parkinson's Disease

Patients who have Parkinson's disease and a *GBA* mutation are more likely to have an earlier age of onset (average of 53 years old for a severe *GBA* mutation and 58 years old for mild mutations, versus 61 to 65 years old for average age of onset). They may also have a higher risk of cognitive impairment, and a lower risk of certain motor symptoms such as tremors, bradykinesia and rigidity[1,7,11]. Lewy body dementia may also be a feature in some individuals.

## Prevention

Currently, there are no established recommendations for the prevention of Parkinson's disease. Research suggests that exercise may be associated with a lower incidence of developing Parkinson's disease. In addition, some individuals with Parkinson's disease have seen slowed progression and fewer symptoms with the implementation of an exercise regimen. Other studies have shown a lower incidence of Parkinson's disease in individuals who use caffeine or nicotine, though additional research regarding these associations is needed[3].

## Disclosure of Parkinson's Risk to *GBA* Carriers

Published literature suggest that the majority of patients undergoing carrier screening want to know about the association between Parkinson's disease and *GBA* mutations. Most individuals stated that this information would not change their decision to undergo carrier screening, and indicated that learning about this association (before or after testing) would be beneficial, not harmful[14].

Commercial laboratories have recently started adding information about the Parkinson's disease and *GBA* association to their carrier screening reports. Various support and foundation webpages also now discuss the link. Ideally, genetic counseling about this link should be tailored to the needs of the case with the following taken into consideration: type of setting, age of patient, timing, patient autonomy, family dynamics and implications to other relatives, anxiety and other psychological sequelae, and potential insurance discrimination[14,23]. It may be appropriate to schedule a follow-up appointment for further discussion of this specific topic.

## Research Opportunities

There is increasing interest in identifying individuals who have inherited mutations in these genes making them the focus of new research initiatives. Researchers at Indiana University School of Medicine have developed a registry called the Widespread Recruitment Database (WRD) to identify and educate people who have undergone or are interested in future genetic testing for mutations that increase their risk of Parkinson's disease, as well as volunteers interested in contributing to new or future Parkinson's disease research initiatives. Genetic counseling may be available to those who enroll in the project. Interested individuals can start the survey at wrd.iu.edu/pd/. To learn more, you may email us at wrd@iu.edu or call 888-830-6299. In addition, more information can be found about other research opportunities at clinicaltrials.gov/.

## Resources

- Genetics Home Reference: https://ghr.nlm.nih.gov/gene/GBA#
- GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1269/
- Genetic Testing Registry: https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2629%5Bgeneid%5DNIH: https://www.nih.gov/news-events/nih-research-matters/rare-disease-gene-linked-parkinsons-disease
- OMIM: http://omim.org/entry/606463
- National Gaucher Association: https://www.gaucherdisease.org/blog/connection-parkinson-disease-brings-new-attention-gaucher/
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