**GBA-associated PD: chances and obstacles for targeted treatment strategies**

Günter Höglinger1,2 · Claudia Schulte3,4 · Wolfgang H. Jost5 · Alexander Storch6,7 · Dirk Woitalla8 · Rejko Krüger9,10,11 · Björn Falkenburger12 · Kathrin Brockmann3,4

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Abstract

Given the clear role of GBA in the pathogenesis of Parkinson’s disease (PD) and its impact on phenotypical characteristics, this review provides an overview of the current knowledge of GBA-associated PD with a special focus on clinical trajectories and the underlying pathological mechanisms. Importantly, differences and characteristics based on mutation severity are recognized, and current as well as potential future treatment options are discussed. These findings will inform future strategies for patient stratification and cohort enrichment as well as suitable outcome measures when designing clinical trials.

Keywords PD · GBA · Lysosomal · α-Synuclein

Introduction

Over the last decades, research in genetically defined forms of Parkinson’s disease (PD) led to the identification of specific pathways underlying the pathophysiology of the disease. Next to defects in vesicular trafficking, mitochondrial and importantly lysosomal dysfunction represent the most relevant pathways (Jankovic and Tan 2020). Studying these early events provide entry points to develop novel therapeutic targets for stratified patient groups as an important step towards precision neurology. The present article exemplifies such strategies focusing on PD patients with different variants in the glucocerebrosidase (GBA) gene (PD_{GBA}). Also, obstacles of translational research into patient cohorts and study designs for clinical trials are discussed.

1 Department of Neurology, Hannover Medical School, 30625 Hannover, Germany
2 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
3 Department of Neurodegeneration and Hertie-Institute for Clinical Brain Research, Center of Neurology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
4 German Center for Neurodegenerative Disease (DZNE), Tübingen, Germany
5 Parkinson-Klinik Ortenau, Wolfach, Germany
6 Department of Neurology, Rostock University, Gehlsheimer Str. 20, 18147 Rostock, Germany
7 German Center for Neurodegenerative Diseases (DZNE) Rostock/Greifswald, Gehlsheimer Str. 20, 18147 Rostock, Germany
8 Department of Neurology, St. Josef-Hospital, Katholische Kliniken Ruhrhalsinsel, Contilia Gruppe, Essen, Germany
9 Transversal Translational Medicine, Luxembourg Institute of Health (LIH), Strassen, Luxembourg
10 Translational Neuroscience, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg
11 Parkinson Research Clinic, Centre Hospitalier de Luxembourg (CHL), Luxembourg, Luxembourg
12 Department of Neurology, Faculty of Medicine, University Hospital Carl Gustav Carus and Carl Gustav Carus, Technische Universität Dresden, 01307 Dresden, Germany
**GBA and Parkinson**

**GBA variants are the most important genetic risk factor for PD**

Biallelic variants in the *GBA* gene cause Gaucher’s disease (GD), the most common lysosomal storage disorder with tissue accumulation of glucosylceramides due to deficiency of the lysosomal enzyme glucocerebrosidase (GCase). Interestingly, about 25% of GD patients report a first- or second-degree relative to present with PD (Goker-Alpan et al. 2004; Halperin et al. 2006). This important clinical observation was the hint to the fact that heterozygous variants in the *GBA* gene are associated with PD. Subsequently, a large multi-centre study across four continents analysed 5691 PD patients of different ethnic origin compared to 4898 controls and confirmed that with an overall odds ratio (OR) of 5.43, heterozygous variants in the *GBA* gene represent the most important genetic risk factor for PD (Sidransky et al. 2009). This has now been confirmed across different ethnic populations with Caucasian, Asian (Japanese, Chinese, Taiwanese), Hispanic, and African ancestry (den Heijer et al. 2020; Neumann et al. 2020). This important clinical observation was the hint to the fact that heterozygous variants in the *GBA* gene are associated with PD. Subsequently, a large multi-centre study across four continents analysed 5691 PD patients of different ethnic origin compared to 4898 controls and confirmed that with an overall odds ratio (OR) of 5.43, heterozygous variants in the *GBA* gene represent the most important genetic risk factor for PD (Sidransky et al. 2009). This has now been confirmed across different ethnic populations with Caucasian, Asian (Japanese, Chinese, Taiwanese), Hispanic, and African ancestry (den Heijer et al. 2020; Neumann et al. 2020; Lesage et al. 2011; Chen et al. 2014; Mahungu et al. 2020).

To date, more than 100 different variants have been associated with the risk of PD. However, the pathogenicity of different variants varies largely (Table 1). Whereas variants classified as severe variants (e.g. p.L444P) show an odds ratio of 10–15 for developing PD, some variants that are non-pathogenic for GD have been proven to increase the risk for PD e.g. p.E326K and p.T369M (Iwaki et al. 2019; Zhang et al. 2018; Straniero et al. 2020). These variants show the lowest odds ratios and are thus classified as risk variants. Consequently, *GBA*-subgroup classification for PD patients is often based on variant severity according to established genotype risks reported for PD (PD*gbasevere, PD*gbamild, PD*gbarisk*). Interestingly, we see a huge variability of variant distribution among different ethnicities. About 20% of PD patients with Ashkenazi Jewish ancestry carry a *GBA* variant, with the large majority harbouring the mild p.N370S (> 70%), whereas the severe p.L444P variant is identified in about 5%. Together, the two variants account for about 80% of variants in Ashkenazi Jewish PD patients. In non-Ashkenazi Jewish PD patients, p.L444P is detected in about 30–40% of patients and p.N370S in about 20%, together accounting for 50–60% of variants (Sidransky et al. 2009), indicating that about 40% of variants could be missed if focusing solely on p.N370S and p.L444P. These findings highlight the need for full-gene sequencing and stratification according to variant severity. Moreover, penetrance and disease risk in PD*gba* are age-dependent (Anheim et al. 2012; Straniero et al. 2020) and further modified by the composite PD-associated polygenic risk score (PRS) and single-nucleotide polymorphisms in SNCA, CSTB and TMEM175, the two latter genes encoding proteins associated with lysosomal homeostasis and protein clearance (Blauwendraat et al. 2020).

**PD*gba*: severe clinical trajectories with early cognitive decline**

Detailed investigation of the phenotypical spectrum, longitudinal trajectories, and rate of progression of motor and non-motor symptoms is of utmost importance to estimate effect sizes and design clinical trials for disease-modifying therapies (duration, sample sizes, progression rates, expected spectrum of symptoms, etc.).

In general, PD*gba* show an earlier age at onset compared to PD patients without *GBA* variants (PD*gbawildtype*) with a median onset in the early 50s (Sidransky et al. 2009; Blauwendraat et al. 2019). Of note, this effect is not only attributable to *GBA* variants per se, but is driven by *GBA* variant severity and variant burden with severe variants as well as homozygous and compound heterozygous variants predisposing to the youngest age at onset (Malek et al. 2018; Thaler et al. 2017). Moreover, age at onset is further reduced in PD*gba* by non-coding variants in SNCA and TMEM175 (Blauwendraat et al. 2020). Although younger, PD*gba* present with a higher prevalence of cognitive impairment and more frequently suffer from additional non-motor symptoms including neuropsychiatric disturbances (depression, anxiety, and hallucination), autonomic dysfunction and sleep disturbances such as REM-sleep-behaviour disorder (RBD) when compared to PD*gbawildtype* (Brockmann et al. 2011; Barrett et al. 2014). These findings have been replicated consistently over the following years in other PD cohorts worldwide, the latest large clinical genome-wide association study in 4093 PD patients (Iwaki et al. 2019). Importantly, *GBA* variants that are classified as severe (PD*gbasevere*) have been associated with a more aggressive clinical phenotype suggesting a relevant effect depending on *GBA* variant severity (Cilia et al. 2016; Thaler et al. 2018; Petrucci et al. 2020; Lerche et al. 2021a).

Data from longitudinally investigated cohorts of PD*gba* confirm findings from cross-sectional evaluations and revealed that PD*gba*, although younger in age and age at onset, present with an accelerated disease progression in terms of motor impairment and cognitive decline as compared to PD*gbawildtype*. Moreover, survival rates are shorter when compared to PD*gbawildtype* (Brockmann et al. 2015b; Cilia et al. 2016). In a British cohort, after 10 years of disease duration, 46% of PD*gba* remained dementia-free in...
Table 1 Excerpt of variants in the *GBA* gene detected in PD patients stratified by mutation severity

| Variant        | Legacy name | Suggested PD severity | References                           |
|----------------|-------------|-----------------------|--------------------------------------|
| p.S5N          | S(-35)N     | VUS                   | PMID: 26000814                       |
| p.R8T          | R(-32)T     | VUS                   | PMID: 26296077                       |
| p.P12S         | P(-28)S     | VUS                   | PMID: 26296077                       |
| p.K13R         | K(-27)R     | VUS                   | PMID: 18160183 PMID: 17059888         |
| p.I20V         | I(-20)V     | VUS                   | PMID: 26422360                       |
| p.L25V         | L(-15)V     | VUS                   | PMID: 23225227                       |
| c.84dupG       |             |                       | PMID: 15525722 PMID: 16185900         |
| p.G39R         | G(-1)R      | VUS                   | PMID: 27397011                       |
| c.115+1G>A     | IVS2+1G>A   | Severe                | PMID: 18434642 PMID: 16185900         |
| p.K46E         | K7E         | VUS                   | PMID: 19286695                       |
| c.149_150insGTAT|            | Severe                | PMID: 28890071                       |
| p.V56F         | V17F        | VUS                   | PMID: 29140481                       |
| p.C62W         | C23W        | Mild/severe           | PMID: 29140481 PMID: 24434810        |
| p.G74A         | G35A        | VUS                   | PMID: 28361101                       |
| p.R78H         | R39H        | VUS                   | PMID: 20425034                       |
| p.Y79C         | Y40C        | VUS                   | PMID: 29140481                       |
| p.R83C         | R44C        | VUS                   | PMID: 20425034                       |
| c.307+1G>A     | IVS3+1G>A   | Mild/severe           | PMID: 28830825                       |
| c.334_338del   |             |                       | PMID: 25518742 PMID: 32764102        |
| p.V117A        | V78A        | Mild/severe           | PMID: 28030538 PMID: 18338393        |
| p.G119R        | G80R        | VUS                   | PMID: 20947659                       |
| p.L144R        | L105R       | Mild                  | PMID: 22803570 PMID: 19793665        |
| p.G152A        | G113A       | Mild/severe           | PMID: 20947659 PMID: 18338393        |
| p.I158L        | I119L       | VUS                   | PMID: 20947659                       |
| p.R159W        | R120W       | Severe                | PMID: 17702778 PMID: 16185900        |
| p.R159Q        | R120Q       | Severe                | PMID: 34779914 PMID: 16185900        |
| p.M162T        | M123T       | Mild                  | PMID: 22173904 PMID: 17059888        |
| p.S164N        | S125N       | Severe                | PMID: 20947659 PMID: 12838552        |
| p.R170C        | R131C       | Severe                | PMID: 19286695 PMID: 16185900        |
| p.R170S        | R131S       | VUS                   | PMID: 18541817                       |
| p.T173P        | T134P       | Mild/severe           | PMID: 26296077 PMID: 16185900        |
| p.D179H        | D140H       | Mild                  | PMID: 20425034 PMID: 16185900        |
| p.L183V        | L144V       | VUS                   | PMID: 22173904                       |
| p.R202*        | R163X       | Severe                | PMID: 20425034 PMID: 16185900        |
| p.R202Q        | R163Q       | VUS                   | PMID: 18541817                       |
| p.Q205*        | R166X       | Severe                | PMID: 29140481                       |
| p.V211L        | V172L       | VUS                   | PMID: 23225227                       |
| p.S212*        | S173X       | Severe                | PMID: 20947659 PMID: 16185900        |
| c.636_637insTTTC|             | Severe                | PMID: 29140481                       |
| p.L213P        | L174P       | VUS                   | PMID: 17462935                       |
| p.S216T        | S177T       | VUS                   | PMID: 23225227                       |
| p.W223R        | W184R       | Severe                | PMID: 23225227 PMID: 10679038        |
| p.K225R        | K186R       | VUS                   | PMID: 19945510                       |
| p.N227S        | N188S       | Severe                | PMID: 19433656 PMID: 12204005        |
| p.N227K        | N188K       | Severe                | PMID: 28890071 PMID: 10649495        |
| p.V230G        | V191G       | Severe                | PMID: 19433656 PMID: 20729108        |
| p.G232W        | G193W       | Severe                | PMID: 19433656 PMID: 27042680        |
| p.G232E        | G193E       | VUS                   | PMID: 19286695                       |
| p.G234W        | G195W       | Severe                | PMID: 28030538 PMID: 16185900        |
| p.G234E        | G195E       | Severe                | PMID: 27717005 PMID: 15967693        |
| Variant | Legacy name | Suggested PD severity | References |
|---------|-------------|----------------------|------------|
| p.S235P | S196P       | Severe               | PMID: 26296077 PMID: 10649495 |
| p.L236F | L197F       | Severe               | PMID: 21856586 PMID: 16185900 |
| p.K237T | K198T       | VUS                  | PMID: 14728994 |
| p.P240H | P201H       | Severe               | PMID: 22387070 PMID: 20729108 |
| p.G241R | G202R       | Severe               | PMID: 20947659 PMID: 16185900 |
| p.Y244C | Y205C       | Severe               | PMID: 27294386 PMID: 11933202 |
| p.F252I | F213I       | Severe               | PMID: 19433656 PMID: 16185900 |
| p.F252V | F216V       | VUS                  | PMID: 28030538 |
| p.F255Y | F216Y       | Mild                 | PMID: 20425034 PMID: 16185900 |
| p.L256P | L217P       | VUS                  | PMID: 23225227 |
| p.Y283* | Y244X       | Severe               | PMID: 29140481 |
| p.F285L | F246L       | VUS                  | PMID: 22282650 |
| p.H294Q | H255Q       | Severe               | PMID: 19383421 PMID: 16185900 |
| p.R296Q | R257Q       | Severe               | PMID: 19286695 PMID: 16185900 |
| p.I299T | I260T       | Severe               | PMID: 22173904 PMID: 15967693 |
| p.R301C | R262C       | VUS                  | PMID: 28030538 |
| p.R301H | R262H       | VUS                  | PMID: 18987351 |
| p.L303I | L264I       | Mild/severe          | PMID: 25518742 PMID: 29625627 |
| p.G304S | G265S       | VUS                  | PMID: 28030538 |
| c.914delC|             | Severe               | PMID: 26296077 PMID: 16185900 |
| p.P305L | P266L       | Severe               | PMID: 27717005 PMID: 11783951 |
| p.S310G | S271G       | Mild                 | PMID: 18541817 PMID: 21779299 |
| p.R316C | R277C       | Mild                 | PMID: 22387070 PMID: 22375149 |
| c.953delT|             | Severe               | PMID: 22968580 PMID: 16185900 |
| p.T336S | T297S       | VUS                  | PMID: 27094865 |
| p.Y343C | Y304C       | Severe               | PMID: 20947659 PMID: 16185900 |
| p.W351R | W312R       | Severe               | PMID: 28030538 PMID: 22429443 |
| p.L353V | L314V       | VUS                  | PMID: 25518742 |
| p.F355I | F316I       | VUS                  | PMID: 26296077 |
| p.T362I | T323I       | Mild                 | PMID: 20425034 PMID: 1301953 |
| p.L363P | L324P       | Mild/severe          | PMID: 23588557 PMID: 16185900 |
| p.E365K | E326K       | Risk                 | PMID: 14728994 PMID: 27648471 |
| p.R368C | R329C       | Mild                 | PMID: 14728994 PMID: 17059888 |
| p.R368H | R329H       | VUS                  | PMID: 19383421 |
| p.L375P | L336P       | Mild/severe          | PMID: 20425034 PMID: 16185900 |
| p.S378L | S339L       | VUS                  | PMID: 21856586 |
| p.G383S | G344S       | VUS                  | PMID: 20425034 |
| p.F386L | F347L       | VUS                  | PMID: 22387070 |
| p.L393P | L354P       | VUS                  | PMID: 23225227 |
| p.W396R | W357R       | VUS                  | PMID: 28830825 |
| p.R398* | R359X       | Severe               | PMID: 21779299 PMID: 16185900 |
| p.S403N | S364N       | Mild/severe          | PMID: 20947659 PMID: 11259172 |
| p.I407T | I368T       | VUS                  | PMID: 28361101 |
| p.T408M | T369M       | Risk                 | PMID: 14728994 PMID: 27648471 |
| p.T408= | T369T       | VUS                  | PMID: 28399184 |
| p.N409S | N370S       | Mild                 | PMID: 14728994 PMID: 16185900 |
| p.N409K | N370K       | Mild/severe          | PMID: 20425034 PMID: 16185900 |
| p.L410I | L371I       | VUS                  | PMID: 20425034 |
| p.V414L | V375L       | Mild                 | PMID: 25518742 PMID: 16185900 |
Table 1 (continued)

| Variant     | Legacy name | Suggested PD severity | References                                      |
|-------------|-------------|-----------------------|------------------------------------------------|
| p.V414G     | V375G       | Mild/severe           | PMID: 23225227 Farah P Daniel P El Khoury G El Rachkidi R Tohme A. Early onset, but late diagnosis of a rare disease. Intern Med Open J. 2019; 3(1): 1–3 |
| p.G416S     | G377S       | Severe                | PMID: 20947659 PMID: 22429443                   |
| p.G416D     | G377D       | VUS                   | PMID: 28830825                                  |
| p.W417G     | W378G       | Severe                | PMID: 21856586 PMID: 32764102                   |
| p.D419N     | D380N       | Severe                | PMID: 20425034 PMID: 21982627                   |
| p.D419A     | D380A       | Severe                | PMID: 19286695 PMID: 16185900                   |
| p.D419V     | D380V       | VUS                   | PMID: 22812582                                  |
| c.1263_1317del | RecΔ5    | Severe                | PMID: 19286695 PMID: 16185900                   |
| p.N425K     | N386K       | Severe                | PMID: 24997549 PMID: 33176831                   |
| p.P426L     | P387L       | Mild/severe           | PMID: 28361101 PMID: 8937765                    |
| p.E427K     | E388K       | VUS                   | PMID: 20947659 PMID: 22820396                   |
| p.P430L     | P391L       | Mild/severe           | PMID: 25957717 PMID: 16185900                   |
| p.N431S     | N392S       | VUS                   | PMID: 22812582                                  |
| p.W432R     | W393R       | Mild                  | PMID: 22173904 PMID: 18847161                   |
| p.W432*     | W393X       | Severe                | PMID: 24126159                                  |
| p.V433L     | V394L       | Severe                | PMID: 18434642 PMID: 16185900                   |
| p.N435T     | N396T       | Mild                  | PMID: 18160183 PMID: 16185900                   |
| p.V437I     | V398I       | Mild                  | PMID: 22968580 PMID: 17059888                   |
| c.1309delG  | L409H       | Severe                | PMID: 17462935 PMID: 16185900                   |
| p.F465V     | F426V       | VUS                   | PMID: 28030538                                  |
| p.P467S     | P428S       | VUS                   | PMID: 24997549                                  |
| c.1439_1445del | K441N   | Severe                | PMID: 22968580 PMID: 22429443                   |
| p.K480N     | K443N       | VUS                   | PMID: 28361101                                  |
| p.D482N     | D443N       | VUS                   | PMID: 19286695                                  |
| c.1447-1466delinsTG | L444P | Severe                | PMID: 14728994 PMID: 16185900                   |
| p.L483P     | L444R       | Severe                | PMID: 27717005 PMID: 16185900                   |
| p.L483R     | L444T       | VUS                   | PMID: 28030538                                  |
| p.A485T     | A446T       | VUS                   | PMID: 20947659                                  |
| p.A485A     | A446A       | VUS                   | PMID: 28830825                                  |
| p.V486E     | V447E       | Mild/severe           | PMID: 28834018 PMID: 22344629                   |
| p.L488L     | L449L       | VUS                   | PMID: 28030538                                  |
| p.P491L     | P452L       | VUS                   | PMID: 20947659                                  |
| p.D492N     | D453N       | VUS                   | PMID: 28030538                                  |
| p.G493D     | G454D       | VUS                   | PMID: 30363439                                  |
| p.V496A     | V457A       | VUS                   | PMID: 28830825                                  |
| p.V496D     | V457D       | VUS                   | PMID: 28030538                                  |
| p.V499L     | V460L       | VUS                   | PMID: 26296077                                  |
| p.V499M     | V460M       | Mild/severe           | PMID: 20425034 PMID: 16185900                   |
| p.N501K     | N462K       | Severe                | PMID: 23413260 PMID: 16185900                   |
| p.R502C     | R463C       | Severe                | PMID: 19286695 PMID: 16185900                   |
| p.R502P     | R463P       | Mild/severe           | PMID: 27717005 PMID: 16185900                   |
| p.R502H     | R463H       | Severe                | PMID: 20947659 PMID: 22429443                   |
| c.1505+1G>T | IVS10+1G>T  | Mild/severe           | PMID: 25249066 PMID: 23430543                   |
| c.1506-1G>A | IVS10-1G>A  | Severe                | PMID: 21745757 PMID: 7694727                    |
| p.S504P     | S465P       | VUS                   | PMID: 23225227                                  |
comparison to 68% of PDGBA_wildtype. After 15 years, 64% of the surviving PDGBA_wildtype remained dementia-free. At that time point, all PDGBA had developed dementia or already died. Mean time to dementia was 8.3 years in PDGBA compared to 13.7 years in PDGBA_wildtype. Similarly, at 5 year disease duration, 67.5% of PDGBA had reached HY stadium 3, compared to 43% of PDGBA_wildtype. Mean time to Hoehn and Yahr staging 3 was 4.7 years in PDGBA compared to 6.8 years in PDGBA_wildtype (Stoker et al. 2020). Similar results were reported in a large longitudinal cohort of Italian patients with a clearly more aggressive pattern depending on GBA variant severity (Cilia et al. 2016). Interestingly, a recent study reports that PDGBA who are treated with deep brain stimulation (DBS) in the subthalamic nucleus (STN) showed an even more rapid cognitive decline compared to PDGBA without DBS as well as PDGBA_wildtype with and without DBS. This finding suggests that the additive effect of GBA variants and STN-DBS negatively impact cognition and that presurgical genetic screening should be considered (Pal et al. 2020). Similar results were reported in a large longitudinal cohort of Italian patients with a clearly more aggressive pattern depending on GBA variant severity (Cilia et al. 2016). Interestingly, a recent study reports that PDGBA who are treated with deep brain stimulation (DBS) in the subthalamic nucleus (STN) showed an even more rapid cognitive decline compared to PDGBA without DBS as well as PDGBA_wildtype with and without DBS. This finding suggests that the additive effect of GBA variants and STN-DBS negatively impact cognition and that presurgical genetic screening should be considered (Pal et al. 2020). Further studies are needed for replication and to evaluate the underlying pathophysiological mechanisms.

The typical motor manifestation of PD is preceded by a prodromal phase that is characterized by a variety non-motor and early motor signs (Berg et al. 2015). Non-motor symptoms include among others hyposmia, autonomic dysfunction, and neuropsychiatric symptoms, whereas reduced arm swing and bradykinesia indicate early motor signs. However, type, prevalence, time of occurrence, and rate of progression of these prodromal symptoms are variable between patients. Given the findings from the manifest disease phase in PDGBA with the pronounced non-motor profile and more rapid disease progression, we retrospectively assessed patient’s perception of their individual prodromal phase before PD diagnosis. Comparing PDGBA and PDGBA_wildtype, we could show that: (i) PDGBA demonstrate a higher prevalence of prodromal symptoms and a shorter prodromal phase with almost parallel beginning of non-motor and early motor signs before PD diagnosis. Contrary, PDGBA_wildtype show a long prodromal interval starting with non-motor symptoms long before early motor signs manifested. (ii) PDGBA with severe variants reported the highest total amount of prodromal signs. These findings suggest that complexity of symptoms known from the manifest disease might be present already in the prodromal phase (Zimmermann et al. 2018). Similarly, prospective studies found that prodromal GBA variant carriers present with more pronounced deterioration of motor and non-motor symptoms, specifically cognitive decline and hyposmia when compared to healthy controls without GBA variant (Avenali et al. 2019; Beavan et al. 2015; Mullin et al. 2019). Another study in patients with REM-sleep behaviour disorder (RBD) reports that GBA variants are associated with accelerated phenoconversion to PD and/or dementia in this specific cohort (Honeycutt et al. 2019).

**GBA variants are an important genetic risk factor for Dementia with Lewy Bodies (DLB)**

The important finding that PDGBA shows pronounced and early development of dementia prompted the community to perform a large multicenter analysis across 11 centres evaluating GBA variants in 721 cases with DLB, which represents a clinico-pathological continuum to PD. With an even higher OR than seen in PD, GBA variants are also strongly associated with DLB (8.28). Similar to PD, GBA variants predispose to an earlier age at onset, more pronounced disease severity, and a more rapid disease course compared to PDGBA_wildtype. This finding suggests that GBA variants represent an important genetic risk factor for DLB and that genetic testing should be considered in patients with a strong family history for PD or DLB.
severity/progression and rather “pure” form of DLB without concomitant Alzheimer’s profile as defined by CSF p-tau/ Aβ1-42 ratio (Nalls et al. 2013; van der Lee et al. 2021). This study further supports GBA variants as a significant genetic risk factor for synucleinopathies and confirmed the overall impression that GBA-associated Parkinsonism predisposes to an increased incidence of dementia (Fig. 1).

Pathomechanisms in PD_{GBA}

Experimental evidence from cell models suggests that GBA variants result in disrupted protein folding of GCase in the endoplasmic reticulum (ER), impaired trafficking of GCase from the ER to Golgi and ultimately in lower lysosomal GCase enzyme activity. This in turn causes a build-up of glucosylceramides (GlcCer) and glucosylsphingosines (GlcSph) (Beutler 1992) and impairs lysosomal function and thereby the degradation of α-synuclein (Mazzulli et al. 2011).

**GBA variants predispose to accelerated α-synuclein aggregation and Lewy-body pathology**

Post-mortem studies show enhanced aggregation and propagation of α-synuclein not only in the substantia nigra and putamen but also wide-spread neocortical Lewy-body pathology in brain tissue of PD_{GBA} and DLB_{GBA} (Neumann et al. 2009; Gundner et al. 2019).
The field of PET imaging markers to assess the cerebral load of α-synuclein in-vivo is difficult. However, this month [03(2022)] first positive results were reported at the AD/PD Conference for a new PET tracer developed by AC Immune to distinguish multiple system atrophy (MSA) from healthy controls and patients with other forms of α-synuclein (PD, DLB). Therefore, research in PD has focused on CSF. Yet, it is unclear whether CSF profiles of α-synuclein species reflect brain pathology. Cross-sectional and longitudinal analyses in PDGBA_wildtype and PDGBA demonstrated decreased CSF levels of total α-synuclein compared to healthy controls with the highest decrease in PDGBA patients carrying severe variants (Malek et al. 2014; Mollenhauer et al. 2019; Lerche et al. 2020, 2021a). Correspondingly, the same pattern was also reported in patients with DLBGBA (Lerche et al. 2019a). However, a substantial inter-individual variability and overlap with healthy controls is seen, so that CSF levels of total α-synuclein are not ideal. Recently, the ultrasensitive assays real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA) have been successfully implemented. These assays exploit the seeding capacities of prion or prion-like proteins (PMCA) have been successfully implemented. These assays exploit the seeding capacities of prion or prion-like proteins as an amplification strategy to reveal minute amounts of disease-specific protein aggregates in CSF (Fairfoul et al. 2016; Shahnawaz et al. 2017). Both methods are highly sensitive (88–96%) and specific (83–98%) for α-synuclein aggregates and Lewy-body pathology in PD and DLB as assessed in matched CSF/brain samples compared to healthy controls and other forms of dementia and parkinsonism (Rossi et al. 2020; Kang et al. 2019). However, histopathological findings in some genetic forms of PD are remarkably variable. While PDGBA show extensive Lewy-body pathology, most PD patients with bi-allelic mutations in the recessive gene PRKN (PDrecessive_bi-allelic) show nigral degeneration without Lewybodies (Schneider and Alcalay 2017). Also, histopathology in PD patients with LRRK2 mutations (PDLRRK2) is variable, including typical Lewy-body pathology, misfolded tau deposition, or nigral degeneration without Lewy-body (Zimprich et al. 2004; Heckman et al. 2016; Kalia et al. 2015). This prompted us to evaluate CSF α-synuclein seeding capacities with RT-QuIC in two large cohorts of PD and DLB patients enriched for genetic forms. Remarkably, PDGBA (93%) and DLBGBA (100%), especially those carrying severe variants, showed the highest percentage of positive α-synuclein seeding and the most pronounced α-synuclein seeding kinetics. In contrast, PRKN (PDrecessive_bi-allelic) did not show CSF α-synuclein seeding at all, whereas those carrying heterozygous mutations in these recessive genes showed less α-synuclein seeding than PDLRRK2 showed a reduced rate of α-synuclein seeding (78%) compared to PDGBA_wildtype (Brockmann et al. 2021). The heterogeneity in α-synuclein seeding activity among the different genetic forms mirrors histopathological findings in these cases and highlight the value of α-synuclein seeding activity as an in-vivo marker of Lewy-body pathology.

The accelerated cognitive decline PDGBA makes this subgroup of PD a good model to study CSF profiles that are associated with cognitive impairment. In general, limbic and/or cortical Lewy-body pathology is hypothesized to be the main substrate forcing driving cognitive decline in PD (Aarsland et al. 2005). In more recent years, it became clear that a considerable proportion of PD patients who developed dementia in their disease course show concomitant amyloid-beta and tau pathology at autopsy in addition to the typical Lewy-body pathology (Halliday et al. 2008; Compta et al. 2011). Correspondingly, reduced CSF levels of Amyloid-beta1-42 (Aβ1-42) and/or elevated CSF levels of total-Tau (t-Tau) and phospho-Tau (p-Tau) have been reported to be associated with cognitive impairment in PD (Brockmann et al. 2015a, 2017; Lerche et al. 2019b; Kang et al. 2016). However, this seems not to be the case in PDGBA as CSF levels of Aβ1-42, t-Tau, and p-Tau are similar to those seen in healthy control individuals. In light of the CSF profiles of reduced total levels of α-synuclein and the prominent α-synuclein seeding activity, the pronounced cognitive decline in PDGBA is driven by α-synuclein aggregation and cortical Lewy-body pathology.

Taken together, these histopathological and CSF characteristics of predominant and accelerated α-synuclein-driven Lewy-body pathology make PDGBA and DLBGBA a role model to study pathways leading to α-synuclein aggregation and highlight these patient cohorts as prime candidates for clinical trials targeting α-synuclein.

GCase deficiency and α-synuclein aggregation

Heterozygous variants in the GBA gene are associated with a reduction of GCase protein levels and GCase enzyme activity in cell and animal models as well as in a variety of patient-derived biomaterials (Lerche et al. 2021a; Alcalay et al. 2015, 2020; Schondorf et al. 2014; Paciotti et al. 2019). Again, the degree of reduction is dependent from variant severity. Interestingly, GCase activity is also reduced in PDGBA_wildtype, albeit to a lesser degree (Parnetti et al. 2017).

There is reasonable evidence from different cell models including induced pluripotent stem (IPS) cell-derived human dopaminergic midbrain neurons and human midbrain organoids that deficiency of the GCase enzyme is paralleled by increased levels of intracellular α-synuclein, specifically α-synuclein species susceptible to aggregation such as high molecular weight and decreased tetramer/monomer ratio (Schondorf et al. 2014; Kim et al. 2018; Magalhaes et al. 2016; Aflaki et al. 2016; Mazzulli et al. 2016; Jo et al. 2021). Correspondingly, post-mortem studies in PDGBA and DLBGBA and to a lesser degree also in PDGBA_wildtype and
DLB

GBA

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Therapeutic targets in GBA-associated PD

Based on the knowledge of the molecular mechanisms underlying PD, pathway-specific treatment options are beginning to emerge.

GCase

The significant reduction of GCcase protein levels and GCcase enzyme activity offer a plausible therapeutic rational to
either increase GCase protein levels or enhance enzyme activity. Unfortunately, intravenous enzyme replacement therapy is not possible due to insufficient central nervous system penetration.

Gene therapy with adeno-associated virus (AAV)-based vectors promoting GBA overexpression. This approach reduced α-synuclein accumulation, improved lysosomal function and lipid turnover, and attenuated deficits in working memory and fine motor performance in α-synuclein mutant/overexpressing wild-type and GD rodent models (Rocha et al. 2015b; Glajch et al. 2021; Sardi et al. 2011). The AAV9-based vector PR001 increased GCase activity, reduced glucolipid substrate accumulation, and improved motor deficits in two mouse models of GCase deficiency (Abeliovich et al. 2021). Based on these results, a phase 1/2a non-randomized clinical trial with a single administration of PR001 into the cisterna magna is currently under investigation in PD patients with at least one pathogenic GBA variant. The study duration is 5 years. During the first year, patients will be evaluated for safety, tolerability, immunogenicity, biomarkers, and clinical efficacy measures. Patients will continue to be followed for an additional 4 years to monitor safety and selected biomarker and efficacy measures (NCT04127578).

GCase-enhancing small-molecule chaperones refold misfolded GCase in the ER and promote proper trafficking, thereby increasing lysosomal GCase protein levels. Interestingly, experimental data in cell and animal models with GBA variants suggest that the expectorant Ambroxol increases GCase availability via such mechanism (Kopytova et al. 2021; Ambrosi et al. 2015; Maegawa et al. 2009; Magalhaes et al. 2018; McNeill et al. 2014; Yang et al. 2022; Migdałska-Richards et al. 2016). These findings led to a proof-of-principle phase 2 open-label study with Ambroxol in 17 PD patients with and without GBA variants. Ambroxol was well tolerated and CSF GCase protein levels as well as CSF levels of α-synuclein increased by 35% and 13%, respectively. However, CSF GCase enzyme activity decreased by 19% which might be explained by an inhibitory effect of Ambroxol on GCase activity within acellular human CSF with a neutral pH (Mullin et al. 2020).

More strikingly, a recent publication could show that the small-molecule S-181 increases wild-type GCase activity in iPSC-derived dopaminergic neurons not only from PDGBA but also from PDwildtype as well as from patients with other PD-related gene mutations in LRRK2, DJ-1, and PARKN who also had decreased levels of GCase activity. S-181 treatment of these PD iPSC-derived dopaminergic neurons partially restored lysosomal function and lowered accumulation of oxidized dopamine, GlcCer, and α-synuclein (Burbulla et al. 2019). These recent findings highlight not only the importance of lysosomal dysfunction in the pathophysiology of the prototype PDGBA but also the significance of this pathway, possibly in concert with additional pathways such as mitochondrial dysfunction, for PD in general.

Substrate reduction therapy

Substrate reduction therapy to reduce GlcCer production with penetration into the central nervous system is available for oral application in GD. Venglustat has been evaluated in a phase 2 randomized trial (MOVES-PD, NCT02906020) in PDGBA. The compound clearly reduced CSF levels of GlcCer in a dose-dependent manner in plasma and CSF. However, the study was stopped prematurely, since patients in the verum group showed enhanced clinical deterioration suggesting an off-target effect with possible anti-dopaminergic activity.

Alpha-synuclein-targeting compounds

Targeting alpha-synuclein also seems a reasonable treatment option given the predominant α-synuclein aggregation and widespread Lewy-body pathology in PDGBA.

Conclusion and outlook

GBA-associated PD is remarkable for several reasons. The phenotypical trajectories show a faster disease progression with pronounced early cognitive decline and a clear dependency based on mutation severity. Importantly, the development of dementia is not associated with Amyloid-β pathology as shown instead in a relevant proportion of PD without GBA variants but rather due to predominant α-synuclein aggregation. The identified pathophysiological mechanisms highlight GCase deficiency and lysosomal dysfunction resulting in disrupted glycosphingolipid homeostasis and ultimately impaired α-synuclein degradation with enhanced aggregation. Again, these are dependent on mutation severity and offer different targets for individualized treatment options. However, the failure of the MOVES-PD trial (NCT02906020) demonstrates the challenges we are facing in translational research. Findings from GD as typical and clearly defined young-onset lysosomal storage lipid disorder due to bi-allelic mutations in GBA are not simply transferable into PD, a multifactorial disease of the elderly with possibly additional contributing factors (e.g., mitochondrial dysfunction and lifetime environmental exposure). Specifically, the pathophysiological mechanisms of impaired glycosphingolipid homeostasis leading to impaired α-synuclein degradation need more investigation. In this context, longitudinal patient cohorts with repeated collections of biomaterials, ideally starting in the prodromal stage followed up until death with brain donation, might inform
us on biomarkers that reflect the underlying pathological processes and possible read-outs for target engagement.

Future clinical trials in PD-GBA might incorporate the knowledge learned over the last years: (i) Patients should be stratified according to GBA variant severity with those carrying severe mutations to be preferentially included in proof-of-concept trials. (ii) The early cognitive decline based on predominant α-synuclein-driven pathology offers the opportunity to address PD-associated dementia with disease-modifying agents in a clearly defined prodromal phase preceding dementia and based on clear biological stratification.

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