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Chapter

Genetic Risk Factors and Lysosomal Function in Parkinson Disease

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Abstract

Parkinson disease is a complex disease that has multiple genetic and environmental factors. To achieve the early diagnosis and to be able to modify the disease progression, efforts are being made to identify individuals at risk. About 20 year ago, an evidence of major prevalence of Parkinsonism in patients with Gaucher Disease reported by studies worldwide led to the putative involvement of the *GBA* gene. Nowadays, the link from a rare disease with a common disease is well known and it is confirmed that mutations in the *GBA* gene are the most important genetic risk factor. Apart from rare mutations, genetic association studied appointed common variants in genes well associated with familial cases as *LRRK2* and *SNCA* may also contribute to the increased risk for sporadic cases. Other common variants in the *MAPT* gene were also reported. At least, genetic studies have been observed an excessive burden of relevant variants in genes with lysosomal function. Thus, a synergistic action of variants in genes that codifies proteins involved with the lysosome may be a mean of modulating the risk. In this chapter, we review the most robust genetic risk factor and the relevance of lysosomal function for Parkinson disease.

Keywords: Parkinson, GBA, risk factor, lysosome, GWAS

1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease in humans and it is characterized by motor symptoms as muscular rigidity, resting tremor, bradykinesia, and postural instability and also by non-motor symptoms (hyposmia, constipation, depression, dementia, and postural hypotension, among others). These symptoms result primarily from the progressive loss of the dopaminergic neurons from the pars compacta of the mesencephalic substantia nigra and subsequent depletion of the dopamine neurotransmitter in the striatum, a central component of the basal ganglia that is responsible for the instigation and coordination of movements (**Figure 1**). The definitive diagnosis of PD is difficult being only confirmed with the presence of Lewy bodies, proteinaceous intracytoplasmic inclusion, in the reminiscent neurons of substantia nigra pars compacta and other regions in the brain postmortem analysis [1].

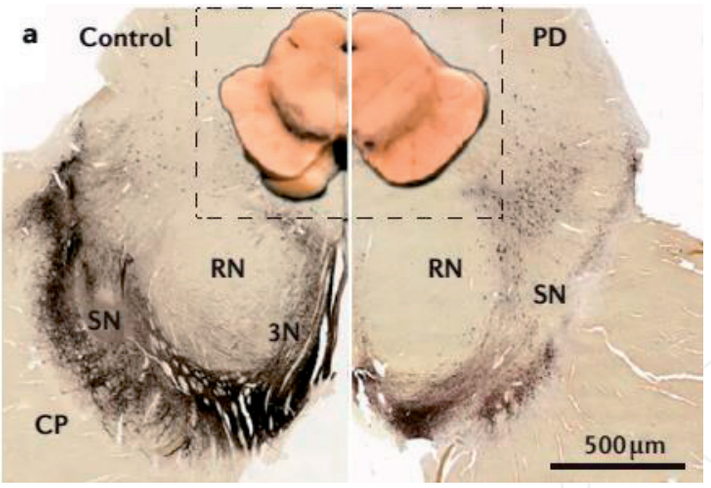

Figure 1.
Depigmentation of the substantia nigra (SN) (right panel) compared with control (left panel). Adapted from Ref. [1].

The etiology is not well understand, but PD is considered a complex disease, which counts with multiple genetic and environment factors. The most common is the sporadic PD for which the onset generally is late, after 60 years old. There is a rare form, the familial PD or monogenic PD (~10% of the cases), for which the disease is caused by mutations in a single gene and may present not only a late onset but also an earlier onset (below 45 years old) in some cases. Although less frequent, the study of monogenic forms of PD and their associated genes helps to understand the molecular basis of disease pathogenesis [1, 2].

Segregation studies of mutations in *SNCA* gene in large families with PD cases led to the discovery of the main protein involved in the disease pathogenesis, the α-synuclein. Shortly afterwards, postmortem studies in patients' brains revealed that this protein is the major component of Lewy bodies, in both sporadic and familial PD patients, reinforcing its important role in the development of PD [2–4]. Be it for genetic, environmental or both factors, the fact is that patients' brains do not have the soluble monomeric form of α-synuclein, which is easily degraded by lysosomal function, but the insoluble oligomeric forms [5, 6].

Nowadays, efforts have been directed to identify the individuals at risk of manifesting PD through clinical, genetic and biochemical markers in order to diagnose early and perhaps be possible to modify the progression of disease. For this purpose, genetic variations with the potential to alter the risk for PD have been widely researched. Both disease-causing variants and risk variants in genes associated with PD vary in frequency depending on ethnic background. Certain genetic variants may be a risk factor in an Asian population, but may not be statically significant in a European population, for example. The most robust and consistently replicated results are appointed to variants in the genes *LRRK2, MAPT, SNCA* and *GBA,* the last being the major genetic risk factor highlighting the importance of lysosomal pathway in the pathogenesis of PD [1–8].

2. Genetic risk factors

More than 20 years ago, Parkinson disease was understood as a disease caused by environmental factors only. It was from genetic analyzes in cases of familial PD that it was discovered that the genetic factor is also important and may even cause certain disease forms. Thus, we have monogenic PD, which can present a pattern

of inheritance defied as autosomal dominant or autosomal recessive. In 1997, the discovery of mutations in the *SNCA* gene as the cause of PD in certain families also helped scientists to better understand the etiopathology of this complex disease through the association between the duplication and triplication of the *SNCA* gene with altered α-synuclein protein expression and the disease progression. Since then, diverse other genes were associated with mutations that cause PD, among them the genes *LRRK2* and *VPS35,* that along with *SNCA* are altered in autosomal dominant cases, and *PINK1*, *PARKIN*, *DJ-1* that are altered in autosomal recessive forms [3, 8].

However, the genetics of PD are not simply composed of variants that cause the disease. More recently, the focus has been on genetic variants that do not lead to PD alone but increase the risk of developing the disease. Among the genetic risk factors associated with sporadic PD, rare high-impact variants and common low-impact variants have been identified by candidate gene studies and genome-wide association studies (GWAS). The complexity of the PD genetic increases even more due to several risk variants for PD that are heterogeneous and dependent on the genetic background of each population. Genetic variants can be associated with PD in some populations, but not in others [8, 9].

Two largest GWAS studies in 2014 and 2017 identified in total 28 independent PD-associated risk loci, mainly in *SNCA*, *LRRK2*, *MAPT* and *GBA*. Genetic risk factors are present in several genes involved in metabolic pathways that may be directly related to α-synuclein metabolism or involved in processes that affect cellular homeostasis [10, 11].

2.1 SNCA

It is worthy to emphasize the fact that genes that carry rare casual mutations of monogenic PD observed in previous family studies are not excluded of the possibility to also carry common variants that confer risk for developing PD. This is the case of *LRRK2* and *SNCA*.

So far, five point mutations (A53T, A30P and E46K) and two copy number variation (duplication and triplication) in the gene *SNCA* are well known to cause autosomal dominant PD indistinguishable of sporadic PD, or an early-onset PD if the triplication of the gene is present [12]. Recently, single nucleotide polymorphisms (SNP) in *SCNA* were reported in non-coding regions, suggesting that those variants play a role in the regulation of the genetic expression through modifications post-transcriptional as interacting with microRNA or altering alternative splicing mechanism [7].

In 1999, the association between REP1, a complex polymorphic microsatellite repeat in the promoter region, and PD was pointed out by [13]. Seven years later, Maraganore [14] confirmed this association with a larger meta-analysis study using more than 5000 samples from 11 sites. Further, functional analysis studies provided evidence that the length of alleles affects the protein expression: the 261 bp-long risk allele is associated with an upregulation of α-synuclein expression mimicking *SNCA* locus multiplication, whereas the 259 bp-long protective variant shows reduced gene expression [15].

In 2009, Simón-Sánchez et al. [16] used GWAS in a great sample and identified additional signals of association with PD from intro 4 to after the 3′ UTR. One year later, Mata et al. [17] showed possible association between rs356219 in the 3′ UTR region and α-synuclein plasma levels. To definitely ascertain which variants in this region alter the risk for PD, more studies are necessary in large and genetically diverse samples.

2.2 LRRK2

In the region of chromosome 12 is localized the *LRRK2* gene where several genetic variants have been found; however, segregation in families with monogenic PD and case-control studies demonstrated that only seven point variants (R1441G, R1441C, R1441H, Y1699C, G2019S, I2020T and N1437H) have enough evidence to be defined as cause of PD. This gene encodes a protein of the same name composed of domains with kinase activity, GTPase and several domains of interaction with other proteins, suggesting that its function changes depending on which proteins form complexes, the type of cells and the stage of development. Mutations in *LRRK2* gene are the most common cause of PD familial cases. The mutation G2019S is the most prevalent worldwide, and it is present in 4% of familial PD and is associated with an indistinguishable phenotype from the clinical manifestations of sporadic PD [12–18].

Besides the prevalence in rare monogenic PD, this mutation can also confer risk in the sporadic PD, being found in 1% of the cases. G2019S has a penetrance variable, and its carrier's risk to develop PD depends on age and ethnic background. The age-related risk has been estimated to be 28% at age 59, 51% at 69, and 74% at 79 years. The frequency is higher in North African, Middle Eastern and Ashkenazi Jewish PD patients [18, 19].

G2019S is frequent in most populations worldwide, but it is very rare in the Asian population where it accounts for less than 1% of *LRRK2* mutations. In contrast, most common genetic variants SNPs G2385R and R1628P are more frequent in Asian populations than in Caucasian populations. Those SNPs are associated with an increased risk of 2.2 fold and 1.84 fold to develop PD, respectively [20, 21]. Lately, regions close to *LRRK2* have been appointed by GWAS as increasing by 1.2 fold the risk for PD. This fact alerts that the regulation of the gene expression is important to develop this disease [8].

Those works reinforce the idea that genes can carry both rare disease-causing variants and common variants that increase the risk for PD, as seen in *SNCA* and *LRRK2*. Additionally, common variants present in those genes enhance the importance of their proteins' role in the disease and implicate that there is a common neurodegenerative process between sporadic and familial PD.

2.3 MAPT

The gene *MAPT* is frequently associated with other neurodegenerative diseases as Alzheimer disease and frontotemporal dementia (FDT). *MAPT* encodes for the microtubule-associated protein tau, whose role is to regulate microtubule dynamics and assemble microtubules into parallel arrays within axons, essential for normal axonal transport in neurons. Polymorphisms in this gene have been found to be an indisputable risk factor of the synucleinopathy. The H1 and H2 haplotypes represent two distinct clades of subhaplotypes ensued from an inversion of ~900 kb on chromosome 17q21, spanning the entire *MAPT* coding region, and are tagged, among others, by genotypes at two SNPs: rs9468 and rs1800547 [4–8].

The H1 haplotype and its subhaplotype H1c have been significantly associated with an increased risk for a number of neurodegenerative diseases. Several studies proposed the most common H1 haplotype as susceptibility factor for PD with an odds ratio of 1.5. Recent studies that investigated the association between H1 and specific PD clinical manifestation also observed the higher prevalence of H1 in patients with cognitive defects, as dementia and H1 homozygous PD patients showed an increased risk to manifest non-tremor dominant subtype, which is a worse clinical prognosis [22, 23].

The underlying biological mechanisms that link the *MAPT* locus (and tau protein) to neurodegeneration are not yet adequately characterized. Through the functional characterization of variants in the *MAPT* gene, some theories of the tau protein effect in PD involve increased tau expression; altered gene splicing promoting aggregation; and altered 4/3 repeated transcript ratio. The emerging concept of H1 pathogenicity points to the role of each tau isoforms expressed rather than the overall number of transcripts.

According to this model, the H1 haplotype is associated with an underexpression of a protective isoform and an overexpression of the detrimental variant, which lead to a subtle neuronal dysfunction that accumulates over the years and induces or accelerates cellular degeneration [22–24]. However this locus harbors many genes and the extended linkage disequilibrium means that the tau protein may be not the cause of neurodegeneration and its DNA sequence is just close to the casual locus. Thus, while *MAPT* is a candidate, we cannot be certain that this is the true biological mediator of risk [7–16].

Diverse studies identified *MAPT* locus variants as a risk factor for PD, but it may not be true to any population. In the Caucasian population, there was this association, while it was absent in the Japanese population. This observation has potential implications for the analysis of complex traits across populations such as genetic heterogeneity, particularly at minor risk loci, highlighting the power of comparing GWAS across different populations [9–16].

Despite having a modest effect (less than 30% of the change in risk), these common variants can have a considerable impact when combined. Results from a 2015 study revealed that patients at an early age of onset of symptoms had a higher polygenic combination of risk variants than patients with a late onset. This demonstrates the possible effect of the synergistic value of the changes caused by these variants to modulate the PD clinic, such as the age of onset of symptoms [12].

3. GBA: the principal genetic risk factor for Parkinson disease

The *GBA* gene was initially described in association with a rare lysosomal storage disease (LSD) called Gaucher disease (GD). When mutated in homozygosis, depending on the mutation present, the resulting enzyme is malformed or even no enzyme is synthesized leading to enzyme glucocerebrosidase (GCase) partial or total deficiency and glucosylceramide (GlcCer) accumulation. The symptoms are multisystemic, with the brain, spleen, liver and bone marrow being the main organs affected. The presence and intensity of those symptoms differ between the three types of GD (GD1, GD2 and GD3). The heterozygous individuals do not present any clinical manifestation; however, in the last years, this perspective has changed [25, 26].

Further a number of studies have recorded the occurrence of parkinsonian manifestations in patients with GD and their relatives [27, 28]. In ref. [29] was showed that *GBA* mutations homozygous individuals have 21.4 fold increased risk to develop PD with probability of 9–12% to manifest motor symptoms before 80 years old. Despite being low, this risk is considerably higher than in the same age group in general population, 3%. The *GBA* and PD association was confirmed in the Jewish Ashkenazi, which showed a prevalence of *GBA* mutations in heterozygosis and homozygosis individuals in the PD population that by far outweighs the reported prevalence of mutations in other susceptibility genes for PD, as *Parkin* and *SNCA* [30].

Researchers worldwide have attempted to validate the same association in populations from many different genetic backgrounds [31–41]. In 2009, an international

and multicenter study with a great sample of approximately 5000 PD patients and equal number of controls provided the definitive proof found for this association with an odds ratio greater than five (OR 5.3) and showed that mutations N370S and L444P are the most frequent in this gene. In other words, *GBA* mutation genes were recognized as the major genetic risk factor for PD until now [42].

In addition to alter the risk to manifest the disease, the presence of *GBA* mutations has also the potential to modify PD phenotype such as age of onset. The modulatory effects best described in the literature investigated the association with age of onset and declined cognitive. The association to other symptoms and patients survival rate has been not yet approached in more detail.

Whether in heterozygosis or in homozygosis individuals (GD patients), the age of onset of symptoms apparently occurs earlier than in PD patients without mutations, usually between the fourth and sixth decade of life [28–43]. In relation to symptoms is noticeable a cognitive decline earlier in PD patients with *GBA* mutations (PD-GBA) [26–45]. Dementia is one of the clinical manifestations that most affects the patient's quality of life and it is more frequent in GBA mutation carriers than in non-carriers. Longitudinal studies have shown that PD-GBA patients have a risk three times higher than patients without GBA mutations to present dementia [26, 44, 46]. Neuroimaging exams support this association by showing more expansive synucleinopathy in the neocortical and subcortical areas of PD-GBA patients, increasing the risk to dementia, psychosis and postural hypotension [46].

A few studies have evaluated the survival rate, if there is a greater risk of death in PD-GBA patients than in those without any mutations. A 2014 study found lower survival for the carrier group, but had a weak statistical value [47]. However, in 2016, a study with the largest sample number ever described replicated the same result with powerful statistical significance reinforcing this conclusion. It was defined in this study that there is a twice greater risk of mortality among PD-GBA patients. One explanation may be the increased presence of non-responsive levodopa motor impairments such as dysphagia and non-motor impairments such as orthostatic hypotension in the group of PD-GBA. There was no difference in disease duration compared to non-carriers, but patients were significantly younger at the time of death [46].

3.1 Genotype-phenotype correlations

Researchers have also observed different *GBA* mutations having a different impact in the clinical manifestations. Mutations generally associated with defined neuropathic forms of GD (GD type 2 and 3), such as L444P, are classified as severe mutations, while others associated with GD type 1, such as N370S, are classified as mild mutations [26–48].

A meta-analysis study included populations from North, Central and South America, Western and Eastern Europe, North Africa, Asia and Ashkenazi Jews, and its results showed a clear and significant differentiated effect comparing mild and severe mutations on the risk of developing PD and the age of onset of symptoms not only in Ashkenazi populations, but also worldwide. Severe mutations such as L444P confer a three to four times increased risk for its carriers to develop PD and are associated with the onset of symptoms 5 years earlier than mild mutations. The average age found for severe mutations was 53.1 (±11.2), whereas the average age for mild mutations was 58.1 (±10.6) [26].

The type of mutation was also relevant in modulating the cognitive impairments of PD patients. Ref. [46] observed that severe mutations conferred a higher risk of dementia for its carriers. The risk was three times greater compared to patients with mild mutations and five times greater when compared to the risk for PD without

GBA mutations. Another longitudinal study with a similar sample number corroborated with the increased risk of dementia for patients with severe mutations versus non-carriers [44]. With regard to other symptoms, motor impairments appear to be similar between patients with mild mutations and non-carriers, while those with severe mutations appear to be more aggravated and seem to have a higher frequency of non-motor symptoms such as psychosis, apathy and postural hypotension [46].

Patients' survival does not seem to differ when comparing the types of mutations with each other. However, when compared separately with non-carriers, mild mutations do not differ statistically from non-carriers, while mortality was shown to be greater for carriers of severe mutations than in non-carriers [46].

Due to the discovery and increasing number of proofs supporting the great influence of *GBA* mutations in PD, some authors consider the possibility of reclassifying them from risk factors for agents causing autosomal dominant PD [43, 49].

4. GBA-associated PD in different populations

Given the multifactorial etiology of PD, the different environment and ethnicity of a population may impact in the different results seen among the papers that investigated the frequency of *GBA* mutations in PD patients. Other possible causes of this variation can be the use of different techniques and methodologies.

The highest frequencies of mutations of the *GBA* gene have been found in PD patients of Ashkenazi Jewish ancestry, with rates of 13.7–31.3% in comparison with 4.5–6.2% in control groups [26–28]. The frequencies recorded in PD patients in non-Jewish populations representing other populations, such as Italians, Caucasian Americans, Greeks, Brazilians, British and Taiwanese, are invariably much lower—3.5% to 12.0%—while controls from the same populations range from 0% to 5.3% [31–41]. Previously, in North Africa, a study found no association between PD and mutations of the *GBA* gene; however, a more recent African study data suggested a risk association between mutations in the *GBA* gene and PD [37]. The lowest rate recorded to date was 2.3% in Norwegian PD patients, compared with 1.7% in the control [49].

The genetic background can also impact the frequency even within the same country. In Brazil, four studies evaluated the association between GBA and PD, with variances in frequencies depending on the region (**Table 1**). The North region had twice as many cases of PD patients with GBA mutations (7.4%) compared to the frequencies of the South and Southeast regions (3.5%) with a similar sample number. The fact may be explained by the different genetic composition of the North region, which, despite also has a European origin, has a higher Amerindian ancestry than the Southern Brazil, which is almost exclusively from European ancestry [31–50].

Greek and Italian studies have found significant differences comparing PD patients and controls from urban and rural areas, and from the North and South regions, respectively. In the Greek study, the frequency of *GBA* mutations between PD patients and controls was statically significant. However, when the cohorts were analyzed separately, there was a difference of frequencies. The difference between PD patients and controls was statistically significant only in the case of the patients of cohort A that is originated from Thessaly, a mainly rural area ($p = 0.021$, OR 4.2, 95% CI = 1.14–15.54) and not in the case of cohort B patients, the majority of which were residents and/or originated from the greater area of Athens, an urban environment ($p = 0.113$, OR 2.5, 95% CI = 0.77–8.42) [34].

In the Italian study, there was a lower frequency of mutations in PD patients (11/395, 2.8%) and in controls (1/483, 0.2%) from the Southern region, and the most common mutation was p.L444P. Conversely, in the Northern region, the most

Studies	Population studied	PD inclusion criteria	Method	Mutation analyzed	Patients mutation frequency	Control mutation frequency	Age of onset	*GBA* mutated PD and familiar history (FH)
Spitz et al. (2007)	65 PD patients and 267 control subjects from Southeastern Brazil	Early onset (<55 years).	PCR-RFLP, restriction endonucleases and electrophoresis	N370S and L444P	2/65 **(3%)**; L444P 2/2 (100%); N370S 0/2 (0%)	0/267	Patient 1 at 46 yr old and patient 2 at 42 yr old	The two patients had FH, no statistical test was used.
Socal et al. (2008)	62 PD patients from Southern Brazil	All patients diagnosed were included.	PCR-RFLP, restriction endonucleases	N370S, L444P and IVS2þ1	2/62 **(3.5%)**; L444P 1/2 (50%); N370S 1/2 (50%)	Not informed	Patients with mutation 37 ± 4 yr Patients without mutation 41.4 ± 10.8 yr	Not informed.
De Carvalho et al. (2012)	347 PD patients and 341 control subjects from Southeastern, Midwestern and Northern Brazil	All patients diagnosed were included.	Direct sequencing	N370S and L444P	13/347 **(3.7%)**; L444P 8/13 (62%); N370S 5/13 (38%)	0/341	Patients with mutation 49.9 ± 11.3 yr Patients without mutation 52.5 ± 13.3 yr	Those with FH and those without FH did not present statistical significance.
Amaral et al. (2018)	81 PD patients and 81 control subjects from Northern Brazil	All patients diagnosed were included.	Amplification of the exon 8–exon 11, PCR-RFLP for N370S and L444P, restriction endonucleases and direct sequencing of N370S and L444P	N370S and L444P	6/81 **(7.4%);** L444P 3/6 (50%); N370S 3/6 (50%)	0/81	Patients with mutation 49.6 ± 17.4 yr Patients without 55.1 ± 11.6 yr	From the 6 patients, 2 had FH. No statistical test was used.

Bold valor are percentage.

Table 1.
GBA mutation among PD patients in different Brazilian regions.

frequent genetic defect found was p.N370S and the frequency of mutations in PD was 4.5% and 0.63% in controls. Therefore, the difference may be due to a particular frequency of *GBA* mutations in regions of Italy or to the sample size [36].

Although the frequency of *GBA* mutations in populations of PD patients has been well characterized worldwide, few data are available on the inverse relationship, that is, the risk of healthy heterozygous for *GBA* mutations in developing PD, since it is not known for sure the degree of influence that this genetic alteration has on the onset of the disease.

Anheim M et al. [43] published in 2012 an estimate of the penetration of PD in healthy heterozygous people for *GBA* mutations and reached a value of 7.6%, 13.7%, 21.4% and 29.7% for 50, 60, 70 and 80 years, respectively, based on a dominance model. However, in the same year, [51] found a lower value: 5% for 60 years and 15% for 80 years of age. Such difference is perhaps due to additional genetic factors or environmental factors, a fact that emphasizes the possibility of variance of the risk of developing PD according to the genetic background of the population. Families that have *GBA* mutations segregation through generations are a group at risk for developing PD and should be monitored for a possible early diagnosis to have better chances in modifying the disease.

5. Pathogenic mechanisms in PD

α-Synuclein is a key protein in the neuropathogenesis of PD, involved in several pathogenic processes. The physiological function of α-synuclein is not well understood, but studies show that it is normally located in presynaptic terminals where it binds to lipids and plays the role of regulating in more than one step the traffic of synaptic vesicles to be released. As cited above, the insoluble forms (oligomers and fibrils) of this protein accumulate and compound the Lewy bodies found in most PD patients and also contribute to neuronal cell death [5].

The reason behind this accumulation can be due to increased synthesis or decreased degradation (**Figure 2**). Mutations, as the triplications of the *SNCA* gene, can enhance the production of α-synuclein, while the interaction between the oligomers and fibrils formed with other mutant proteins can result in the deficiency of certain metabolic pathways and contribute to slowing down α-synuclein proteolysis. On the other hand, the initial deficiency of certain metabolic pathway caused by mutations in genes, advanced age or environmental factors can also be the trigger to accumulate α-synuclein resulting in the insoluble forms. This last theory has been

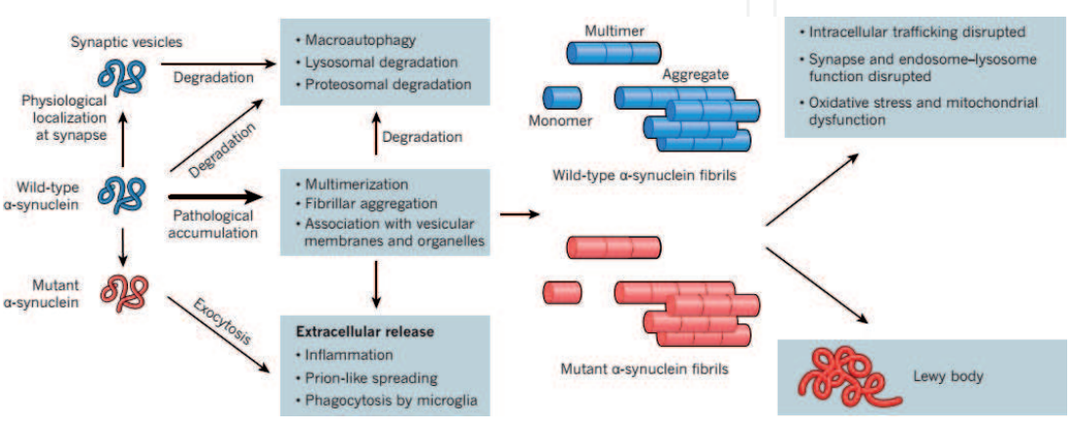

Figure 2.
The proposed physiological and PD-associated pathological functions of α-synuclein in neurons. Adapted from Ref. [6].

reinforced by the confirmed association of diverse genes involved in autophagy, endocytosis and lysosomal pathways as the *GBA* and *LRRK2* gene [1–6].

5.1 Lysosomal function-related genes and PD

The endosome-lysosome traffic processes, autophagy and lysosomal degradation, are essential functions for cell homeostasis, especially for neurons. The differentiated neurons have to maintain their homeostasis during the aging through degradation pathways since they do not divide in the same way as other eukaryotic cells. Moreover, cellular and animal models have also shown that the process of lysosome-autophagy and ubiquitin-proteasome has its activity reduced with natural aging. It may cause the accumulation of proteins whose homeostasis depends on those processes, such as α-synuclein. Indeed, the stimulation of degradation by macroautophagy through drugs proved to decrease intracellular levels of α-synuclein in experimental models [1–6].

Reciprocally, the accumulation of α-synuclein in the substantia nigra in experimental models leads to a reduction in lysosomal enzymes such as GCase, cathepsin B, β-galactosidase and hexosaminidase causing the inhibition of macroautophagy and ubiquitin-proteasome processes as a consequence enzyme transport to the lysosome interruption through dysfunction of vesicles and endosomes. The result is a vicious cycle where α-synuclein degradation mechanisms are inefficient resulting in the protein accumulation and it reinforces the inhibition of degradation activity [5–52].

Both GCase deficiency and the accumulation of its substrate (GlcCer) have been described to be associated with neurodegeneration (**Figure 3**). Feany M et al. [53] suggested that the connection of the α-synuclein to lipidic membranes would protect this protein from inadequate and clumped folding. Mutations of the *GBA* gene would alter the lipid composition of the membrane, which would favor a build-up of α-synuclein in the cytosol and subsequently in the Lewy bodies. Knockdown *GBA* in neuronal cells or in mouse models impairs α-synuclein clearance, whereas increasing glucocerebrosidase activity has the opposite effect, perhaps giving support to the loss-of-function theory in which the reduced or absent lysosomal enzyme is the trigger to α-synuclein accumulation [54].

Even excluding *GBA*, there was evidence for a burden damaging alleles in association with PD. In 2017, Ref. [55] performed a large study to examine the overlap between genes responsible for LSD and PD. More than half of PD cases in their cohort harbors one or more putative damaging variants among the 54 LSD genes. Specially, risk alleles in the genes *SMPD1* (Niemann-Pick type A/B), *GALC* (Krabbe disease), *SLC17A5* (Salla disease), *ASAH1* (Farber lipogranulomatosis) and *CTSD* (neuronal ceroid lipofuscinosis) have been candidate genes well replicated in different studies. *SMPD1* and *ASAH1,* along with *GBA*, participate in ceramide metabolism, and this fact can be evidence of the ceramide-associated process being relevant in a scenery of lysosomal dysfunction in PD [10–55].

The genes appointed as risk factor for PD to date explain only a fraction of PD heritability, suggesting the involvement of additional loci. Besides, the fact that *GBA* is the major genetic risk factor for PD makes other LSD genes attractive candidate risk factors. The results of [55] suggest that many genes that encode lysosomal enzymes besides *GBA* likely contribute to susceptibility for PD in Caucasian population.

Not only the lysosomal function is important, but also the previous steps necessary for the vesicle content to reach this organelle. In [10], a GWAS meta-analysis study found that PD-associated signals were enriched for autophagy and lysosomal function. *SCARB2* encodes a membrane protein (LIMP-2) required for correct targeting of GCase enzyme to the lysosome. Independent large GWAS have replicated

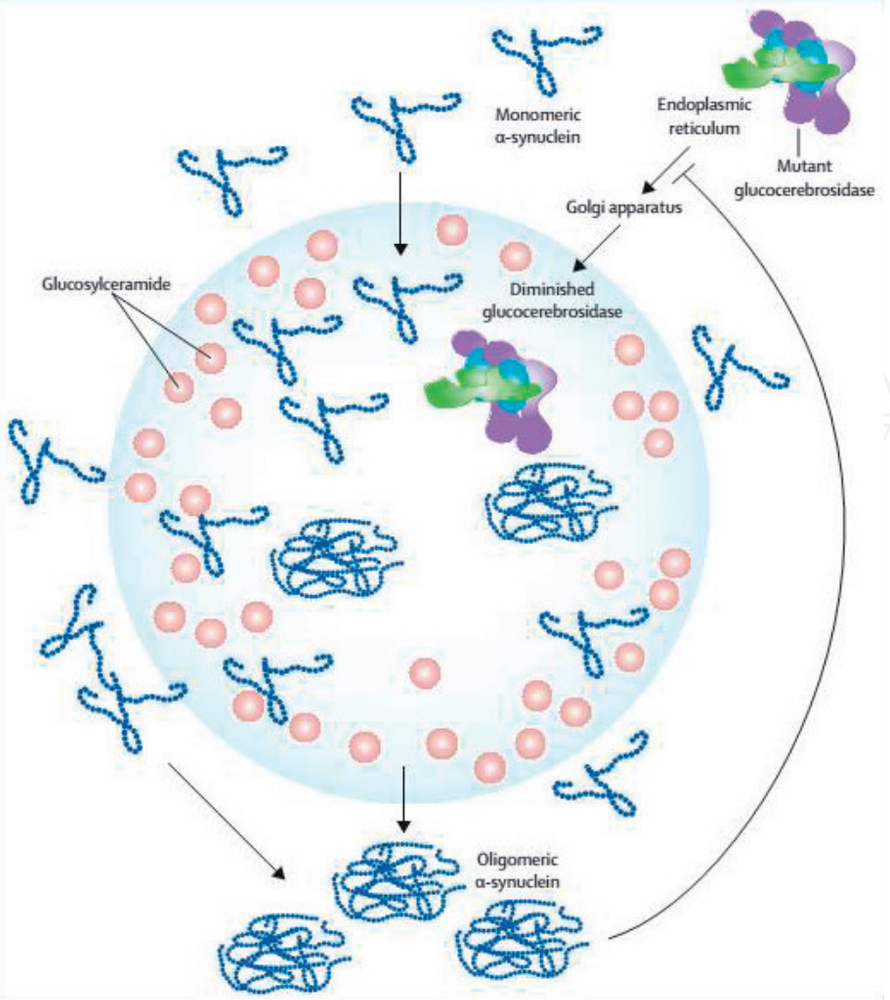

Figure 3.
The vicious cycle between the GCase and α-synuclein. Decreased glucocerebrosidase increases the lysosomal concentrations of glucosylceramide, which increases the formation of soluble α-synuclein oligomers. These oligomers also disrupt transport of newly synthesized glucocerebrosidase between the endoplasmic reticulum and Golgi apparatus, further compounding the problem. Adapted from reference [52].

common risk alleles in this gene. Functional analysis in cellular and animal model has shown that the reduction of LIMP-2 impairs the clearance of α-synuclein [55]. Those data reinforce that both the malfunction and the absence of the GCase, through mutations or impairment in the pathway, can result in α-synuclein accumulation.

The protein LRRK2 is complex and can work together with diverse proteins in different pathways, but for PD, the most relevant seems to be its endosome-to-lysosome trafficking function. Mutations in the kinase domain of the LRRK2 protein, such as the most common G2019S, compromise the traffic of the endosomal content to the lysosome through accentuated phosphorylation resulting in the dysregulation of proteins of the Rab family, responsible to target vesicles to the correct organelle membranes, including the lysosome [6–18].

In support of vesicular trafficking to lysosome impairment in PD, in 2009, two GWAS collaborative studies examining Caucasian and Asian subjects revealed significant risk alleles in *PARK16* locus for PD. This locus is a large linkage disequilibrium block that includes a Rab protein member of a subfamily that is implicated in vesicular transport to lysosomes and to lysosome-like organelles, the Rab-7 L1 (also known as RAB29) [9–16].

Mutations in the *VPS35* gene are one of the causes for autosomal dominant PD. Its protein is also involved in trafficking to lysosomes as a member of the

retromer complex, which has the role to regulate the delivery of the protein content within endosomes to organelles. Some of the proteins carried by this complex are cation-independent mannose-6-phosphate receptors, necessary for the transport of lysosomal enzymes to the lysosome. In the dysfunction of the retromer complex, the receptors are not returned to the Golgi complex, thus impairing the lysosomal function. In addition, mutations in *ATP13A2* are a rare cause of recessive juvenile-onset Parkinsonism and dementia and are associated to lysosomal dysfunction. This gene codifies a lysosomal P-type ATPase [1, 6].

Interestingly, potentiated retromer function might suppress the altered trafficking and toxicity that are associated with mutations in *LRRK2* or the overexpression of α-synuclein85, which suggests a potential therapeutic avenue. This fact emphasizes the possibility that different genes can interact with each other influencing the lysosomal function and as a consequence modifying the PD progression.

These common and rare risk alleles in *ATP13A1, RAB7L1*, *LRRK2* and *VPS35*, which support a model of partial loss-of-function variants in genes regulating lysosomal activity by cellular trafficking, result in an increased vulnerability to α-synuclein mechanisms in PD [55]. Ref. [10], the largest GWAS meta-analysis study, concluded that PD-associated signals were enriched for autophagy and lysosomal function. It replicated the results for *GBA* and *TMEM175* genes, which encode a potassium channel involved in the regulation of lysosome and identified three novel candidate genes, *CTSB* (a lysosomal cysteine protease), *ATP60A1* (an ATPase) and *GALC* (a lysosomal enzyme).

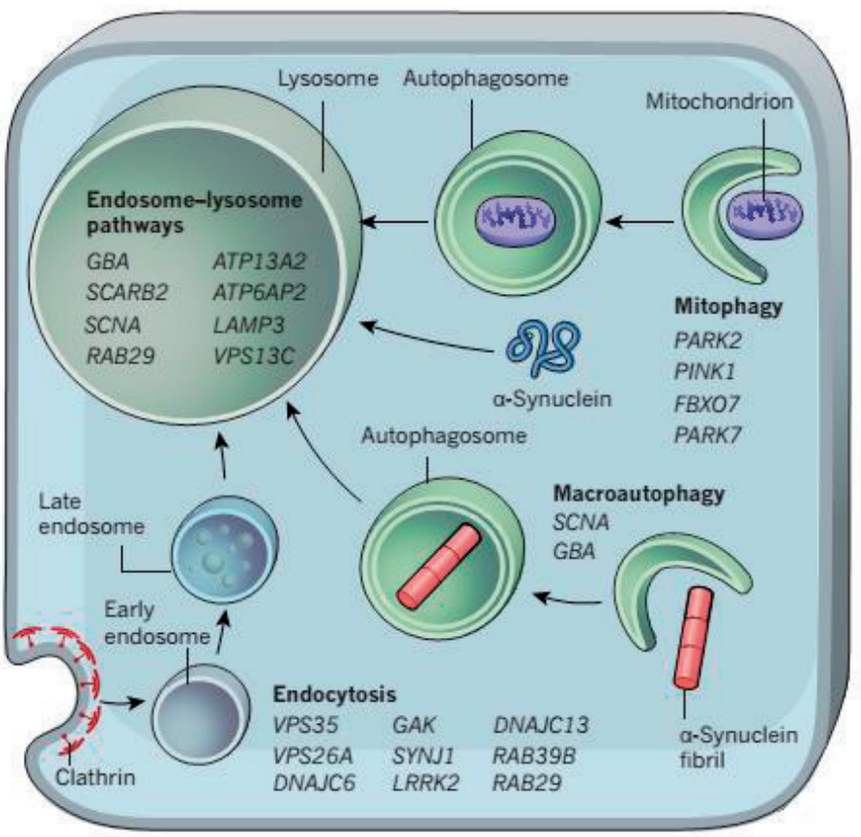

Figure 4.
Some of the PD-related genes associated with trafficking to the lysosome. Genes that encode intracellular trafficking components are associated with common sporadic and familial forms of PD, as well as related syndromes that share some of the clinical features of PD. Most of these genes are known to affect trafficking to the lysosome in the context of late endosome-to-lysosome pathways, clathrin-dependent endocytosis, macroautophagy or mitophagy. Wild-type α-synuclein (blue) can also enter lysosomes through chaperone-mediated autophagy. Adapted from Ref. [6].

Besides *GBA*, loss-of-function alleles are known as frequent PD risk factors, and some of those genes had the functional characterization made by analysis studies that showed knockout mice manifesting tremor phenotype with cerebral and cerebellar atrophy, thus corroborating with lysosome loss-of-function hypothesis to be involved with α-synuclein dysfunction and PD pathogenesis [10].

Therefore, advances in genetic and experimental model for PD have illuminated an important role for defects in intracellular transport pathways to lysosomes (**Figure 4**). The probability of discovering rare PD disease risk alleles at a single locus is low; however, if a set of lysosomal-related genes is investigated in conjunction, the chance of finding significant genetic variations is increased. Also, the candidate genes here appointed need further studies including even larger case–control studies and experiments in PD cellular or animal models.

6. Conclusion

Currently, genetic testing for PD is not a routine procedure, being restricted only to cases with a positive family history, with early onset or with the presence of specific atypical symptoms. In the future with the advance of genetic research, however, there is a possibility to use genetic variants to provide a perspective of the patient's clinical evolution. For this purpose, it is important to replicate risk variants for PD in large and genetically diverse samples due to the different results among populations. Genetic studies need to be a collaboration of the whole world to understand the genetics of a complex disease. In addition, candidate genes here appointed need further experiments in PD cellular or animal models understanding of the underlying pathology and molecular pathogenesis to provide perhaps the basis for the development of new therapies able to target mutated proteins that cause impairment in relevant pathways for PD as endosome trafficking, lysosome function and autophagy.

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