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REVIEW

The genetic background of Parkinson's disease and novel therapeutic targets

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ABSTRACT

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. The median age of disease onset is around 60 years. From a genetic point of view, PD is basically considered a sporadic, idiopathic disease, however, hereditary components can be detected in 5–10% of patients. Expanding data are available regarding the targeted molecular therapy of the disease.

Areas covered: The aim of this current review article is to provide brief clinical and molecular insight into three important genetic forms (LRRK2, SNCA, GBA) of hereditary PD subtypes and to present the human clinical trials in relation to these forms of the disease.

Expert opinion: These small hereditary subgroups are crucially important in drug development, because the general trend is that clinical trials that treat PD patients as a large group, without any separation, do not meet expectations. As a result, no long term conclusions can currently be drawn regarding the effectiveness of the molecules tested in these phase 1 and 2 studies. Further precise studies are needed in the near future.

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GBA; genetic; LRRK2; Parkinson's disease; SNCA

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide [1].

The disease affects around 2–3% of the population ≥ 65 years of age [1]. The primary feature of PD is the degeneration and loss of dopaminergic neurons in the substantia nigra, which results in a striatal dopaminergic deficit [1]. The median age of onset of clinical symptoms (bradykinesia, rigidity and/or rest tremor) is around 60 years [2]. From a genetic point of view, PD is basically considered a sporadic disease, but 5–10% of patients have a positive family history. However, confirmed hereditary cases following Mendelian inheritance are rare [3]. Clinical differentiation of sporadic and hereditary forms of PD is very challenging and sometimes impossible [2]. Nevertheless, it can be stated that genetic variations underlying monogenic forms of PD can be identified more often in early-onset cases [3]. To date, the number of genetically confirmed genes and loci causing PD in monogenic form is thirteen (PARK1, –2, –6-10, –12-17). Furthermore, four, so far unconfirmed, PARK loci are known as well (PARK3, –5, –11, –18) [4]. In terms of inheritance, these genes show autosomal dominant (e.g. *LRRK2, SNCA*), recessive (e.g. *PRKN, PINK1, DJ-1*) and X-linked (e.g. *RAB39B*) patterns [5]. Furthermore, *GBA* mutations in heterozygous form are the most important risk factors for developing PD [6]. Table 1 illustrates the main characteristics of the most important hereditary disease forms (Table 1).

The gold standard for treatment of PD is still levodopa [7]. Although levodopa is an excellent symptomatic drug, it does not slow or reverse the progression of the disease. Considering that since the introduction of dopaminergic therapy decades ago, no further significant breakthrough in the pharmacotherapy of PD has been made, alternative approaches have come to the fore. However, clinical trials aimed at the treatment of heterogeneous PD groups often fail. These results increasingly emphasize the importance of targeted therapies in certain genetically diagnosed groups of PD patients. As the number of patients carrying one of these genetic alterations is low, clinical trials have been started within the framework of international collaborations [8].

The aim of this current review article is to provide brief clinical and molecular insight into three important genetic forms of hereditary PD subtypes and to present the human clinical trials in relation to these forms of the condition.

1.1. Leucine-rich repeat kinase 2 (*LRRK2*) – targeted therapies

LRRK2 gene mutations are one of the most common genetic alterations behind familial forms of PD [2]. From a clinical perspective, the onset of motor symptoms is quite variable. Although mutations in this gene are mostly detected in late-onset cases (mean age of onset: 58–61 years), they can be found in younger patients as well [2]. *LRRK2*-associated PD is levodopa responsive [2]. It tends to have a milder progression and some non-motor symptoms are unusual (e.g. cognitive deterioration, psychiatric disturbances) [2,5]. The neuropathological picture of the disease is variable, because Lewy body pathology and pure forms of substantia nigra degeneration

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Article highlights

- Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide.
- The median age of clinical symptoms (bradykinesia, rigidity and/or rest tremor) onset is around 60 years.
- Positive family history is found in 5-10% of patients.
- Three important genetically determined forms are *LRRK2*-, *SNCA*- and *GBA*- related subtypes.
- Phase 1 and 2 targeted studies are currently underway for this three genetic subtypes.
- No long-term conclusions can currently be drawn regarding the effectiveness of the molecules tested, further precise studies are needed in the near future.

without Lewy bodies have both been described, as well as the varying presence of neurofibrillary tangles [9].

The *LRRK2* gene contains 51 exons, which encode a 2527 amino acid long protein [5]. The LRRK2 protein is a homodimer with GTPase and kinase functions, harboring the following domains: (1) protein-protein interaction domains: armadillo (ARM), ankyrin-like (ANK), leucine-rich repeat (LRR) and WD40; (2) serine-threonine kinase domain; (3) Ras of complex protein (Roc) – C-terminal of Roc (COR) tandem domain [10]. The vast majority of pathogenic mutations identified to date are located close to the carboxyl terminus of the protein [10]. The most frequent mutation is c.6055 G > A (p.G2019S) [10]. The penetrance of mutations in the *LRRK2* gene is variable. The biological function of the LRRK2 protein is not yet known in detail, however, it may have an effect on cell signaling and subcellular transport processes [10].

All common *LRRK2* mutations result in increased kinase activity, so the pharmaceutical industry has focused on kinase inhibitors. During the development of the LRRK2 kinase inhibitor, possible pulmonary damage arose as an important safety issue in rodents and non-human primate animal studies. However, the toxic pathomechanism, involving primarily type II pneumocytes and resulting in a deposition of lamellar bodies, is presumably reversible, so the testing of individual LRRK2 kinase inhibitor compounds in clinical phases still occurred [11,12]. Regarding clinical trials, six relevant studies were performed (Table 2, 3). DNL201 was the first clinically tested small, selective LRRK2 kinase inhibitor, which can penetrate the central nervous system. 122 healthy volunteers and 28 PD patients were involved in a phase 1b study (NCT03710707) [13]. DNL201 was tested for 28 days at low and high doses [13]. The molecule inhibited LRRK2 kinase activity, and it improved lysosomal function as well [13]. During the testing period no relevant safety issues appeared [13]. In the second, 28 day long, relevant clinical trial (NCT04056689), another LRRK2 kinase inhibitor (DNL151) was tested in three doses. 34 PD patients were enrolled in the phase 1b study [14]. Although the results are not yet fully available, the safety of the molecule, which was monitored along with the detection of lysosomal biomarkers, appeared satisfactory [14]. No serious adverse event occurred [14]. A different, larger study (NCT04557800, phase 1, 186 healthy volunteers) further strengthened the previous results, i.e. DNL151 is a safe and well-tolerated molecule. Further clinical trials are currently underway (antisense oligonucleotide – BIIB094 – Phase 1 – NCT03976349; LRRK2 inhibitor – BIIB122 (other name: DNL151) – Phase 2 – NCT05348785; LRRK2 inhibitor – BIIB122 (other name: DNL151) – Phase 3 – LIGHTHOUSE study), for which exact results are not yet known.

1.2. Alpha-synuclein (*SNCA*) – targeted therapies

Although the incidence of PD associated with a mutation in the *SNCA* gene is much lower than *LRRK2*-associated cases (about 140 reported cases), it is a population of critical importance for a more precise understanding of the pathomechanism of the disease [12]. Clinically, *SNCA*-associated PD is an early-onset (< 50 years) form, which shows rapid progression [5,19]. The presence of neurocognitive disturbance is very common [19]. This form shows a dramatic levodopa response after treatment initiation; however, this effect diminishes over the course of the disease [5]. In the scientific literature, some atypical presentations have also been reported (myoclonus, central hypoventilation, pyramidal signs, cerebellar signs) [2,5]. Lewy bodies are present in various important brain regions associated with movement control and movement organization (e.g. substantia nigra, cerebral cortex) [20].

Table 1. Comparison of the main hereditary subtypes associated with Parkinson's disease.

Genetic subtype	Mean age of onset range	Inheritance	Mutation type	Clinical characteristics	Response to levodopa and deep brain stimulation treatments
LRRK2	4th-10th decade	Autosomal dominant	Missense	Milder progression. Some non-motor symptoms are unusual.	Levodopa responsive. Excellent motor response to subthalamic nucleus DBS.
SNCA	2nd-7th decade	Autosomal dominant	Missense/ multiplications	Frequent cognitive decline, psychiatric disturbances. Some atypical presentations were also reported (myoclonus, central hypoventilation, pyramidal signs, cerebellar signs).	Variable levodopa responsiveness. DBS: improvement of motor symptoms. Higher rate of cognitive complications.
GBA	4th-8th decade	Autosomal dominant	Missense/deletions	Frequent presence of postural instability with gait difficulty, neurocognitive disorder, dysautonomia and other psychiatric disturbances.	Levodopa responsive. DBS: can be beneficial, but cognitive complications are common.

(Abbreviations: DBS – deep brain stimulation; GBA – glucocerebrosidase gene; LRRK2 – Leucine-rich repeat kinase 2 gene; SNCA – α-synuclein gene.)

Table 2. Completed major clinical trials related to *LRRK2, SNCA* and *GBA*.

Genetic subtype	Clinical trial	Phase	Tested molecule	Target, effect	Participants	Duration (treatment period or time frame of the study)	Main results	Reference
LRRK2	NCT03710707	1b	DNL201; low and high doses	LRRK2 inhibitor	28 PD	28 days	DNL201 is safe and well tolerated. It appears that it has the ability to correct lysosomal dysfunction.	Jennings *et al.*, 2022 [13]
	NCT04557800	1	DNL151; single daily doses (from 15 mg to 300 mg – 28 days)/ twice daily doses (up to 400 mg – 14 days)	LRRK2 inhibitor	186 healthy volunteers	14 and 28 days	DNL151 was safe and generally well tolerated.	clinicaltrials.gov
SNCA	2011–002650-31, 2013–001774-20, 2014–002489-54, 2015–004854-16	1	PD01A	Active immunization	24 PD	221–259 weeks	Repeated administrations of PD01A were safe and well tolerated. It caused a measurable humoral immune response.	Volc *et al.*, 2020 [22]
	NCT02095171	1b	Prasinezumab (/PRX002/ RO7046015)	Passive immunization	40 participants	3 months	Good safety and tolerability. The serum level of the alpha-synuclein was reduced.	Schenk *et al.*, 2017 [23]
	NCT03100149 (PASADENA)	2	Prasinezumab	Passive immunization	316 participants	52 weeks	Prasinezumab therapy had no meaningful effect (neither clinically nor radiologically /DaT-SPECT/).	Pagano *et al.*, 2022 [24]
	NCT03716570	1	BIIB054 (/cinpanemab)	Passive immunization	24 participants	72 weeks	Terminated	clinicaltrials.gov
	NCT03318523 (SPARK)	2	BIIB054 (/cinpanemab)	Passive immunization	357 participants	52 weeks	The trial was terminated, because of lack of efficacy (UPDRS). DaT-SPECT imaging showed no differences between placebo and cinpanemab group.	Lang *et al.*, 2022 [25]
	NCT04208152	1	Anle138b	Disruption of α-synuclein aggregation	68 participants	~ 90 days	Good safety and tolerability.	Levin *et al.*, 2022 [15]
	n.a.	1	PBT434	Iron attenuating agent	18 healthy volunteers	8 days	PBT434 has proportional pharmacokinetics and was well tolerated in healthy volunteers.	Stamler *et al.*, 2019 [16]
	NCT03589976	2	Rapamycin (sirolimus)	Enhancing autophagic activity	47 participants	48 weeks	Terminated	clinicaltrials.gov
	NCT02281474	1	Nilotinib	Enhancing autophagic activity	12 participants	6 months	Good safety and tolerability.	Pagan *et al.*, 2016 [17]
	NCT02954978	2	Nilotinib	Enhancing autophagic activity	75 participants	12 months	Reduced plasma and CSF level of alpha-synuclein.	Pagan *et al.*, 2019 [18]
	NCT03205488	2	Nilotinib	Enhancing autophagic activity	76 participants	6 months	Poor CSF penetration. No clinical improvement.	Simuni *et al.*, 2020 [26]
	NCT03316820	1	K0706/SCC-138	Enhancing autophagic activity	24 participants	26 days	Good safety and tolerability.	clinicaltrials.gov
	NCT03445338	1	K0706/SCC-138	Enhancing autophagic activity	18 participants	8 days	Good safety and tolerability.	clinicaltrials.gov
	NCT02970019	1	K0706/SCC-138	Enhancing autophagic activity	60 participants	4 weeks	Good safety and tolerability.	clinicaltrials.gov

(*Continued*)

Table 2. (Continued).

Genetic subtype	Clinical trial	Phase	Tested molecule	Target, effect	Participants	Duration (treatment period or time frame of the study)	Main results	Reference
GBA	NCT02941822	2	Ambroxol	Increasing glucocerebrosidase activity	18 PD	6 months	It was well-tolerated and safe. Glucocerebrosidase level was elevated in CSF, there was a significant decrease in CSF α-synuclein concentration. Motor scores improved.	Mullin *et al.*, 2020 [30]
	NCT02906020	2	Venglustat	Glucosylceramide synthase inhibitor	273 participants	36 weeks	Terminated	clinicaltrials.gov
	NTR6598 and NTR6705	1	LTI-291	Increasing glucocerebrosidase activity	~ 40 participants	n.a.	There were no safety events. Good tolerability.	Schneider *et al.*, 2020 [19]

(Abbreviations: *GBA* – glucocerebrosidase gene; *LRRK2* – Leucine-rich repeat kinase 2 gene; n.a. – not available; PD – Parkinson's disease; *SNCA* – α-synuclein gene.) (Table 2 is based on the work of Jasutkar [21] and Schneider [19], as well as data from clinicaltrials.gov.)

Table 3. Ongoing major clinical trials related to *LRRK2, SNCA* and *GBA*.

Genetic subtype	Clinical trial	Phase	Tested molecule	Target, effect	Participants	Duration (treatment period or time frame of the study)	Main results	Reference
LRRK2	NCT04056689	1b	DNL151; 3 tested doses; once daily, up to 300 mg.	LRRK2 inhibitor	34 PD	28 days	Detailed results are not available.	Ding and Ren, 2020 [14]
	NCT03976349	1	BIIB094; single and multiple doses	Antisense oligonucleotide; LRRK2 degradation	82 participants (62 PD)	n.a.	Detailed results are not available.	clinicaltrials.gov
	NCT05348785	2b	BIIB122	LRRK2 inhibitor	640 participants	48 weeks	Detailed results are not available.	Pharmaceutical company sites
	LIGHTHOUSE study	3	BIIB122	LRRK2 inhibitor	400 participants	96 weeks	Detailed results are not available.	Pharmaceutical company sites
SNCA	NCT02618941	1	PD01A	Active immunization	26 participants	12 months	n.a.	clinicaltrials.gov
	NCT01885494	1	PD01A	Active immunization	30 participants	52 weeks	n.a.	clinicaltrials.gov
	NCT02216188	1	PD01A	Active immunization	28 participants	6 months	n.a.	clinicaltrials.gov
	NCT01568099	1	PD01A	Active immunization	32 participants	12 months	n.a.	clinicaltrials.gov
	NCT02267434	1	PD03A	Active immunization	36 participants	12 months	n.a.	clinicaltrials.gov
	NCT04075318	1	UB-312	Active immunization	70 participants	13 weeks	n.a.	clinicaltrials.gov
	NCT04777331	2	Prasinezumab (/PRX002/RO7046015)	Passive immunization	575 participants	76 weeks	n.a.	clinicaltrials.gov
	NCT03272165	1	MEDI1341	Passive immunization	50 participants	13 weeks	n.a.	clinicaltrials.gov
	NCT04449484	1	MEDI1341	Passive immunization	25 participants	28 weeks	n.a.	clinicaltrials.gov
	NCT03611569	1	Lu AF8242	Passive immunization	74 participants	84 days	n.a.	clinicaltrials.gov
	NCT04685265	1	Anle138b	Disruption of α-synuclein aggregation	48 participants	30 days	n.a.	clinicaltrials.gov
	NCT02606682	1	NPT200-11	Disruption of α-synuclein aggregation	55 participants	7 days	n.a.	clinicaltrials.gov
	NCT03047629	2	ENT-01	Disruption of α-synuclein aggregation	50 participants	10 months	n.a.	clinicaltrials.gov
	NCT04483479	2	ENT-01	Disruption of α-synuclein aggregation	28 participants	14 weeks	n.a.	clinicaltrials.gov
	NCT03781791	2	ENT-01	Disruption of α-synuclein aggregation	144 participants	10 weeks	n.a.	clinicaltrials.gov
	n.a.	1	YTX-7739	Stearoyl-CoA desaturase inhibitor	n.a.	n.a.	n.a.	Pharmaceutical company sites
	NCT03655236	2	K0706/SCC-138	Enhancing autophagic activity	504 participants	40 weeks	n.a.	clinicaltrials.gov
	NCT03996460	2	K0706/SCC-138	Enhancing autophagic activity	45 participants	12 weeks	n.a.	clinicaltrials.gov
	NCT04691661	2	Radotinib	Enhancing autophagic activity	40 participants	2 weeks	n.a.	clinicaltrials.gov
	NCT04165837	1	FB101	Enhancing autophagic activity	48 participants	7 days	n.a.	clinicaltrials.gov
	NCT04350177	1	ikT-148009	Enhancing autophagic activity	101 participants	14 days	n.a.	clinicaltrials.gov
	NCT03888222	2	Bosutinib	Enhancing autophagic activity	26 participants	3 months	n.a.	clinicaltrials.gov
GBA	NCT02914366	2	Ambroxol	Increasing glucocerebrosidase activity	75 participants	52 weeks	n.a.	clinicaltrials.gov
	NCT04588285	2	Ambroxol	Increasing glucocerebrosidase activity	172 participants	18 months	n.a.	clinicaltrials.gov
	NCT04405596	2	Ambroxol	Increasing glucocerebrosidase activity	15 participants	52 weeks	n.a.	clinicaltrials.gov

(*Continued*)

Table 3. (Continued).

Genetic subtype	Clinical trial	Phase	Tested molecule	Target, effect	Participants	Duration (treatment period or time frame of the study)	Main results	Reference
	n.a.	1b/2a	RTB101	TORC1 inhibitor	45 PD	n.a.	n.a.	Schneider *et al*., 2020 [19]
	NCT04127578	1/2a	PR001	AAV9-mediated GBA replacement	24 participants	5 years	n.a.	clinicaltrials.gov
	n.a.	1	ESB-1609	S1P5 receptor agonist	n.a.	n.a.	n.a.	Jasutkar *et al*., 2022 [21]

(Abbreviations: *GBA* – glucocerebrosidase gene; *LRRK2* – Leucine-rich repeat kinase 2 gene; n.a. – not available; PD – Parkinson's disease; *SNCA* – α-synuclein gene.) (Table 3 is based on the work of Jasutkar [21] and Schneider [19], as well as data on clinicaltrials.gov.)

The *SNCA* gene contains six exons which encode the 140 amino acid long α-synuclein protein. The protein has three domains: (1) amino-terminal region (1–60); (2) central hydrophobic domain (61–95); (3) carboxy-terminal domain (96–140) [5]. So far, a few recurrent genetic alterations have been described in the scientific literature: three missense mutations (p.A53T, p.A30P, p.E46K), duplications and triplications [5]. The three missense point mutations disrupt the amino-terminal region and modify the conformation of the protein (leading to the formation of more stable beta sheets), so they can be considered toxic gain of function mutations [5]. The Lewy bodies detected during neuropathological examinations are presumably remnants of the degenerative process, but the exact pathomechanism is still unknown [5].

The mechanisms of drug action used in clinical trials can be classified as follows: (1) immunotherapy – active or passive; (2) disruption of α-synuclein aggregations; (3) promotion of the degradation of α-synuclein; (4) targeting other diseased-related genes, which may aggravate α-synuclein production (this fourth part is detailed in other subsections) [21].

During active immunization, an antigen is administered into the body via vaccination to induce an immune response. In contrast, during passive immunization, antibodies are directly administered [19]. The hypothesis is that the injected or produced antibody binds to the pathological extracellular proteins, resulting in their removal, which alleviates disease progression [19]. To date, more than 15 relevant clinical trials have been performed with active and passive immunization in PD [21]. The following synthetic peptide molecules were tested in active immunotherapy studies: PD01A (2011–002650-31, 2013–001774-20, 2014–002489-54, 2015–004854-16, NCT02618941, NCT01885494, NCT02216188, NCT01568099), PD03A (NCT02267434) and UB-312 (NCT0407 5318). For detailed results, please see Tables 2 and 3. The overall conclusion of the above-mentioned studies is that PD01A and PD03A resulted in a measurable immune response and these molecules are generally safe and well-tolerated (the UB-312 study is currently active, no results are available) [22]. Five molecules were tested in passive immunization trials: Prasinezumab (/PRX002/RO7046015) (NCT02095171, NCT03100149 (PASADE NA), NCT04777331), BIIB054 or cinpanemab (NCT03716570, NCT03318523 (SPARK)), MEDI1341 (NCT03272165, NCT04449484) and Lu AF82422 (NCT03611569). Prasinezumab is a humanized IgG1 monoclonal antibody. The results of the phase 1 study showed that it has a good safety and tolerability profile [23]. The serum level of α-synuclein was reduced. The PASADENA study was terminated because prasinezumab therapy had no meaningful effect (either clinically or radiologically /DaT-SPECT/) [24]. The results of the other prasinezumab (NCT04777331) phase 2 study are not yet available. The two BIIB054 (cinpanemab) studies (NCT03716570, NCT03318523 (SPARK)) were terminated because they did not meet primary and secondary outcome measures [25]. The results of the MEDI131 and Lu AF8242 studies have not yet been published.

The following molecules belong to the second group, which disrupt α-synuclein aggregation [21]. Anle138b (NCT04208152, NCT04685265); NPT200-11 (NCT02606682); ENT-01 (NCT03047629, NCT04483479, NCT03781791); PBT434 and YTX-7739. Anle138b, NPT200-11 and ENT-01 inhibit alpha-synuclein formation through the disturbance of oligomerization and by displacing α-synuclein from membranes. PBT434 also blocks α-synuclein aggregation by lowering iron levels (a novel quinazolinone compound with a moderate affinity metal-binding motif). In contrast, YTX-7739 works via the inhibition of the stearoyl-CoA desaturase enzyme. Despite the limited availability of study results, we know that Anle138b and PBT434 are safe and tolerated in phase 1 clinical trials.

The general hypothesis in connection with the elimination of α-synuclein is that its soluble form is eliminated via the ubiquitin-proteasome system, while the autophagy/lysosomal system may be responsible for the breakdown of aggregates [21]. In the available clinical studies, the following molecules, acting primarily via the activation of the autophagy/lysosomal system, were tested [19,21]: Rapamycin (sirolimus) (NCT03589976), Nilotinib (NCT02281474, NCT02954978, NCT03205488), K0706/SCC-138 (NCT03316820, NCT03445338, NCT02970019, NCT03655236, NCT03996460), Radotinib (NCT04691661), FB101 (NCT04165837), ikT-148009 (NCT04350177), Bosutinib (NCT03888222). The first tested drug, namely rapamycin, acts via enhancing autophagic processes by inhibiting the mechanistic target of rapamycin (mTOR). Despite the first promising results, the applicability of rapamycin appears to be limited, given that severe side effects are expected due to the broad cellular usage of the mTOR signaling pathway. Nilotinib, as a c-Abl tyrosine kinase inhibitor, has been studied in detail. However, despite initially promising data, the molecule showed poor CSF penetration and lacked meaningful clinical effects [26]. The phase 1 studies of K0706/SCC-138 showed good safety and tolerability, both in healthy and PD patients. Two phase 2 trials are currently underway. Detailed clinical results of trials related to Radotinib, FB101, ikT-148009 and Bosutinib molecules are not currently available.

1.3. Glucocerebrosidase (*GBA*) – targeted therapies

β-glucocerebrosidase (*GBA*) heterozygous mutations are one of the most well-established risk factors of PD with variable penetrance depending on age [5]. The *GBA* gene encodes the lysosomal enzyme β-glucocerebrosidase, which has important roles in glycolipid metabolism (breakdown of glucocerebroside and glucosylsphingosine). Both autosomal recessive and dominant mutations increase the possibility of developing parkinsonism, however, the autosomal recessive form is more severe, and is called Gaucher disease, which is the most common lysosomal storage disease (with annual incidence of 1/60.000) [27]. From a clinical perspective, *GBA*-associated PD starts between the 4th and 8th decade (mean age of onset: 56.8 years). In this form of the disease there is a higher occurrence of postural instability with gait difficulty, dementia, dysautonomia and other psychiatric disturbances [5]. Pathologically, the brain alterations of patients with heterozygous *GBA* mutations are very similar to idiopathic PD patients, however, the cortical spreading of Lewy bodies are more prominent in some cases [19].

The *GBA* gene contains 11 exons. The protein has three domains: (1) domain I (residues 1–27 and 383–414) – antiparallel β sheet and two disulfide bridges (residues 4–16 and 18–

23); (2) domain II (residues 30–75 and 431–497) – immunoglobulin-like domain; (3) domain III – catalytic domain (residues 76–381 and 416–430) [28]. The exact mechanism of how heterozygous *GBA* mutations lead to the increased risk of developing PD has not been fully elucidated, but the most widely accepted mechanism is a bidirectional feedback loop between glucocerebrosidase and α-synuclein. The abnormal functioning of the glucocerebrosidase enzyme disrupts the lysosomal protein degradation process, which results in the accumulation of α-synuclein. Furthermore, α-synuclein inhibits normal neuronal lysosomal-glucocerebrosidase interaction [21,29].

Regarding the treatment of *GBA*-associated PD, it is a great advantage that many clinical trials have already been conducted in connection with Gaucher disease. However, enzyme replacement therapy (ERT), which seems to be very effective in Gaucher disease, cannot be used in GBA-associated PD, since ERT does not cross the blood-brain barrier [19]. Currently the following targeted treatments were tested in this population [19,21]: (1) – ambroxol (AiM-PD study); (2) – venglustat (MOVES-PD study); (3) – RTB101; (4) LTI-291; (5) PR001; (6) ESB-1609. Ambroxol is a well-known mucolytic agent, which binds to the active site of glucocerebrosidase and increases its activity. In the AiM-PD study (NCT02941822), 17 PD patients (8 with *GBA* mutations) were involved and the drug was given for 186 days [30]. It was well-tolerated and safe. Glucocerebrosidase level was elevated in cerebrospinal fluid (CSF), furthermore, there was a significant increase in CSF α-synuclein concentration [19]. Currently, three (NCT02914366, NCT04588285, NCT04405596) clinical trials are in progress, in which specific subpopulations are being tested (PD dementia, Lewy body dementia). Another molecule, namely venglustat, is an oral glucosylceramide synthase inhibitor. Venglustat was tested in a phase 2 multicenter, randomized, double-blind, placebo-controlled study (NCT02906020 – MOVES-PD), however, the trial was terminated because the results did not meet the primary or secondary endpoints. Only limited data are available on the other four molecules (RTB101, LTI-291, PR001, ESB-1609 under testing). However, we know from documented personal communication that LTI-291 might have a good safety and tolerability profile [19].

2. Conclusion

Although hereditary components can only be proven to be present in a very small number of cases of PD, these subpopulations are of particular importance regarding the development of personalized drugs. In this article, the three most relevant and widely tested hereditary subgroups were analyzed (*LRRK2, SNCA, GBA*). Overall, it can be concluded that many clinical studies have been carried out in connection with these targeted therapies, the vast majority being phase 1–2. From the perspective of *LRRK2*, the most promising compounds are DNL201 and DNL151. The results of clinical trials showed that these two molecules are safe and well tolerated. Among the *SNCA* immunization studies, it seems that within the active immunization procedures, PD01A may be relevant for future treatments. Anle138b, one of the α-synuclein disrupting agents, showed good tolerability and safety in the phase 1 trial, while K0706/SCC-138. Ambroxol and LTI-291 also showed good tolerability and safety during clinical trials in PD patients with the *GBA* heterozygous mutation. In conclusion, it can be declared that phase 2 and 3 studies in precisely defined subpopulations are mandatory in order to more accurately assess the effectiveness of the above-mentioned individual molecules.

3. Expert opinion

Although PD is still considered a sporadic disease, owing to the genes identified by genome-wide association studies (GWAS) it seems that a small portion of PD patients have a genetically determined etiology. These small hereditary subgroups are crucially important for drug development, because the general trend is that clinical trials involving a large heterogeneous group of PD patients, without any separation, do not meet expectations [31–33]. Our incomplete understanding of the disease mechanism, a lack of strong biomarkers which would make it possible to detect PD in the very early stages, and pathological, molecular, and environmental diversity make it difficult to identify future treatment options. Most of the clinical trials detailed in the manuscript are currently at phase 1 or 2 levels. As a result, at present no long-term conclusions can be drawn regarding the effectiveness of the molecules tested in these studies.

The main difficulty of future clinical trials on genetically defined subpopulations stems primarily from the small number of patients, so international collaborations and patient registry development are necessary. Additionally, considering that the individual forms of the disease are very rare, it can be challenging to assess the effectiveness with the often-used clinical condition assessment scales (e.g. Unified Parkinson's Disease Rating Scale). However, it seems that genetic testing is important, not only from the perspective of drug development, but also to provide a precise prognosis. The knowledge related to individual genetic subtypes is constantly increasing. The disease course, the effectiveness of levodopa and deep brain stimulation treatment can be predicted by specifying the exact genetic subtypes. With knowledge of that information, patients can receive personalized counseling and the opportunity to make individual decisions.

The organization of future clinical trials on a genetic basis presents many additional challenges. First of all, there is the question of which patients should be offered genetic testing in connection with PD before being involved in a clinical trial. Although early-onset of the disease, a characteristic phenotype, and a positive family history can help in making decisions, patients without these features may also have genetic backgrounds. A negative family history can be explained by a reduced penetrance, different age of onset, de novo mutations, etc. If genetic testing occurs, mainly in the form of clinical exome sequencing, the interpretation of the obtained results is often challenging. In the optimal case, a known pathogenic mutation in a disease-causing gene is confirmed, so there is no obstacle to patient inclusion in a targeted clinical trial. However,

clinical settings are rarely so ideal. In most cases, unknown variants (variant of unknown significance – VUS) are detected or negative results are obtained. Although in a framework of international collaboration, it is possible to create a small number of patient groups in which the participants carry a mutation in the same gene, the phenotype of these patients and their responses to molecular therapy may still be different. Knowing this, pharmaceutical companies have the following options if they want to organize a precision clinical trial: (1) – during preclinical animal studies, they identify patients with mutations in the same gene that allow them to be classified into one clinical trial group; (2) – design drugs for hot-spot mutations (e.g. *LRRK2* Gly2019Ser).

In conclusion, the authors' opinion is that in the 21st century, genetic testing should be part of the workup of PD patients before exposing them to additional, non-conventional (e.g. targeted molecular therapies) treatments.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Poewe W, Seppi K, Tanner C, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3(1):17013.
• **An excellent review paper of Parkinson's disease.**
2. Riboldi GM, Frattini E, Monfrini E, et al. A practical approach to early-onset Parkinsonism. J Parkinsons Dis. 2022;12(1):1–26.
• **A practical summary of the forms of early-onset Parkinson's disease.**
3. Lin CH, Chen PL, Tai CH, et al. A clinical and genetic study of early-onset and familial parkinsonism in Taiwan: an integrated approach combining gene dosage analysis and next-generation sequencing. Mov Disord. 2019;34(4):506–515.
4. Wagh AR, Bose K. Emerging roles of mitochondrial serine protease HtrA2 in neurodegeneration. In: Chakraborti S, Dhalla N, editors. Proteases in physiology and pathology. Singapore: Springer. 2017;15:325–353.
5. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2(1):008888.
• **An excellent summary of the genetic background of Parkinson's disease**
6. Senkevich K, Rudakou U, Gan-Or Z. New therapeutic approaches to Parkinson's disease targeting GBA, LRRK2 and Parkin. Neuropharmacology. 2022;202:108822.
• **A review with special focus on the novel therapeutic approaches related to LRRK2, GBA and PRKN genes**
7. Rogers G, Davies D, Pink J, et al. Parkinson's disease: summary of updated NICE guidance. BMJ. 2017;358:1951.
• **Treatment guidelines for Parkinson's disease**
8. Tolosa E, Vila M, Klein C, et al. LRRK2 in Parkinson disease: challenges of clinical trials. Nat Rev Neurol. 2020;16(2):97–107.
• **A great summary about the difficulty of organizing precision clinical trials.**
9. Poulopoulos M, Levy OA, Alcalay RN. The neuropathology of genetic Parkinson's disease. Mov Disord. 2012;27(7):831–842.
• **Detailed description of the neuropathological features of genetic forms of Parkinson's disease**
10. Azeggagh S, Berwick DC. The development of inhibitors of leucine-rich repeat kinase 2 (LRRK2) as a therapeutic strategy for Parkinson's disease: the current state of play. Br J Pharmacol. 2022;179(8):1478–1495.
11. Fuji RN, Flagella M, Baca M, et al. Effect of selective LRRK2 kinase inhibition on nonhuman primate lung. Sci Transl Med. 2015;7(273):273ra15.
12. Baptista MAS, Merchant K, Barrett T, et al. LRRK2 inhibitors induce reversible changes in nonhuman primate lungs without measurable pulmonary deficits. Sci Transl Med. 2020;12(540):eaav0820.
13. Jennings D, Huntwork-Rodriguez S, Henry AG, et al. Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. Sci Transl Med. 2022;14(648):2658.
Clinical study of the DNL201 molecule.
14. Ding X, Ren F. Leucine-rich repeat kinase 2 inhibitors: a patent review (2014-present). Expert Opin Ther Pat. 2020;30(4):275–286.
15. Levin J, Sing N, Melbourne S, et al. Safety, tolerability and pharmacokinetics of the oligomer modulator anle138b with exposure levels sufficient for therapeutic efficacy in a murine Parkinson model: a randomized, double-blind, placebo-controlled phase 1a trial. EbioMedicine. 2022;80:104021.
16. Stamler D, Bradbury M, Wong C, et al. A first in human study of PBT434, a novel small molecule inhibitor of α-synuclein aggregation. Neurology. 2019;92:S4.001.
17. Pagan F, Hebron M, Valadez EH, et al. Nilotinib effects in Parkinson's disease and dementia with Lewy bodies. J Parkinsons Dis. 2016;6(3):503–517.
18. Pagan FL, Hebron ML, Wilmarth B, et al. Nilotinib effects on safety, tolerability, and potential biomarkers in Parkinson disease: a phase 2 randomized clinical trial. JAMA Neurol. 2020;77(3):309–317.
19. Schneider SA, Hizli B, Alcalay RN. Emerging targeted therapeutics for genetic subtypes of Parkinsonism. Neurotherapeutics. 2020;17(4):1378–1392.
• **Nice summary of the clinical trials related to genetic forms of Parkinson's disease**
20. Polymeropoulos MH, Higgins JJ, Golbe LI, et al. Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science. 1996;274(5290):1197–1199.
21. Jasutkar GH, Oh SE, Mouradian MM. Therapeutics in the pipeline targeting α -synuclein for Parkinson's disease. Pharmacol Rev. 2022;74(1):207–237.
• **A review with special focus on the novel therapeutic approaches related to the SNCA gene**
22. Volc D, Poewe W, Kutzelnigg A, et al. Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial. Lancet Neurol. 2020;19(7):591–600.
23. Schenk DB, Koller M, Ness DK, et al. First-in-human assessment of PRX002, an anti-α-synuclein monoclonal antibody, in healthy volunteers. Mov Disord. 2017;32(2):211–218.

24. Pagano G, Taylor KI, Anzures-Cabrera J, et al. Trial of prasinezumab in early-stage Parkinson's disease. N Engl J Med. 2022;387(5):421–432.
25. Lang AE, Siderowf AD, Macklin EA, et al. Trial of cinpanemab in early Parkinson's disease. N Engl J Med. 2022;387(5):408–420.
26. Simuni T, Fiske B, Merchant K, et al. Efficacy of nilotinib in patients with moderately advanced Parkinson disease: a randomized clinical trial. JAMA Neurol. 2021;78(3):312–320.
27. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci. 2017;18(2):441.
•• **Summary of Gaucher disease.**
28. Do J, McKinney C, Sharma P, et al. Glucocerebrosidase and its relevance to Parkinson disease. Mol Neurodegeneration. 2019;14(1):36.
29. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011;146(1):37–52.
30. Mullin S, Smith L, Lee K, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial. JAMA Neurol. 2020;77(4):427–434.
31. Prasuhn J, Brüggemann N. Genotype-driven therapeutic developments in Parkinson's disease. Mol Med. 2021;27(1):42.
32. Brüggemann N, Klein C. Will genotype drive treatment options? Mov Disord. 2019;34(9):1294–1299.
33. Poortvliet PC, O'Maley K, Silburn PA, et al. Perspective: current pitfalls in the search for future treatments and prevention of Parkinson's disease. Front Neurol. 2020;11:686.