Genetic and clinical pharmacology studies in GBA1-associated Parkinson's disease

Heijer, J.M. den

CHAPTER 4

Experience in genetic counseling for *GBA1* variants in Parkinson's disease

J. M. den Heijer, MD[1,2], J. J. van Hilten, MD, PHD[2],
A. J. A. Kievit, MD, PHD[3], V. Bonifati, MD, PHD[3],
G. J. Groeneveld, MD, PHD[1,2]

1. Centre for Human Drug Research, Leiden, NL
2. Leiden University Medical Center, Leiden, NL
3. Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, NL

Apart from the GWAS risk loci, variants in the *GBA1* gene are the most common risk factor known to date to develop Parkinson's disease (PD).[1,2] Genetic testing and - counseling of *GBA1* variants is not yet part of common clinical practice, but the need for this will likely increase, since research into this topic has increased considerably over the past two decades and genetic testing will become more common. Several studies show that PD patients have a very positive attitude towards genetic testing.[3–5]

Genetic counseling is offered to support patients in clarifying gaps of knowledge regarding PD genetics as well as the risks, benefits, and limitations of genetic testing and to support them in their decision making process.[6] We use a whole exome sequencing panel of genes associated with movement disorders in familial PD and/or complex PD and/or PD with an early onset, less stricter than formulated in the European guidelines.[7,8] In monogenetic Parkinson disease, with variants in *SNCA*, *PRKN* or *PINK1*, it is relatively straightforward to clarify the inheritance pattern, inform relatives about their risk and discuss the options of predictive- and reproductive testing. If a variant is found associated with reduced penetrance like the founder mutation p. G2019S-mutation in *LRRK2* and especially if the variants are associated with mild differential effects on the risk and expression of PD, like heterozygous variants in *GBA1*, this is more difficult for the patient and relatives to handle and raises a need for genetic counseling tailored to the nature of the variant. *GBA1* encodes the lysosomal enzyme glucocerebrosidase, and is considered one of the most promising potential targets for the development of a disease-modifying drug for PD.[6] In light of these developments, a growing number of patients with PD are being screened for *GBA1* variants.

We recently performed a large-scale full *GBA1* gene screening in 3402 people with PD in the Netherlands.[9] In most populations, 4-12% of PD patients carry a heterozygous *GBA1* variant and in Ashkenazi Jewish PD patients this is approximately 20%.[2,10] In our Dutch cohort, a remarkably high prevalence of 15. 5% exonic or splice site variants was found. Subsequently, 528 patients with PD carrying a variant in the *GBA1* gene were counseled. In this viewpoint we wish to provide some background on *GBA1* in PD and share our experience in counseling of people with PD about the risks of a *GBA1* variant.

The *GBA1* gene is primarily known by the lysosomal storage disorder Gaucher's disease (GD), caused by a bi-allelic damaging variant in this gene. Important to note is that over 400 variants in the *GBA1* gene have been reported to be able to cause GD.[11,12] Some variants have been associated with a more severe phenotype of GD (e.g. L444P (p. Leu483Pro) is associated with the severe type 2-3 GD and N370S (p. Asn409Ser) is associated with the mild type 1 GD), but generally there is a weak genotype-phenotype correlation.[13] Having a heterozygous damaging variant will not cause GD, but it may increase the risk of developing PD. Several variants have been associated with an increased risk in PD, that in homozygous state will not cause GD (like E326K (p. Glu365Lys) and T369M (p. Thr408Met)).[14,15] Within PD, indications of a *GBA1* variant 'dose-effect' on age at onset, motor and non-motor symptoms have been described.[9,16,17].

Carriers of *GBA1* variants have an increased risk to develop PD (GBA-PD) with an earlier onset and possibly a faster motor and non-motor disease progression.[17–22] However, for counseling purposes it is important to acknowledge the existence of large variation in genotype-phenotype correlations and therefore the low predictability for an individual patient. For example in our cohort the mean (range) of age at diagnosis in non-carriers was 60.6 (27-92) years as compared to 56.9 (25-84) years in carriers of *GBA1* variants.

Motor impairment scores are generally worse in GBA-PD compared to idiopathic PD (iPD), but the structurally large standard deviations make an individualized prediction impossible.[17,18,21] Similarly for cognitive decline, this is generally worse in GBA-PD compared to iPD. A meta-analysis shows an OR of 2. 40 (95% CI 1.71-3.38) for developing PD dementia in *GBA1* variant carriers compared to iPD.[22] Nevertheless, between patient variability is again high, making it impossible to individually predict cognitive decline.[20,21,23]

The risk of PD in those who carry a *GBA1* variant is increased by an estimated overall 2-7-fold. Heterozygous and homozygous (potential GD) carriers have similar ORs.[24] Higher ORs have been reported for specific variants, but these are usually based on studies with a small number of carriers.[2,10,25,26] To our knowledge, no extended families have been reported with PD in multiple relatives with a *GBA1* variant as a possible high-penetrance (monogenic) causative factor, making any larger estimated risks unlikely.

Penetrance of *GBA1* is age-dependent and estimated to be between 1-14% at 60 years of age and 10-30% at approximately 80 years of age.[24,27–29] The higher end of these ranges is reported in subjects with familial PD and therefore possibly an overestimation, due to additional genetic burden in these familial cases.[30] The lower end of these ranges is based on parents of GD patients, which are obligate *GBA1* variant carriers, but do not necessarily carry any other genetic risk factors for PD other than *GBA1*.[24,29] A recent study in unselected PD patients (so both patients with and without a positive PD family history) showed an intermediate penetrance of 10. 0% at 60 years and 19. 4% at 80 years.[28] Penetrance was higher in carriers compared to noncarriers, but no statistically significant difference was found between carriers of mild (e.g. N370S) and severe (e.g. L444P) GD-associated variants.[24,27,28] All in all, most people with a homozygous or heterozygous variant will never develop PD.[24,31,32]

To account for the 'dose effect' of different *GBA1* variants, three categories were defined for counseling PD patients:

1. 'Low risk variants', if the allele has been reported in PD, but not as GD-causing
2. 'Moderate risk variants', if the allele has been reported in at least a single GD case, either in a homozygous state or in a compound heterozygous state with other GD-associated variants
3. 'Unknown variants', if a variant was not reported before.

A further 'dose-effect' within all variants previously reported in GD (here 'moderate risk variants') seems plausible, but sample sizes are generally very small for these (over 400!) different variants and therefore these cannot currently be differentiated reliably for personalized counseling.

When counseling a *GBA1* variant, it is important to provide a relevant context. For example, for a 'moderate risk variant' case: 'Of people of 60 years and older, approximately 1% will develop PD. With a *GBA1* variant, there would be an approximate 2-7% risk of developing PD at this age. This also means there is a 93-98% chance of *not* having developed PD at this age'. The age-specific incidence rate of PD of course increases beyond the age of 60 years.[33] *GBA1* can therefore be seen as a modifier of the PD risk, or risk factor in PD, and play a role in the complex disease etiology as such.

Considering the low absolute increase in risk of developing PD, the inability to predict disease progression, and the current lack of therapeutic consequences, we deemed it appropriate to primarily counsel the PD patients by phone and provide similar written information by mail. Patients had the opportunity to request a meeting in person. Only sporadically a patient returned a phone call for additional questions.

A transcript was created for the three *GBA1* categories (supplementary box 2A,B,C). Prior to presenting the transcript, it is advisable to give a brief simplified explanation of genetic principles (supplementary box 1). The primary concern of carriers in our study was often related to the consequences for their children. There is of course a 50% chance of inheriting the *GBA1* variant, but it is important to stress that the risks attributed to *GBA1* are very small so that presymptomatic testing for the *GBA1* variant is, in our view, not justified.

So far, the clinical relevance of having a *GBA1* variant is very limited for an individual. However, a study on deep brain stimulation (DBS) is worth mentioning, in which at 7.5 years after DBS, 6 out of 10 (60%) *GBA1* variant carriers had severe cognitive impairment, compared to 1 out of 16 (6%) in non-carriers.[34] This finding needs validation in a larger cohort, but this could be relevant for DBS decision-making. Furthermore, the prospect of possibly being eligible for a clinical trial based on carrying a *GBA1* variant, may be relevant for an individual as well.

Perhaps, when genotype-phenotype correlations will have been elucidated further in future larger cohorts, a variant-specific counseling can be tailored further.

In conclusion, the increasing amount of genetic testing being performed in Parkinson's disease creates an exciting time in which hopefully important steps are being made towards a personalized disease-modifying treatment. Accompanying this development, we should not forget to adequately inform patients about these findings and their clinical context, and to bring nuance when appropriate.

REFERENCES

1 Bandres-Ciga S, Diez-Fairen M, Kim JJ, Singleton AB. Genetics of Parkinson's disease: An introspection of its journey towards precision medicine. Neurobiol Dis. 2020;137:104782.
2 Gan-Or Z, Amshalom I, Kilarski LL, Bar-Shira A, Gana-Weisz M, Mirelman A, et al. Differential effects of severe vs mild GBA mutations on Parkinson disease. Neurology. 2015;849:880-7.
3 Falcone DC, Wood EM, Xie SX, Siderowf A, Van Deerlin VM. Genetic testing and Parkinson disease: assessment of patient knowledge, attitudes, and interest. J Genet Couns. 2011;204:384-95.
4 Gupte M, Alcalay RN, Mejia-Santana H, Raymond D, Saunders-Pullman R, Roos E, et al. Interest in genetic testing in Ashkenazi Jewish Parkinson's disease patients and their unaffected relatives. J Genet Couns. 2015;242:238-46.
5 Maloney KA, Alaeddin DS, von Coelln R, Dixon S, Shulman LM, Schrader K, et al. Parkinson's Disease: Patients' Knowledge, Attitudes, and Interest in Genetic Counseling. J Genet Couns. 2018;275:1200-9.
6 Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns. 2006;152:77-83.
7 Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol. 2013;201:16-34.
8 Erasmus MC;Pageshttps://www. erasmusmc. nl/nl-nl/patientenzorg/laboratoriumspecialismen/klinische-genetica on 09 September 2020.
9 den Heijer JM, Cullen VC, Quadri M, Schmitz A, Hilt DC, Lansbury P, et al. A Large-Scale Full *GBA1* Gene Screening in Parkinson's Disease in the Netherlands. Mov Disord. 2020.
10 Ruskey JA, Greenbaum L, Ronciere L, Alam A, Spiegelman D, Liong C, et al. Increased yield of full GBA sequencing in Ashkenazi Jews with Parkinson's disease. Eur J Med Genet. 2019;621:65-9.
11 Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;1366:665-77.
12 Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008;295:567-83.
13 Hassan S, Lopez G, Stubblefield BK, Tayebi N, Sidransky E. Alleles with more than one mutation can complicate genotype/phenotype studies in Mendelian disorders: Lessons from Gaucher disease. Mol Genet Metab. 2018;125(1-2):1-3.
14 Huang Y, Deng L, Zhong Y, Yi M. The Association between E326K of GBA and the Risk of Parkinson's Disease. Parkinsons Dis. 2018;2018:1048084.
15 Mallett V, Ross JP, Alcalay RN, Ambalavanan A, Sidransky E, Dion PA, et al. GBA p. T369M substitution in Parkinson disease: Polymorphism or association? A meta-analysis. Neurol Genet. 2016;25:e104.
16 Thaler A, Gurevich T, Bar Shira A, Gana Weisz M, Ash E, Shiner T, et al. A 'dose' effect of mutations in the GBA gene on Parkinson's disease phenotype. Parkinsonism Relat Disord. 2017;36:47-51.
17 Cilia R, Tunesi S, Marotta G, Cereda E, Siri C, Tesei S, et al. Survival and dementia in GBA-associated Parkinson's disease: The mutation matters. Ann Neurol. 2016;805:662-73.
18 Davis MY, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, et al. Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. JAMA Neurol. 2016;7310:1217-24.
19 Jesus S, Huertas I, Bernal-Bernal I, Bonilla-Toribio M, Caceres-Redondo MT, Vargas-Gonzalez L, et al. GBA Variants Influence Motor and Non-Motor Features of Parkinson's Disease. PLoS One. 2016;1112:e0167749.
20 Malek N, Weil RS, Bresner C, Lawton MA, Grosset KA, Tan M, et al. Features of GBA-associated Parkinson's disease at presentation in the UK Tracking Parkinson's study. J Neurol Neurosurg Psychiatry. 2018;897:702-9.

21 Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, et al. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016;311:95-102.
22 Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D. Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. Am J Med Genet B Neuropsychiatr Genet. 2018;1772:232-41.
23 Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012;7818:1434-40.
24 Alcalay RN, Dinur T, Quinn T, Sakanaka K, Levy O, Waters C, et al. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes. JAMA Neurol. 2014;716:752-7.
25 Lesage S, Anheim M, Condroyer C, Pollak P, Durif F, Dupuits C, et al. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet. 2011;201:202-10.
26 Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;36117:1651-61.
27 Anheim M, Elbaz A, Lesage S, Durr A, Condroyer C, Viallet F, et al. Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. Neurology. 2012;786:417-20.
28 Balestrino R, Tunesi S, Tesei S, Lopiano L, Zecchinelli AL, Goldwurm S. Penetrance of Glucocerebrosidase (GBA) Mutations in Parkinson's Disease: a Kin Cohort Study. Mov Disord. 2020.
29 Rana HQ, Balwani M, Bier L, Alcalay RN. Age-specific Parkinson disease risk in GBA mutation carriers: information for genetic counseling. Genet Med. 2013;152:146-9.
30 Sidransky E, Hart PS. Penetrance of PD in Glucocerebrosidase Gene Mutation Carriers. Neurology. 2012;791:106-7.
31 Rana AQ, Siddiqui I, Yousuf MS. Challenges in diagnosis of young onset Parkinson's disease. J Neurol Sci. 2012;323(1-2):113-6.
32 Sidransky E. Heterozygosity for a Mendelian disorder as a risk factor for complex disease. Clin Genet. 2006;704:275-82.
33 Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014;2913:1583-90.
34 Lythe V, Athauda D, Foley J, Mencacci NE, Jahanshahi M, Cipolotti L, et al. GBA-Associated Parkinson's Disease: Progression in a Deep Brain Stimulation Cohort. J Parkinsons Dis. 2017;74:635-44.

SCAN ME

SUPPLEMENTARY MATERIAL

H4sT1