

# Applications of iPSC-derived models of Gaucher disease

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Gaucher disease (GD) is an autosomal recessive disorder caused by loss-of-function mutations in the *GBA1* gene, which codes for the lysosomal hydrolase glucocerebrosidase (GCase). GCase deficiency leads to accumulation of un-metabolized glycolipid substrates, primarily in cells of the macrophage lineage. GD usually manifests with visceral, hematological, and skeletal involvement, and common symptoms include hepatosplenomegaly, anemia, thrombocytopenia, and osteopenia. More severe enzyme deficiency can also lead to neuronal glycolipid accumulation and central nervous system symptoms.

GD research has long sought effective cell models in order to pursue a better understanding of the pathophysiology of GD and to develop novel therapeutics. In the past few years the field has quickly pivoted towards the development of induced pluripotent stem cell (iPSC) lines from patients with GD. Recently, our group published a paper introducing several new iPSC lines derived from patients with GD, and characterizing macrophages differentiated from these GD iPSC lines. We also demonstrated that GD iPSC-derived macrophages phenocopy primary macrophages derived from peripheral blood monocyte cells (PBMCs) of patients with regards to several important disease-related traits, including enzyme deficiency, lipid storage, impaired chemotaxis, and impaired respiratory burst (1).

A recent editorial in this journal by Wheeler and Silence commented on our publication, highlighting the impact that this model and other similar iPSC macrophage models may have on both our understanding GD pathogenesis and the development of novel GD drugs (2). Other investigators have also begun to use GD iPSCs to explore defects in hematopoiesis, which has offered insight into elements of GD pathogenesis outside of macrophages (3). Additionally,

these cells also have the potential to help us better evaluate and understand the vast phenotypic variation that is encountered in this single gene disorder (4). However, the use of GD iPSCs as a research tool is still plagued by many of the same problems—most notably, low yield—that face PBMC-derived macrophages. In addition, due to the resource-intensiveness of iPSC production and use, in many situations it will remain advantageous to utilize PBMC-derived macrophages in order to study macrophages in GD. However, one field in which the use of GD iPSCs will be invaluable is in the rapidly expanding exploration of the link between *GBA1* and Parkinson disease (PD). As the number of publications regarding this topic continues to grow, we would like highlight some of the challenges of utilizing iPSCs in exploring this link.

## iPSCs and the link between *GBA1* and PD

It is now established that individuals bearing *GBA1* mutations have a significantly heightened risk of developing PD, a common neurodegenerative disease caused by loss of dopaminergic neurons in the substantia nigra pars compacta. And while there is some evidence that individuals with GD (i.e., with homozygous or compound heterozygous *GBA1* mutations) have an earlier average age of PD onset than carriers, individuals with GD and carriers have a similar likelihood of developing PD by the age of 80 (5). These findings suggest that GCase deficiency impacts some aspect of dopaminergic neuron function and/or survival. Furthermore, GCase activity is reduced in the brains of individuals with PD who have no *GBA1* mutations (6,7), suggesting that GCase may play a role in PD pathogenesis more broadly. However, the nature of this *GBA1*-PD link is still a matter of intense debate.

The details of PD pathogenesis are still largely a mystery, which complicates attempts to determine the role of *GBA1* in the disease. However, it is generally accepted that the self-assembly of  $\alpha$ -synuclein into neurotoxic oligomers and fibrils plays a direct causative role in PD (8). Much of the current discussion of this link asserts that, in cases where *GBA1* mutations are present, GCase deficiency plays a direct role in  $\alpha$ -synuclein accumulation and aggregation (9,10). However, only a small minority of *GBA1* mutation carriers goes on to develop PD (5,11). Compare this to the G2019S *LRKK2* mutation, which leads to PD in an autosomal dominant pattern with a penetrance of up to 74% by age 79 (12). While GCase likely plays a key role in PD pathogenesis, this low penetrance strongly suggests that GCase deficiency is not a direct or essential factor in  $\alpha$ -synuclein oligomerization (13).

In individuals with *GBA1* mutations that do develop PD, the disease likely arises in much the same way as sporadic PD—that is, as a result of a confluence of a variety of environmental and genetic factors. We have previously posited that in some cases, *GBA1* mutations may constitute a “second hit”, acting in concert with one or more additional sensitizing mutations to drive PD pathogenesis (14). Some families with *GBA1* mutations have no history of PD, while in other families the same *GBA1* mutations can lead to PD inheritance in an approximately autosomal dominant fashion. The existence of these two extremes supports the notion that *GBA1* combines with other genetic factors to drive PD pathogenesis (15). On the other hand, the fact that monozygotic twins bearing *GBA1* mutations can be discordant for PD indicates that environmental and acquired epigenetic factors also play a vital role in the development of *GBA1*-associated PD (16). Therefore, while a better understanding the *GBA1*-PD link may open the door to a better understanding of sporadic PD, in truth we may need to first uncover the environmental, epigenetic, and genetic factors that feed into the development of sporadic PD. Investigations of the *GBA1*-PD link using iPSC-derived neurons from single patients with both *GBA1* mutations and PD pathology are complicated by the difficulty of distinguishing which findings are the result of GCase deficiency and which are caused by more general PD-associated dysfunction, which remains poorly understood.

However, iPSCs from individuals with *GBA1* mutations may still be able to help us to sort this out. A recent study investigated the differences between iPSC-derived neurons from monozygotic twins with *GBA1* mutations who were

discordant for PD (16). Continued studies of iPSCs from twins or family members discordant for PD may help to elucidate specific factors that lead some individuals with *GBA1* mutations to develop PD while others do not. Also, comparing results in lines from multiple patients with GD disease and Parkinsonism with equal numbers of aged-matched patients with GD without PD may yield relevant differences. These studies may also identify “protective factors” that could provide insights into new therapeutic targets. Importantly, these same genetic or non-genetic risk factors identified in *GBA1*-associated Parkinsonism may play a role in the development of sporadic PD, which remains by far the most common form of the disease.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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