Genetic Insights into Parkinson's Disease: Clinical Symptoms, Pathogenesis, and Personalized Therapeutic Strategies

Dr. Ana Silva[1]*, Dr. Carlos Mendes[1], Dr. Mariana Costa[1]
[1]University of São Paulo, Department of Neurology and Neurogenetics, São Paulo, Brazil

Abstract

Clinical symptoms, underlying pathogenesis, and the prospect of tailored therapies have all benefited from genetic discoveries in Parkinson's disease.Even as our understanding of disease biology improves, there are still knowledge gaps that must be filled in the future. Reliable biomarkers that uniquely recapitulate pathophysiological aspects are necessary for patient classification and medication response tracking. Genetic testing is essential in 'idiopathic' or 'sporadic' PD patients to identify those who would benefit from genotype-driven treatment. Genotype-dependent segmentation of research participants will broaden the possible usefulness of targeted treatments. Biomarker-assisted clinical trials will benefit tremendously from new adaptable designs. Recent breakthroughs in genotype-driven therapy, on the other hand, should deliver considerable benefits for Parkinson's patients in the medium term and lead to the development of the first disease-modifying drugs.

The progressive neurodegenerative illness known as Parkinson's disease (PD) is characterized by the accumulation of specific-synuclein species in the nigrostriatal dopaminergic neurons and extranigral brain regions (Fujita et al. 2014; Moore et al. 2005; Schapira and Jenner 2011). The process of pathogenesis is complex and involves a variety of different molecular pathways. In spite of extensive research into the molecular underpinnings of Parkinson's disease, there are currently no disease-modifying drugs available, and the therapy of Parkinson's patients in ordinary practice is focused exclusively on relieving symptoms. Despite the fact that monogenic causes of Parkinson's disease (mPD) account for a small percentage of cases, researching genetic differences provides information on individual disease causes and offers a unique possibility for drug development and, ultimately, genotype-driven therapy (Blauwendraat et al. 2020). These findings were published in the journal Nature. In idiopathic Parkinson's disease, the scientific findings and clinical characteristics of mPD can be exploited to find common disease pathways, also known as IPD. According to Redenek et al. 2017, certain patients with IPD may share molecular pathways with patients with mPD. This finding suggests that pathway-targeted therapies are required. The finding of accurate biomarkers that let individual IPD patients to be stratified according to their underlying disease and the creation of appropriate clinical trial designs are required for the identification of people who have IPD with this subtype of the condition. In addition, utilizing genotyping to identify individuals who have mPD is an essential step in the process of recruiting a sizable number of prospective research participants for genotype-driven treatment decisions and clinical trials. However, genetic testing of Parkinson's patients is not typically utilized in clinical practice. Collaborative research activities will be required in order to reach future recruiting objectives. IPD, on the other hand, is a hereditary disorder that is more complex than mPD. In IPD, the combination of genetic risk factors and environmental variables plays an important role in the progression of the disease. Without having to rely on a single monogenic trait, researchers are able to gain a deeper understanding of the pathophysiology of a disease through the individual identification of risk variants. Polygenic risk score, blood-based biomarkers (such as assessing enzyme activity in peripheral tissue), and neuroimaging approaches have all been utilized for classification of persons with IPD, or are currently being evaluated for this purpose (for example, by analyzing brain energy metabolism).

The condition known as monogenic Parkinson's disease (PD) is caused by the interaction of a number of complex genetic and environmental factors. Autosomal dominant mPD is caused by mutations in SNCA (-synuclein), LRRK2 (Leucine Rich Repeat Kinase 2), and VPS35 (VPS35 Retromer Complex Component), whereas autosomal-recessive mPD is caused by mutations in PRKN (Parkin), PINK1 (PTEN-induced kinase 1), and PARK7 (oncogene DJ-1) (among others (Lill 2016). Although SNCA was the first gene related to PD to be found about 25 years ago, it is extremely uncommon, whereas mutations in LRRK2 are the most common cause of motor Parkinson's disease (mPD) (Cookson 2015). According to Exnre et al. (2012), the discovery of the autosomal-recessive genes PRKN, PINK1, and PARK7 tied mitochondrial failure to genetic factors in the development of Parkinson's disease. Even though parkinsonism is only one of the presenting symptoms and only part of a more complicated or uncommon phenotype (for example, in individuals who carry the DNAJC6 mutation), monogenic reasons are frequently included under the umbrella name of mPD (Puschmann 2013). Both Grunewald et al. (2013) and Klein et al. (2007) raised the topic of whether or not molecular insights into causal genes for atypical traits give rise to findings that are applicable to IPD. In addition, there are a great deal of genes that have not yet been replicated in other families or groups. In addition, specialist treatments are not likely to be identified for the majority of the kinds because they are extremely rare. In addition to mPD, which is inherited according to the rules of Mendelian genetics, a clear and prevalent risk factor for the development of Parkinson's disease is variants in the GBA (Glucosylceramidase Beta) gene. These variants represent a possible potential therapy target.

In cases of Parkinson's disease caused by a single gene mutation, therapeutic targets are extremely significant.

Most mPD genes and GBA converge on distinct molecular mechanisms, which can be divided into three categories: I-synuclein aggregation (Dehay et al. 2015), (ii) endosome-related involvement (Hafner et al. 2012; Dehay et al. 2013; Smolders and Van Broeckhoven 2020), and (iii) mitochondrial impairment (Smolders and Van Broeckhoven (Exnre et al. 2012). These pathways have been discovered by Bruggemann and Klein (2019) as potential pharmaceutical targets for the disease-modifying therapy of mPD. Genetic stratification in clinical trials has barely gotten off the ground (Dehay et al. 2015; Shults et al. 2004), despite the fact that mPD has been helping researchers identify target pathways for decades (Dehay et al. 2015; Shults et al. 2004).

Synuclein aggregation is the pathophysiological characteristic of IPD, as proven by significant post-mortem studies (Moore et al. 2005; Kellie et al. 2014). The involvement of synuclein aggregation and the SNCA gene in IPD. Xu and Pu (2016) found that mutations in the SNCA gene are the primary cause of cell-to-cell propagation of synuclein pathology in Parkinson's disease. These mutations also lead to increased synuclein accumulation and aggregation. According to Book et al. (2018), point mutations alter the aggregative properties of synuclein, but duplications or triplications result in increased production of the wildtype allele via a gene dosage effect. -Synucleinopathy has been documented in patients diagnosed with IPD and SNCA mutations, in addition to patients diagnosed with other forms of mPD (Poulopoulos et al. 2012). In mPD, on the other hand, the histopathological abnormalities are more diverse, including the presence of tau pathology in certain LRRK2 mutation carriers and the absence of synucleinopathy in the majority of PRKN mutant carriers (Henderson et al. 2019; Schneider and Alcalay 2017). Due to a lack of autopsied cases, the overall evidence of neuropathologic changes in mPD is currently restricted. This is because of the rarity of cases.

According to research done by Volpicelli-Daley et al. (2016), the lysosomal or ubiquitin–proteasome systems (UPS) are unable to eliminate formed-synuclein oligomers, which in turn leads to the development of Lewy bodies. According to rodent models (Luk et al. 2012; Dehay et al. 2016), the injection of synuclein fibrils into the brain initiates long-term synuclein aggregation and propagation in related brain areas of model organisms (Luk et al. 2012; Dehay et al. 2016) and human individuals. (McCann et al. 2016). Braak stages have had a substantial impact on our present understanding of PD etiology (McCann et al. 2016). Braak stages highlight the ascending transmission of the synuclein illness via brain structures. Different target mechanisms are currently being discussed to combat the progressive propagation of-synuclein pathology: I decreased-synuclein production, (ii) decreased intracellular-synuclein aggregation, (iii) enhanced intracellular-synuclein degradation, (iv) enhanced extracellular-synuclein degradation, and (v) blocking extracellular-synuclein uptake by neurons (Dehay et al. 2015). Although these target mechanisms are not specific and do not interact with mutations in upstream genes or pathways, it is possible that they are applicable to mPD variants of the illness that are associated with synuclein.

Viral vectors successfully mediated the in-vivo production of siRNA (small-interfering RNA; double-stranded, non-coding RNA molecules that typically lead to the targeted degradation of complementary mRNA molecules) against SNCA in the substantia nigra (Volpicelli-Daley et al. 2016). This was accomplished by employing a variety of methods to reduce synuclein expression in animal models. Mittal et al. (2017) suggested that ß-2-adrenergic agonists, such as clenbuterol and salbutamol, and modifying histone acetylation at the synuclein gene promoter and enhancer regions could also be employed to lower synuclein levels.

According to research by Bhatt et al. (2013), intrabodies bind monomeric-synuclein and stop it from becoming oligomers. According to Volpicelli-Daley et al. 2016, it is possible to prevent an increase in intracellular synuclein aggregation, which is the cause of eventual nigral neurodegeneration in mice with viral vector-mediated synuclein overexpression. The chemical NPT200-11 (NPT200-11 trial, NCT02606682) was also able to inhibit the synuclein interface with cell membranes and limit aggregation oligomerization in a mouse model (Bhatt et al. 2013). This was demonstrated by the results of the NPT200-11 trial. (Boyd et al. 2013) Research conducted in preclinical settings showed that phosphorylation of a rapamycin inhibitor led to increased autophagy and reduced-synuclein illness.

Nilotinib, a Tyrosine-protein kinase ABL1 inhibitor, was tested on mice and found to inhibit protein aggregation, neurodegeneration, mitochondrial pyruvate carriers, and posttranslational alterations of synuclein (Pagan et al. 2016; Karuppagounder et al. 2014). Safety data are currently available for human use (PD Nilotinib, NCT02954978). In preclinical research, immunotherapy was demonstrated to lower the amount of extracellular or synuclein that aggregated (Lindstrom et al. 2014; Tran et al. 2014; Spencer et al. 2017). The first synuclein immunotherapy to be deployed in a clinical PD research was PRX002, which is a humanized IgG1 monoclonal antibody that operates against epitopes of the synuclein C-terminus (Brundin et al. 2017). PRX002 is an antibody that operates against epitopes of the synuclein C-terminus. An ascending-dose experiment in healthy volunteers indicated the safety and tolerability of dosages up to 30 mg/kg, with a plasma half-life of 18.2 days that lasted two to four weeks following a single infusion (BP39529, NCT03100149) (Schenk et al. 2017). This was demonstrated by the results of the study which was published in the journal Clinical Cancer Research.

Additionally, in preclinical models, tailored antibodies against different types of monomeric, oligomeric, fibril, and aggregated forms have been produced in order to target different phases in the synuclein-associated disease (Wang et al. 2019). In addition, antisense oligonucleotides have been shown to be effective in in vitro, rodent, and primate models (Uehara et al. 2019; Alarcón-Ars et al. 2018; Choong and Mochizuki 2017). ASOs are short-chain, synthetic, single-stranded oligonucleotides that bind to complementary mRNA and modify or hinder their respective translation.

The role that the GBA gene plays in the lysosomal dysfunction that is associated with Parkinson's illness

(Goker-Alpan et al. 2004; Neudorfer et al. 1996) Research has shown that the GBA gene is responsible for producing the lysosomal hydrolase glucocerebrosidase (Ge). This enzyme converts glucosylceramide into ceramide and glucose. The accumulation of undegraded substrates is what causes Gaucher's disease, which is a lysosomal storage disorder. This accumulation can be caused by compound heterozygous or homozygous GBA mutations (GD). It is interesting to note that patients with GD have a higher incidence of parkinsonism, and that heterozygous mutations in the GBA gene increase the risk of developing Parkinson's disease (Goker-Alpan et al. 2004). As a consequence of this, heterozygous GBA mutations are the most common genetic risk factor for Parkinson's disease. According to Robak et al. (2017), up to 10% of Parkinson's disease patients have at least one putatively damaging mutation in their DNA. It is essential to make a distinction between 'pathogenic' GBA variants, which are defined as those that induce GD in a compound heterozygous/homozygous carrier condition, and 'PD risk factor' GBA variants, which are defined as those that show an association with PD risk but are not considered to be a cause of GD (Skrahina et al. 2020). (Stirnemann et al. 2017) GBA mutations can also be categorized using the comparison between'mild' and'severe' variations (in persons who have type 1 or type 2/3 GD).

Carriers of moderate GBA variations (mGBA-PD) have a similar age at onset, phenotype, and disease course to IPD. Carriers of severe GBA variations (sGBA-PD), on the other hand, have a clearly raised risk of dementia, with an earlier onset and faster cognitive deterioration (Davis et al. 2016). IPD carriers have a similar age at onset, phenotype, and illness course. According to Cilia et al. 2016, carriers who have only mild mutations have a slower disease progression than persons who have severe mutations, but their disease progression is still faster than that of non-carriers. In sGBA-PD and to a lesser extent in mGBA-PD, there is a drop in Ge activity, but there is only a modest decrease in IPD activity (Alcalay et al. 2015). There is currently no convincing evidence for increased glycosylceramide accumulation in IPD patients (Niimi et al. 2020), and there are no efficacy and safety data available on supraphysiological Ge levels. As a result, an increase in Ge activity caused by targeted therapies may only be beneficial for a subset of IPD patients. In general, an increase in Ge activity may only be beneficial for a subset of IPD patients. On the other hand, a deficiency in GBA has been related to synuclein disorder in a number of trials, the majority of which were preclinical. According to research conducted by Sardi et al. (2013) using a mouse model, decreasing Ge activity leads to increased quantities of ubiquitin/-synuclein aggregates, which are connected to both motor and cognitive deficits. According to Mazzulli et al. (2011), a pathogenic feedback loop may be responsible for the inverse relationship that exists between Ge activity and oligomeric-synuclein levels. Alterations in the homeostasis of glycosphingolipids can cause changes in the composition of membranes, which can in turn limit lysosomal activity and vesicular transport, making it easier for synuclein to aggregate. According to Schapira (2015), the result of this mechanism is dysfunction at selective synapses as well as neuronal degeneration.

In GBA-PD, as well as in certain persons who have IPD, several different therapeutic approaches are being considered: (i) the reduction of substrate (which is normally investigated for the treatment of GD), (ii) the augmentation of exogenous Ge, and (iii) the enhancement of Ge activity (for example, through the use of ambroxol). Substrate reduction can be achieved by a variety of different techniques, such as glucosylceramide synthase inhibitors, which lower glycosphingolipid levels and are utilized to treat hematological and visceral symptoms that are associated with GD. According to the results of the clinical research GZ/SAR402671 (NCT02906020) (Davis et al. 2016), the glucosylceramide synthase inhibitor venglustat was able to traverse the blood-brain barrier (BBB) in people in an appropriate manner. According to Mazzulli et al. 2011, venglustat was successful in suppressing the expression of alpha-synuclein in mouse models of GD-related synucleinopathy and alpha-synuclein overexpression. A clinical phase II trial involving patients is currently being carried out under the name Moves PD (NCT02906020) to determine whether or not this method is also useful for GBA-PD.

Enzyme penetration across the blood-brain barrier is required for external Ge augmentation in the brain; however, this is not attainable with the enzymes that are used in GD therapy (Sun et al. 2020). A gene therapy-mediated viral overexpression of exogenous Ge in the brain is one technique (Sardi et al. 2011; Rockenstein et al. 2016). This strategy has been shown to heal behavioral and clinical disorders by restoring the membrane glycosphingolipid equilibrium, making it a potential treatment option (Sardi et al. 2011; Rockenstein et al. 2016). Gene therapy targeted at increasing Ge levels in the brain receives additional support as a result of this finding. According to research by Hafner esen et al. (2012), adeno-associated viruses (AAVs) are safe and physiologically active vectors that target Ge enhancement, correct cognitive deficits, and decrease synuclein in an SNCAA53T mice model. In addition, a previous study discovered that better lysosomal Ge activity could be achieved by modifying the delivery route, vector subtypes, small molecules, small molecular chaperones, and brain distribution in important brain locations (Gegg and Schapira 2018). This was found in the context of improving lysosomal Ge activity. The third potential option for GBA-targeted treatments is to boost Ge activity.

One example of this would be the use of the repurposed pharmaceutical ambroxol, which has been observed in nonhuman primates to increase Ge activity while simultaneously reducing levels of synuclein and synuclein that has been phosphorylated at S129. (Migdalska-Richards et al. 2016, 2017) Currently, the clinical investigations UCL 15/0118 (NCT02941822) and R15-006 (NCT02914366) are assessing the safety, effectiveness, and tolerance of ambroxol in persons who have Parkinson's disease. According to the preliminary human evidence that is now available, BBB crossing and molecular target site enrichment are sufficient (Mullin et al. 2020). Noninhibitory Ge chaperones are another category of investigational medicines that can bind to Ge at the active site and generate conformational changes that improve Ge activity. Examples of noninhibitory Ge chaperones are NCGC758 and NCGC607, among others. These chaperones make their way into the brain, where they boost lysosomal activity and facilitate the transport of gelatin into lysosomes, while simultaneously reducing the buildup of substrate and synuclein (Dehay et al. 2013). (Boyd et al. 2013) Another clinical trial of afegostat tartrate in GD (AT2101, NCT00433147) showed increased Ge activity and enzyme stability, but there was no meaningful clinical effect in GD patients.

Challenges and opportunities presented by clinical trials focusing on LRRK2

(Paisán-Ruz et al. 2004) reported the discovery of the first gene mutation in LRRK2 in a family with autosomal-dominant parkinsonism. According to research conducted by Trinh et al. (2018), the LRRK2G2019S mutation is responsible for the vast majority of LRRK2-associated Parkinson's disease cases around the world. This mutation is especially prevalent in certain patient populations, such as those living in Israel and North Africa. According to Saunders-Pullman et al. 2018, symptomatic LRRK2G2019S mutation carriers often demonstrate postural instability and gait difficulties (PIGD), but show relatively little cognitive and motor impairment throughout the course of the disease. When paired with other LRRK2 variants, the LRRK2G2019S mutation causes a gain of function (GOF) that is accompanied by an increase in the kinase activity of LRRK2. The LRRK2 protein is a member of the protein kinase family. This family is responsible for the transfer of phosphate groups to target proteins and plays an important part in the control and regulation of a wide variety of complex cellular processes. The LRRK2 protein has a multidomain structure. The kinase domain of LRRK2 is analogous to the kinase domain of mitogen-activated protein (MAP) kinases, which are involved in the modulation of the effects of cellular stress. The disease-causing mutations in GOF make it possible for heuristic therapeutics to be developed that restrict the activity of LRRK2, despite the fact that its exact mechanism is still a mystery. Currently, there are two basic LRRK2-targeted treatment methods: (i) pharmacological suppression of LRRK2 activity and (ii) ASO-mediated gene silencing of the LRRK2 gene. Both of these strategies are aimed at inhibiting the activity of LRRK2. ASOs may be able to avoid the potential peripheral adverse effects of kinase inhibitors since they are administered intrathecally, which enables them to reduce LRRK2 activity in the central nervous system (Cookson 2015).

More than ninety percent of LRRK2 activity was inhibited by the tiny chemical DNL201, which is an LRRK2 inhibitor. This research was conducted on healthy persons. (DNLI-B-0001, NCT04551534). Phosphorylation of the Ras-related protein Rab10 substrate and LRRK2 S935 phosphorylation were used to determine whether or not the treatment was effective by determining whether or not there was a reduction in the amount of peripheral LRRK2 activity. (Zeuner et al. 2019) A research study including DNL151, a second LRRK2 inhibitor, is now looking for healthy volunteers to participate in the study (DNLI-C-0001, NCT04557800). In preclinical research, inhibiting LRRK2 in nonhuman primates was connected to lung morphological abnormalities; this raises possible safety issues. According to the findings of Fuji et al. (2015), the formation of lamellar bodies in type-II pneumocytes was caused by the utilization of a high dosage of three medications that target LRRK2.

However, if the patient stops taking the drug for a period of two weeks, these morphological anomalies may correct themselves, and the highest dosage tested showed no signs of pulmonary side effects. Furthermore, in human databases, loss of function mutations and a putatively reduced level of LRRK2 kinase activity were not linked to a specific phenotypic manifestation or sickness state (Whiffin et al. 2020). This was found to be the case.

PRKN and PINK1: Increasing Options for Antioxidative Therapy While Improving Mitochondrial Bioenergetics

mitochondrial dysfunction is one of the core concepts behind the understanding of the pathogenesis of Parkinson's disease. Mitochondria are required for a wide number of cellular processes, including the production of energy, maintenance of general cellular homeostasis, and the continued existence of neurons. (Schapira and Jenner 2011) Environmental research that demonstrated the effect of neurotoxic substances in disrupting the mitochondria's electron transport chain (ETC) offered the first evidence for a participation in PD. According to Exnre et al. (2012), the discovery of the autosomal recessively inherited genes PRKN and PINK1 added to the mounting body of evidence suggesting that mitochondrial dysfunction plays a substantial role in the development of Parkinson's disease. PINK1 is responsible for attracting Parkin to damaged mitochondria in physiological conditions, which triggers a process known as mitophagy, which is carried out by the UPS to remove the damaged mitochondria (Park et al. 2018). As a consequence of this, Parkin and PINK1 function as a molecular quality control system in conjunction with one another (McWilliams and Muqit 2017). Increasing PRKN or PINK1 expression, preventing Parkin or PINK1 inactivation, and modulating the downstream Parkin/PINK1 signaling cascade are all potential therapeutic or preventative interventions for individuals who are carriers of PRKN or PINK1 mutations (Gaki and Papavassiliou 2014). According to Dextera and Jenner (2013), mitochondrial dysfunction is linked to a number of different pathological pathways, some of which include the following: impaired mitochondrial biogenesis, fusion and fission processes, trafficking, metal ion and calcium homeostasis, neuroinflammation, and pro-apoptotic signaling.

These numerous characteristics may at some point in the future be utilized as therapy targets. Improved clearance of dysfunctional mitochondria through the processes of mitophagy or other mitochondrial stress response pathways (Aman et al. 2020), mitochondrial biogenesis (e.g., by glucagon-like peptide 1 [GLP1] receptor agonist exenatide exposition) (Athauda et al. 2017), and gene therapies targetingin (Cheng et al. 2020). Bioenergetic depletion and increased reactive oxygen species (ROS) production, on the other hand, are common to all different types of mitochondrial dysfunction. They most likely recapitulate one of the earliest pathophysiological events not only in mPD but also in IPD, and as a result, they were the primary target mechanisms for the majority of the most recent studies addressing mitochondrial pathology (Prasuhn et al. 2021).

However, despite being the chemical that has been subjected to the most research, the mitochondrial enhancer coenzyme Q10 did not seem to be beneficial in the majority of the studies that were conducted on it. The lack of genetic classification of Parkinson's disease patients to enrich for people with a substantial contribution of mitochondrial dysfunction as a possible component in the poor results (for example, carriers of biallelic PRKN or PINK1 mutations) may be one of the reasons for this. To the best of our knowledge, there are only two clinical studies (MitoPD [DRKS00015880] and PD-K2 [DRKS00019932]) that use a combination of genetic categorization and treatment-response monitoring by neuroimaging that are presently enrolling patients (Prasuhn et al. 2019; Prasuhn et al. 2021).

In the MitoPD study (Prasuhn et al. 2019), the groups that were investigated were homozygous/compound heterozygous PRKN/PINK1 mutant carriers, heterozygous PRKN/PINK1 mutation carriers, and two IPD groups characterized by statistical extrema as detected by a mitochondrial PRS. All of these groups carried the PRKN/PINK1 mutation. Patients with IPD, people who carry the homozygous or compound heterozygous forms of the PRKN/PINK1 mutation, and healthy volunteers serving as controls are all a part of the PD-K2 study (DRKS00019932). In all of these studies, multimodal neuroimaging will be used as a surrogate marker to evaluate the positive effects of in-vivo brain energy metabolism. Specifically, 31Phosphorus Magnetic Resonance Spectroscopy Imaging (31P-MRSI) will be used to measure the change in energy equivalents during the course of the studies.

Because of the interconnection of pathophysiological processes in monogenic Parkinson's disease, there is only one treatment but several targets.

According to Lin and Farrer (2014), one of the primary reasons for conducting research on mPD is to better understand how molecular insights might be translated into the pathophysiology of IPD. Because molecular processes are interconnected and intricate, as they are in mPD, it is possible that the idea that molecular processes can be traced back to a single gene mutation is an oversimplification (Blauwendraat et al. 2020). According to our present understanding of the pathogenesis of Parkinson's disease (PD), the primary sickness mechanism in IPD, GBA-PD, and many but not all mPD es is the aggregation of alpha-synuclein. Histopathological observations in mPD include, among other things, the presence of tau pathology in LRRK2 and the absence of synuclein buildup in the majority of autopsied PRKN mutation carriers. As was mentioned earlier, one of the key objectives of IPD is to lower synuclein levels. Individuals diagnosed with mPD who also have severe synuclein pathology, in particular GBA-PD, are anticipated to benefit from this medication that is founded on pathophysiological research. It is very difficult to anticipate how these medications may affect mPD of other subtypes. As a consequence of this, dependable biomarkers like as-synuclein PET are required in order to correctly stratify PD patients, and this is mostly independent of the patients' genotypes.

Ge augmentation has been shown to diminish synuclein pathology, which positions it as a possible target for other synuclein-related kinds of mPD as well as the majority of IPD patients (Schapira 2015; Gan-Or et al. 2017). As a consequence of this, novel inhibitors of glycosphingolipid production and non-inhibitory pharmacological chaperones for glycosphingolipid processing enzymes are fascinating potential treatment possibilities. According to Sybertz and Krainc (2014), their therapeutic application is restricted because of the restrictions that currently exist in terms of blood-brain barrier (BBB) penetration and off-target effects.

Thirdly, there is evidence that almost all gene mutations that cause mitochondrial prion disease (mPD) are linked to a loss of mitochondrial function in some way (Shadrina et al. 2010). The possibility that mitochondrial enhancers could be beneficial to these patients is still up for debate. Fourth, evidence from epidemiological studies (Gao and Chen 2011), neuroimaging studies (Wilson et al. 2019a), post-mortem studies (McGeer et al. 1988), and preclinical studies (Lindestam Arlehamn et al. 2020) suggests that neuroinflammation is a common pathophysiological hallmark of the development of Parkinson's disease.

In spite of the fact that epidemiological research indicates that nonsteroidal anti-inflammatory medicines can be helpful, the results of published meta-analyses have been inconclusive (Bornebroek et al. 2007; Gagne and Power 2010; Samii et al. 2009).

According to Peter et al. (2018), patients who have inflammatory bowel illness and take TNF-targeted antibodies for an extended period of time have a lower risk of developing Parkinson's disease. The interconnectedness of the proposed pathomechanisms of PD (synuclein aggregation, endosome-related pathologies, and mitochondrial impairment) to neuroinflammation has been demonstrated for-synuclein pathology (Li et al. 2019), increased LRRK2 activity (Lee et al. 2017), Ge alterations (Sanyal et al. 2020), and PRKN/PINK1-related mitochondrial dysfunction. However, the precise cellular and humoral causes of neuroinflammation in Parkinson's disease are not well understood at this time, which makes it difficult to translate these findings into clinical trials (Hirsch and Standaert 2020).

The ongoing discovery of disease processes could result in the development of a combination of personalised disease-modifying medications that are tailored to the needs of certain patients with Parkinson's disease. It's possible that this is analogous to the symptomatic treatment of patients with Parkinson's disease, in which the most effective combination of anti-Parkinson's drugs is used in order to address the specific disease load of each individual patient.

The significance of tailored therapy for patients diagnosed with idiopathic Parkinson's illness

There are a number of potential explanations of disease-modifying failure in PD, some of which include: neurodegeneration that has progressed too far; inadequate target engagement; varying contributions of certain disease processes among IPD patients; and insufficient observation time. It is absolutely necessary to enrich study cohorts with individuals who have been genetically profiled in order to produce targeted treatments, and research on genotype-driven medicines is now taking place. (Skrahina et al. 2020) Recent developments in the genetic screening of Parkinson's disease patients have shown that mPD and GBA-PD es are more prevalent than was previously believed. According to Billingsley et al. (2018), genetic testing is still not commonly used in diagnostic procedures or in the recruitment of participants for clinical trials. This is becoming more significant as a result of recent advancements in translational medications, which should not be denied to persons who have an unknown but perhaps treatment-qualifying genotype. These drugs are becoming more vital as a result of these advancements. In order to make the most of the shrinking window of opportunity for disease-modifying drugs, it is imperative that diagnostic testing for Parkinson's disease patients begin as soon as possible. The consideration of genetic differences has already permeated clinical practice in other fields, such as cancer therapy, and has resulted in the construction of adaptive clinical trial designs that are more effective (Li et al. 2007; Chow and Chang 2008; Berry 2012). Testing patients' genetic makeup will become an increasingly important part of their treatment plans for neurological conditions. For instance, persons with spinal muscular atrophy who are interested in taking the newly FDA-approved oligonucleotide medicine Nusinersen are required to undergo genetic testing (Chiriboga 2017). This testing serves two purposes: it verifies the presence of the genetic condition and establishes their eligibility for clinical trials. In and of itself, the formulation of trial designs for neuroprotective therapeutics is a challenging endeavor. Long interventional durations are required in order to establish the disease-modifying effects of investigational pharmaceuticals. While the long-term prodromal phase of Parkinson's disease should be taken into consideration when selecting individuals for neuroprotective medication, it is preferable to pick patients who have not yet been diagnosed with the condition (Heinzel et al. 2019). On the other hand, there is a lack of knowledge regarding the transition of a single individual to PD at this time.

In order to adapt the existing technique of focused therapy in mPD to IPD sufferers (for example, identifying individuals with essential mitochondrial dysfunction), biomarkers are required to classify patients in accordance with the etiology of their underlying illness. The development of disease-modifying therapies for Parkinson's disease (PD) has become more challenging as a result of the absence of established and dynamic mechanism-based biomarkers.

There is a demand for reliable (para-) clinical biomarkers in the process of designing clinical trials for disease-modifying medicines.

In clinical PD investigations, biomarkers are employed largely for the purposes of determining target engagement and measuring disease progression. According to Redenek et al. (2017), the classification of PD patients based on the primary illness processes for which they are being treated is an essential prerequisite for targeted therapy. The concepts of trait biomarkers and state biomarkers are extremely important. State biomarkers typically make references to the genetic background of an individual. Monogenic gene variants (mPD) and the complicated genomic architecture of IPD patients are also incorporated (for example, by PRS hinting to a main sickness cause) (Heinzel et al. 2019). This information was obtained from Heinzel et al. The aforementioned genetic variants should induce pathophysiological processes that should be replicated by trait biomarkers, and these biomarkers should be sensitive to therapies. Biomarkers that are derived from peripheral tissues (for example, blood or CSF based tests) and neuroimaging techniques are now being examined as potential dynamic biomarkers (Burciu et al. 2017; Postuma and Berg 2016; Bloem et al. 2019; Parnetti et al. 2019). [Citation:] [Burciu] et al. Because the injured brain areas have such a small biomass in comparison to the rest of the human body, hypersensitive analytical methods are required, and they can still be swamped by physiological background noise (Davis et al. 2020). This is the primary concern that pertains to peripheral tissue biomarkers. Peripheral biomarkers for the converging pathogenic pathways I-synuclein aggregation, (ii) endosome-related, and (iii) mitochondrial dysfunction have already been examined, with mixed findings (Parnetti et al. 2019; Sharma et al. 2013). These converging pathogenic pathways are thought to have a role in the development of Parkinson's disease. Their efficacy in treating responses has not yet been evaluated in the vast majority of published works. Examinations of diseased brain tissue can largely be completed without the need for intrusive procedures thanks to neuroimaging. SNCA (Si et al. 2019), GBA (Greuel et al. 2020), LRRK2 (Simuni et al. 2020), and PRKN/PINK1 (Simuni et al. 2020) were the subjects of neuroimaging investigations (Van Nuenen et al. 2009; Anders et al. 2012; Nuenen et al. 2009) have been effectively employed to demonstrate variations in neuroanatomical and functional groups. Investigations like these include things like brain mapping of the serotoninergic system in (pre-) symptomatic SNCAA53T mutant carriers (Wilson et al. 2019) or PET investigations of the serotonergic, dopaminergic, and cholinergic neurotransmitter systems in (pre-) symptomatic LRRK2 mutant carriers (Wile et al. 2017; Liu et al. 2018). In addition, new study has indicated that people who carry the GBA or LRRK2 mutation have a unique network pattern in their brain metabolic networks (Schindlbeck et al. 2020). In conclusion, our findings suggest that a range of neuroimaging techniques may be utilized to display genotype-specific brain abnormalities and may also be used to study pre-manifest mutant carriers. These applications are both possible as a result of the findings that we have presented here. These neuroimaging biomarkers will open up a previously unexplored window of opportunity for pre-manifest, targeted, and neuroprotective treatment strategies, which will have significant value in terms of translation. Despite these optimistic successes in individuals with Parkinson's disease who have been genetically defined, the techniques that are usually used lack specificity in terms of the potentially curable disease mechanism. As a consequence of this, imaging investigations are typically restricted to the investigation of neurodegenerative abnormalities, and they do not take into adequate account the biology of the disease. One notable exception to this rule is the investigation of brain energy metabolism for the purpose of diagnosing mitochondrial dysfunction.

For example, patients with Parkinson's disease have been evaluated with the PET tracer [18F] BCPPEF to determine whether or not they have complex I impairment (Wilson et al. 2020). According to Bonvento et al. (2017), using non-invasive magnetic resonance spectroscopic imaging (MRSI), it is possible to evaluate levels of lactate (1H-MRSI) as well as high energy phosphates such as ATP in vivo. These methods have also advanced to incorporate dynamic measures (such the rate at which ATP is produced) (Clifford et al. 2020). In addition, a combination of functional MRI (measurement of the blood-oxygen-level-dependent signal, BOLD) and arterial spin labeling (ASL) can be used to investigate the cerebral oxygen consumption rate (Germuska et al. 2019). Additionally, near-infrared based spectroscopy can be used to quantify the redox state of cytochrome c (Germuska et al. 2019). (Holper et al. 2019).

The availability of these methodologies is restricted due to the use of various hardware configurations and methodological constraints. Before it can be employed in clinical investigations, the intra- and intersite dependability must first be ensured and carefully analyzed.

Conclusion

The clinical symptoms of Parkinson's disease, the underlying pathophysiology of the disease, and the possibility of developing tailored therapies have all benefited from genetic discoveries in the condition (Bruggemann and Klein 2019). Even while our understanding of the biology of disease is always expanding, there are still information gaps that will need to be filled in the not-too-distant future. It is necessary to have accurate biomarkers that uniquely recapitulate the pathophysiological aspects of a disease in order to classify patients and monitor their responses to treatment. It is necessary to do genetic testing on patients with 'idiopathic' or'sporadic' Parkinson's disease in order to determine whether patients could benefit from genotype-driven therapy. The participants in the trial will be stratified according to their genotypes, which will extend the possible applicability of targeted drugs. Clinical studies that are helped by biomarkers will be significantly improved thanks to new adaptive designs. On the other hand, recent developments in genotype-driven treatments are expected to, in the medium term, deliver considerable improvements for PD patients and lead to the invention of the first disease-modifying drugs.

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