3. Results

3.1. Patient disposition

Of 266 patients who provided consent to participate in this study, 182 were eligible for inclusion and enrolled (Fig. 1). All patients who entered the study received the investigational product. Of these, 49 discontinued treatment mainly due to AEs ($n=24$) and withdrawal of consent ($n=16$). A total of 133 patients completed the 52-week treatment period. Nearly all patients who completed the treatment period and approximately one-third of those who withdrew during the treatment period entered the dose-tapering and follow-up periods. One patient violated the study protocol; the remaining, 181 patients were included in the FAS.

3.2. Patient characteristics

The baseline characteristics of the patients in the FAS ($n=181$) are shown in Table 1. The mean (±SD) age was 54.9±12.2 years, body weight was 60.2±9.4 kg, and body mass index was 23.0±2.6 kg/m^2. The mean duration of RLS was 10.6±11.0 years, and 18 patients (9.9%) had a family history of RLS.

3.3. Treatment duration and dose changes

The mean duration of treatment with GEn was 283 days, and the overall compliance rate was 91.4%. Of 182 patients treated with GEn, the daily dose was increased to 1500 mg in four individuals because of insufficient efficacy. None of these patients withdrew from the study after the dose increase. The dose of GEn was reduced to 900 mg in 18 patients because of AEs (Table 1). These patients, except for one who discontinued the treatment due to withdrawal of consent, completed the trial period.

Table 1
Baseline characteristics of the patients (FAS, $n=181$).

Parameter	
Sex M/F, n (%)	88 (48.6)/93 (51.4)
Age, mean (range), years	54.9±12.2 (21–76)
BMI, mean (range), kg/m^2	23.0±2.6 (18.5–29.6)
Duration of RLS morbidity, years	10.6±11.0
IRLS total score	24.4±5.1
Final daily dosage prior to tapering, n (%)	
600 mg[a]	8 (4.4)
900 mg	18 (9.9)
1200 mg	151 (83.4)
1500 mg	4 (2.2)

Values are expressed as mean±SD. FAS: full analysis set.
[a] Patients who discontinued treatment during the first 3 days, before uptitration to 1200 mg/day.

3.4. Efficacy

The mean (±SE) baseline IRLS score was 24.4±0.4 and decreased to 14.5±0.6 after 1 week of treatment, representing a statistically significant change from baseline of −9.9±0.6 ($p<0.001$). As shown in Fig. 2, the IRLS score continued to decrease throughout the treatment period, and the decrease remained statistically significant through to week 52. The IRLS score at week 52 was 6.3±0.6, representing a change from baseline of −18.0±0.6. The IRLS responder rate was 80.3% at week 52, while the ICGI and PCGI responder rates were 87.1% and 87.1%, respectively. The time-course of changes in IRLS, ICGI and PCGI responder rates is depicted in Fig. 3.

The scores for PSQI and SF-36 at week 52 were significantly improved in comparison with the baseline values (all domains, $p<0.001$ except for Use of Sleep Medicine (C6) of PSQI, $p=0.041$,

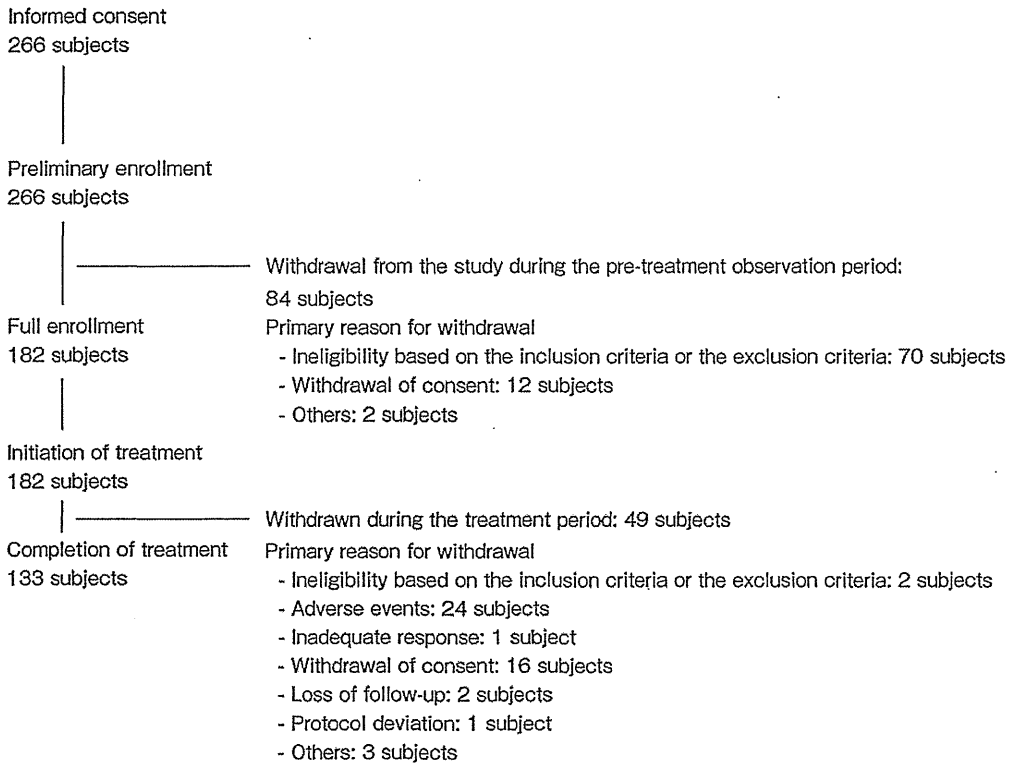

Fig. 1. Patient disposition.

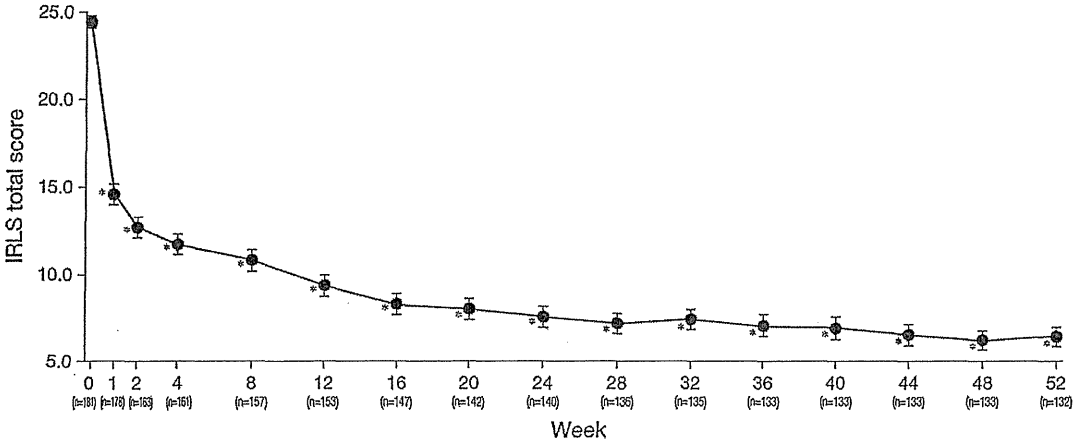

Fig. 2. Change in IRLS total score over 52 weeks of treatment with GEn (FAS). Values are expressed as mean ± SE. *$p<0.001$ vs week 0 (paired t-test).

and Physical Functioning of SF-36, $p=0.003$, Table 2). At the completion of treatment, the change in the total PSQI score from baseline was −2.9 ± 3.41. Changes in subscores were as follows: −0.6 ± 0.85 for Sleep Quality (C1), −0.6 ± 1.06 for Sleep Latency (C2), −0.5 ± 0.84 for Sleep Duration (C3), −0.5 ± 0.98 for Habitual Sleep Efficacy (C4), −0.2 ± 0.56 for Sleep Disturbance (C5), −0.1 ± 0.43 for Use of Sleep Medicine (C6), and −0.4 ± 0.97 for Daytime Dysfunction (C7). Score changes in each SF-36 subscale at the completion of treatment from baseline were 2.00 ± 11.793 for Physical Functioning, 1.64 ± 26.794 for Role Physical, 8.01 ± 24.662 for Bodily Pain, 4.69 ± 15.264 for General Health, 5.46 ± 20.994 for Vitality, 3.36 ± 25.292 for Social Functioning, 1.00 ± 23.421 for Role Emotional, and 3.17 ± 19.764 for Mental Health.

3.5. Multiple regression analysis and logistic model analysis

Multiple regression analysis revealed that a high baseline IRLS total score and male sex were significantly associated with the reduction in IRLS score (baseline IRLS total score: $\beta=-0.59$, $p<0.001$; male sex: $\beta=-4.23$, $p=0.001$). Meanwhile, logistic regression analysis showed that low baseline IRLS total score and male sex were significantly associated with higher responder rates to treatment with GEn (baseline IRLS total score: OR = 0.928, 95% CI = 0.868–0.992, $p=0.0275$; male sex: OR = 0.417, 95% CI = 0.204–0.853, $p=0.0166$). On the other hand, age and BMI were not associated with the reduction in IRLS score or the IRLS responder rate.

3.6. Safety

AEs and treatment-related AEs were reported in 96.2% and 90.7% of patients, respectively. Serious AEs occurred in 3 of 182 patients (1.6%), including one death due to lymphoma that was considered possibly related to treatment with GEn on the basis of a temporal relationship. AEs arising in ≥5% of patients are summarized according to their frequency and severity in Table 3. The most common AEs included dizziness ($n=84$; 46.2%), somnolence ($n=75$; 41.2%), and nasopharyngitis ($n=55$; 30.2%). Moderate AEs reported in at least two patients included dizziness in 18 patients, somnolence in 17 patients, nausea in four patients, blood creatine phosphokinase increased in three patients, and headache in three patients.

AEs led to discontinuation in 24 patients (13.2% of total subjects). All of these AEs were mild or moderate in severity and most commonly included dizziness ($n=8$; 4.4%), nausea ($n=5$; 2.7%), followed by vertigo, headache and somnolence ($n=3$; 1.6% each). AEs led to a reduction of GEn dose in 18 patients (9.9%).

Laboratory values and vital signs after the start of treatment were comparable with those before stating GEn. During treatment, one patient experienced two episodes of QT prolongation that were not

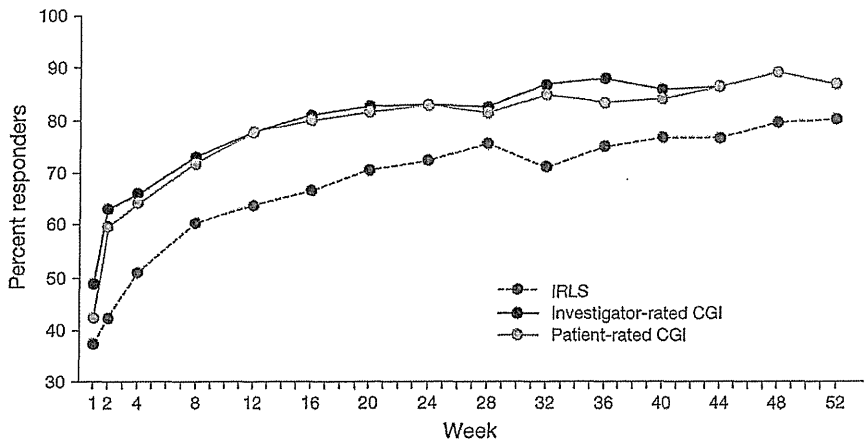

Fig. 3. Time-course of responder rates for IRLS (IRLS total score ≤10), ICGI and PCGI ("much improved" or "very much improved").

Table 2
Comparisons of PSQI and SF-36 scores between baseline and week 52 of the treatment period.

	Baseline ($n=181$)	Week 52 ($n=132$)	p value[a]		Baseline ($n=181$)	Week 52 ($n=132$)	p value[a]
PSQI total score	8.5	4.9	$p<0.001$	SF-36			
Sleep Quality (C1)	1.8	1.0	$p<0.001$	Physical Functioning	89.36	93.22	$p=0.003$
Sleep Latency (C2)	1.8	1.0	$p<0.001$	Role Physical	86.15	93.61	$p<0.001$
Sleep Duration (C3)	1.8	1.3	$p<0.001$	Bodily Pain	71.99	83.73	$p<0.001$
Habitual Sleep Efficacy (C4)	0.8	0.2	$p<0.001$	General Health	60.33	67.29	$p<0.001$
Sleep Disturbance (C5)	1.0	0.7	$p<0.001$	Vitality	56.84	66.43	$p<0.001$
Use of Sleep Medicine (C6)	0.1	0.0	$p=0.041$	Social Functioning	84.32	92.61	$p<0.001$
Daytime Dysfunction (C7)	1.1	0.6	$p<0.001$	Role Emotional	85.50	92.05	$p<0.001$
				Mental Health	69.12	75.95	$p<0.001$

Values are means.
[a] Paired t-test (two sided, $\alpha=0.05$).

considered clinically significant but were reported as AEs possibly related to the investigational product. Both events were mild and resolved during the study.

No specific AEs suggestive of withdrawal symptoms were reported during the dose-tapering or follow-up period. No incidence of investigator-reported augmentation was noted.

3.7. Dizziness and somnolence

Since dizziness and somnolence were the most common AEs, we analyzed the incidence and the prevalence of these AEs in each 4-week period of the study. In most patients, dizziness and somnolence occurred early during the treatment period, usually within 4 weeks after starting treatment (Fig. 4). The incidence of these specific AEs gradually declined as the study progressed. The rates of new-onset dizziness and somnolence were 42.3% and 37.4%, respectively, in the first 4 weeks of treatment. After week 4, the rates of new onset dizziness and somnolence were 0.0–2.4% and 0.0–1.4%, respectively. The prevalence of these events gradually decreased over time (dizziness: 42.3% (0–4 weeks) to 9.2% (week 52); somnolence: 37.4% (0–4 weeks) to 13.7% (week 52)).

4. Discussion

In this study conducted in Japanese patients, treatment with GEn for 52 weeks elicited marked improvements of RLS symptoms as well as both patient- and investigator-rated assessments of the disease. These findings extend those reported in previous studies of GEn, which revealed significant improvements of RLS symptoms that were observable as early as 1–2 weeks after starting treatment (Kushida et al., 2009; Walters et al., 2009). Notably, the magnitude of improvements of symptoms observed in our study is broadly comparable with that seen in long-term studies of DAs such as pramipexole (Inoue et al., 2010; Montplaisir et al., 2006a; Partinen et al., 2008), rotigotine (Oertel et al., 2008; Trenkwalder et al., 2008a) and ropinirole (Garcia-Borreguero et al., 2007; Montplaisir et al., 2006b). Furthermore, our study was the first to show that GEn improved other outcome measures, including aspects of QoL and subjective sleep disturbance. These findings are consistent with the results of previous studies evaluating the use of DAs or short-term GEn for the treatment RLS (Giorgi et al., 2006; Kushida et al., 2009; Winkelman et al., 2006b).

Table 3
Adverse events (AEs) occurring in ≥5% of patients according to frequency and severity (SAS, $n=182$).

Preferred term	n (%)	Severity, n (%)	
		Mild	Moderate
Dizziness	84 (46.2)	66 (36.3)	18 (9.9)
Somnolence	75 (41.2)	58 (31.9)	17 (9.3)
Nasopharyngitis	55 (30.2)	55 (30.2)	–
Blood CPK increased	29 (15.9)	26 (14.3)	3 (1.6)
Blood uric acid increased	18 (9.9)	18 (9.9)	–
Constipation	15 (8.2)	15 (8.2)	–
Feeling abnormal	14 (7.7)	13 (7.1)	1 (0.5)
Back pain	13 (7.1)	12 (6.6)	1 (0.5)
Eosinophil count increased	12 (6.6)	11 (6.0)	1 (0.5)
Glucose urine present	12 (6.6)	12 (6.6)	–
Abdominal discomfort	10 (5.5)	10 (5.5)	–
ALT increased	10 (5.5)	10 (5.5)	–

ALT: alanine aminotransferase, CPK: creatine phosphokinase, SAS: safety analysis set.

We conducted exploratory analyses to identify factors that might influence the magnitude of change of IRLS score from baseline to week 52 and the IRLS responder rate. Multiple regression analysis revealed that the change in IRLS total score was significantly greater in patients with high baseline scores than in patients with low baseline scores. On the other hand, logistic regression analysis showed that patients with low baseline scores were significantly associated with being IRLS responders following GEn treatment. The discrepancy between these results suggests the difficulty in identifying the treatment response of GEn from the severity of the disorder before starting the treatment. Our exploratory analyses also detected significant differences between the sexes, with a greater reduction of IRLS score and a higher IRLS responder rate in men than in women. The underlying reason for this finding is unclear; possibly it is an artifact of the fairly small sample size. Further research with a larger sample of patients may shed more light on the possibility of a differential response to GEn between the sexes.

In this study, the most frequently observed AEs were, as expected from previous studies of GEn in RLS (Bogan et al., 2010; Kushida et al., 2009), nervous system-related disorders such as dizziness and somnolence, infections such as nasopharyngitis, and gastrointestinal disorders such as abdominal discomfort and constipation. Although somnolence and dizziness occurred in almost half of our patients and dizziness, at a rate of 4.4%, was the most frequently noted AE leading to discontinuation, the majority of AEs were mild to moderate in intensity and resolved during the study. On the other hand, the relatively high incidence rate of AEs observed during this study (>90%) and the higher rates of dizziness and somnolence arising in Japanese patients compared with those in patient populations in Western countries (Bogan et al., 2010) should be considered, and caution exercised when prescribing GEn, particularly during the early period of treatment.

Interestingly, in the present study, the prevalence of dizziness and somnolence gradually decreased over time, indicating that these symptoms were transient and resolved spontaneously. Most cases were mild and symptoms led to a dose reduction in only 18 patients, most of whom were able to continue treatment after reducing the dose. These findings suggest good tolerability of GEn for long-term treatment of RLS. Furthermore, unlike in previous studies of dopaminergic agents, no episodes of augmentation were reported during long-term treatment with GEn in the present study.

This study has some limitations that should be considered. Most importantly, this study was an observational study and not a randomized, controlled trial. The protocol followed an open-label design and

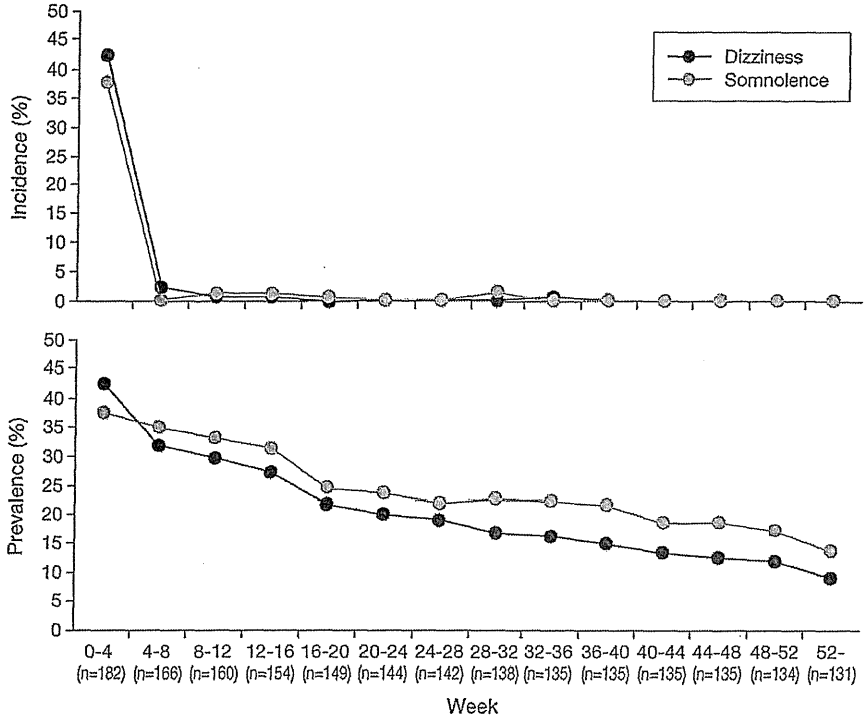

Fig. 4. Incidence (new onset) and prevalence (all cases) of dizziness and somnolence.

there was no control group. Thus, it was not possible to determine whether the improvements in RLS symptoms observed in this study were solely due to the prescribed treatment, or to what extent there was a placebo effect—as is normally the rule rather than the exception in studies using IRLS score as efficacy endpoint (Fulda and Wetter, 2008). Nevertheless, the marked reduction in IRLS score, clear improvement of measures of sleep disturbance and QOL, and the high IRLS responder rate demonstrate the clinical usefulness of GEn in Japanese patients with RLS. Randomized, double-blind, placebo/active-controlled trials are desirable to confirm these preliminary results.

5. Conclusion

In conclusion, this study revealed that long-term treatment with GEn improved RLS symptoms as well as investigator- and patient-reported outcomes in Japanese patients with moderate-to-severe RLS, along with an acceptable safety profile. Therefore, GEn seems to be a useful new addition to the treatment armamentarium against RLS.

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Role of the funding source

Astellas Pharma Inc. was involved in the study design and data collection but not in the writing of the report or in the decision to submit the paper for publication.

Authors' contributions

All authors contributed to study conception/design and writing of the report. YI performed data analysis and interpreted the results. All authors read and approved the final manuscript.

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Patient Related Outcome Measures

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ORIGINAL RESEARCH

Patient perspectives on Parkinson's disease therapy in Japan and the United States: results of two patient surveys

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Background: Despite evidence suggesting that patient attitudes towards therapy may influence treatment outcomes, the impact of these factors on treatment for Parkinson's disease is poorly understood. These two surveys, based in Japan and the US, investigated the attitudes of patients towards antiparkinsonian medications, the complications of these therapies, and how these differ across geographies.

Methods: The US PRELUDE survey collected data from May 13 to May 20, 2003, from 300 interviews with patients with Parkinson's disease from the National Parkinson Foundation. The Japanese survey was carried out from June to December 2008 in a stepwise manner using questionnaires (n = 3548) followed by interviews with those who had consented to participate in the questionnaire (n = 407). Both surveys assessed the attitudes of patients towards therapies for Parkinson's disease and associated complications.

Results: Dyskinesia was not a major challenge of therapy for Parkinson's disease, and wearing-off caused greater concern in the US, while hallucinations had a greater emphasis in Japan. Patients who had previously experienced dyskinesia were less concerned about this side effect than those who had not. Although pill burden was thought to be a concern in the US, Japanese patients did not indicate that pill burden would limit their drug intake. There were also discrepancies between the perspectives and concerns of patients and those of their treating physicians.

Conclusion: Recognizing patient perspectives regarding therapies for Parkinson's disease and associated complications, as well as certain cultural influences, is important in the management of parkinsonian symptoms. Acknowledging these concerns may improve the standard of care in patients with Parkinson's disease. In addition, improved patient education and effective patient–physician communication in both countries may improve compliance and treatment outcomes in patients with the disease.

Keywords: Parkinson's disease, patient concerns, dyskinesia, wearing-off, hallucinations

Introduction

It is generally accepted that patient health and therapeutic outcomes are influenced by beliefs about and attitudes toward medications, and expectations from therapy, as well as level of education and awareness about the disease and its management.[1,2] This is particularly true for long-term, chronic illnesses, whereby patients must make lifestyle adjustments to accommodate increasing disability.[2,3] Patient decisions to follow a recommended treatment are also likely to be influenced by beliefs about medications and understanding about a medical illness. For example, despite the prevalence of available therapies, there is a high rate of early treatment discontinuation in patients suffering from depression, owing to factors such as a perceived stigma of mental

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health problems, which consequently impacts therapeutic outcome.[4] Although it is evident that these factors play a role in treatment outcomes, the influence of patient perspectives towards therapy has not been well documented.

Patient attitudes regarding Parkinson's disease (PD) may influence the types and dosing frequencies of medications available for symptomatic treatment. PD is a progressive, chronic illness that impacts motor abilities and quality of life. The armamentarium for PD management includes many agents that are associated with a wide range of benefits and potential risks. For example, levodopa is associated with an increased risk of motor complications, including dyskinesia and motor fluctuation (wearing-off), while the side effects of dopamine agonists include hallucinations, somnolence, edema, and impulse control disorders.[5,6] Tailoring therapy according to individual unique symptoms is important to achieve successful treatment outcomes.[5] Patient perspectives on treatment strategies, and the differences in these factors across different geographies, are poorly defined. Understanding these differences may improve therapeutic outcomes.

To this end, two surveys were conducted, one in the US and another in Japan, to investigate the attitudes and concerns of patients regarding PD therapy. The results of these surveys suggest unmet needs regarding PD therapy, as well as discrepancies between patient and physician perspectives. They also identify cultural differences in patient attitudes.

Materials and methods

PRELUDE (PRoject to Examine Levodopa Utilization DEcisions) was a two-part survey carried out in the US, comprising patient and physician questionnaires.

Patient survey

Data were collected from May 13 to May 20, 2003, from 300 interviews of people with PD currently using levodopa-carbidopa therapy. The respondents were sampled from the National Parkinson Foundation list of 10,000 email newsletter recipients; invitations to participate in the survey were embedded in the National Parkinson Foundation email newsletter and sent each day until all 300 questionnaires were completed. Each respondent was assigned an individual identification number and password to ensure that patients only completed the survey once. For each participant, a US $15 honorarium for completing the study and a US $15 donation to the National Parkinson Foundation were given.

Physician survey

In this part of the survey, data were collected online between April 16 and 29, 2003, from 328 general neurologists, 74 movement disorder specialists, and 54 primary care physicians. To qualify, all physicians must have treated patients with PD (at least some with levodopa-carbidopa) and have been in practice for ≥2 years and ≤30 years.

Japanese survey

This survey focused on patient attitudes toward PD and its treatment, and was completed in Japan from June to December 2008 in a stepwise manner, initially with questionnaires, then interviews with those who had consented in the questionnaire to be interviewed.

Questionnaires were sent to approximately 7000 members of the Japan Parkinson Disease Association and about 1200 nonmembers. Data were collected from 4011 respondents between July and August 2008. A total of 387 participants who received deep brain stimulation were excluded, and 3548 evaluable respondents were assessed. A total of 2316 of these patients provided their consent to participate in interview-based research. Patients were extracted at random.

A total of 407 of the patients who responded to the questionnaire-based survey participated in the on-site, interview-based survey between August and December 2008. Thirty-six participants who received deep brain stimulation were excluded from the analysis relating to drug medication.

The presence of wearing-off or dyskinesia was determined in both parts of the survey. In the questionnaire-based survey, this was accomplished by enquiring about the efficacy of medication. During the interview part of the survey, patients were asked to record the severity of symptoms in relation to timing of each dose in a diary for one day prior to the interview. Symptom severity was based on patient self-perception and was measured using the Hoehn and Yahr scale by examining physicians.

Results

Patient characteristics

Patient characteristics for both the Japanese and US PRELUDE studies are summarized in Table 1. Patients with potential motor fluctuations and several years of treated PD were recruited in both surveys. In Japan, 95% of patients were receiving levodopa, mostly as therapy supplementary to dopamine agonists or monoamine oxidase B inhibitors. Between 70% and 80% of the US PRELUDE respondents were receiving levodopa therapy; around half of these

Table 1 Patient characteristics

Patient characteristics	Japanese study	US study
Mean age (years)	69	N/A
Duration of PD (years)	3–9 (majority)	7 (mean)
Patients receiving levodopa (%)	95	70–80
Patients receiving DAs (%)	85	57
Patients receiving MAO-B inhibitors (%)	42	N/A
Patients receiving COMT inhibitors, including entacapone (%)	25	29

Abbreviations: PD, Parkinson's disease; DA, dopamine agonists; MAO-B, monoamine oxidase B; N/A, not applicable; COMT, catechol-*O*-methyl transferase.

received dopamine agonist treatment before initiating levodopa-carbidopa therapy.

Attitude towards motor complications and other adverse effects

Wearing-off is a concern for PD patients

In the US PRELUDE study, more PD patients were concerned about wearing-off (55%) than about dyskinesia (23%, Figure 1). Although primary care physicians generally agreed with this concern (63%), specialists considered dyskinesia to be a greater concern (32% of neurologists and 50% of movement disorder specialists, compared with 7% of primary care physicians).

Balance between adverse effects and efficacy of medication

In Japan, more than half of patients experiencing fluctuations preferred to avoid the adverse effects of antiparkinsonian medication rather than obtain effective relief from bradykinesia (Figure 2). However, the number of patients preferring relief from bradykinesia gradually increased with escalating symptom severity during off periods. This preference for avoiding adverse effects was similar in patients with (47.6%) and without (47.9) wearing-off. When interviewed, Japanese patients who preferred to avoid adverse effects were more concerned about hallucinations (44.6% of unaided responses) than other adverse effects such as constipation (12.2%), drowsiness (9.5%), or nausea (6.8%). In fact, compared with hallucinations, dyskinesia was identified as an important adverse effect by fewer Japanese patients (Figure 3).

Balance between dyskinesia and efficacy of medication

In the overall population, Japanese patients experiencing on/off fluctuations preferred to avoid dyskinesia (about 45%) rather than achieve relief from bradykinesia (about 25%). Patients who had not yet experienced dyskinesia were more keen to avoid this complication (approximately 55%) rather than obtain relief from bradykinesia (approximately 45%), whereas patients who had already developed dyskinesia were less concerned about this adverse effect (approximately 40%). Reasons for this concern in patients who had not yet experienced dyskinesia included anticipation of the mental burden of this adverse effect from observing it in other patients. They were also concerned that dyskinesia might prevent them from carrying out normal daily activities, such as working, and were worried about others' reactions to these abnormal movements when in public. In contrast, patients with mild dyskinesia tended to prefer improved mobility versus avoiding dyskinesia (nearly 42% versus 32%). However, patients who had experienced severe dyskinesia indicated they would rather avoid this adverse effect (about 42%) than obtain relief from bradykinesia (around 37%).

Patient attitudes towards medication

In the US, patients' main concerns about levodopa-carbidopa were wearing-off, long-term side effects of levodopa-carbidopa therapy, and disease progression (Table 2). Although generally

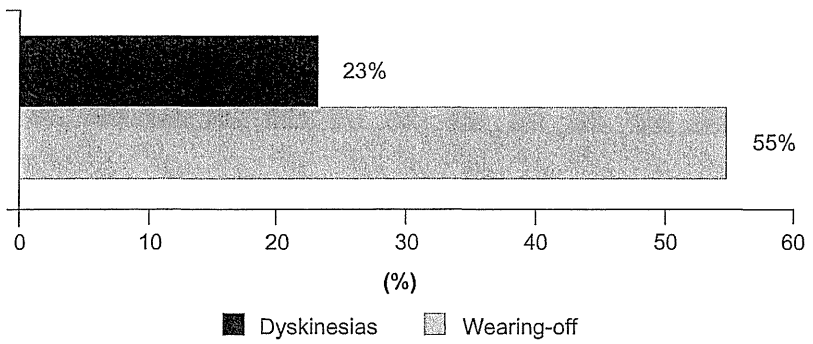

Figure 1 Percentage of patients in the US survey reporting dyskinesias or wearing-off as the greatest challenge of therapy.

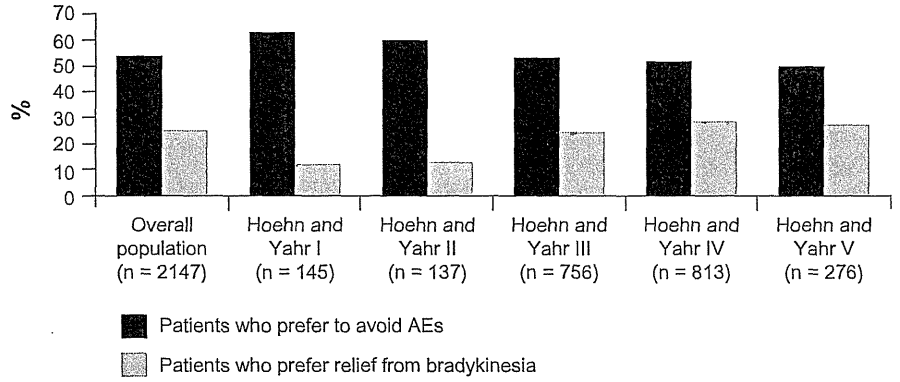

Figure 2 Percentage of patients in the Japanese survey who preferred to avoid adverse events compared with those who preferred relief from bradykinesia.
Note: Hoehn and Yahr[7] measurements were taken during off periods.
Abbreviation: AE, adverse effect.

satisfied with levodopa-carbidopa, 55% of US patients with PD were at least somewhat concerned about taking levodopa-carbidopa, mostly owing to information gathered from the Internet (69%) or from varied sources (58%). In addition, 26%–34% of patients indicated that their concern stemmed from information from physicians, support groups, or newsletters.

In Japan, the percentage of patients dissatisfied with current pharmacotherapy tended to increase with a longer duration of PD. In addition, patients who were not suffering from wearing-off were more satisfied with their current pharmacotherapy than those who were experiencing wearing-off symptoms (49% versus 36%, respectively).

Attitudes towards drug intake and dose increases

In the US, physicians felt strongly that patients would be more satisfied with reduced pill burden (96.3%). They also believed that drug dissatisfaction stemmed from inconsistencies in symptom control achieved with generic formulations of levodopa-carbidopa (62.6%).

When interviewed, Japanese patients generally preferred to obtain relief from bradykinesia (about 50%) rather than limit their medication intake (about 40%). This preference for symptomatic relief was similar in patients with or without wearing-off. The main reason for this preference was a desire to carry on with day-to-day activities, such as employment or housework. Patients who preferred to limit drug intake and dose were concerned about the adverse effects associated with increased pharmacotherapy (68.5%); concern about wearing-off accounted for 10.5% of unaided responses. Other reasons for preferring to limit dose intake included compliance (4.8%) and the apprehension that drugs may affect health (6.5%).

Interestingly, the levodopa-equivalent dose of antiparkinsonian medication did not differ between satisfied and dissatisfied patients in Japan. According to a survey of 121 Japan-based physicians at the 2008 Movement Disorders

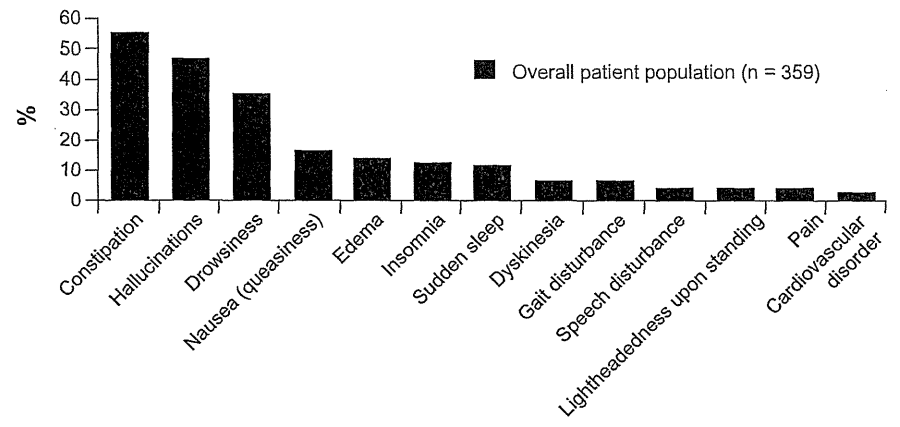

Figure 3 Adverse effects of antiparkinsonian medication that concerned patients in the Japanese survey.
Note: Patients who did not include a specific response were excluded from this analysis.

Table 2 Reasons patients in the US thought they were switched to levodopa-carbidopa, and why they were concerned about taking levodopa-carbidopa

Perceived reasons for being switched to LC[a]	**Patients (%)**[a]
My PD symptoms were getting progressively worse	55
My PD symptoms did not get worse, but I did not get good symptom control with previous treatments	16
I do not know/my doctor recommended it	15
I could not tolerate the side effects of previous treatments	10
Other reason	5
Concerns about taking LC	**Patients (%)**
Long-term side effects of LC, such as dyskinesias (uncontrolled movements, wiggles)	52
Benefits may begin to wear off sooner than desired	49
An indication that my PD might have advanced to a more severe stage	46
Immediate side effects of LC, such as nausea and vomiting	34
Fear that LC might make my PD worse	23
Being able to afford LC	21

Notes: [a]Respondents who were not initiated on levodopa (n = 110); patients who did not provide a specific response were excluded from this analysis.
Abbreviations: LC, levodopa-carbidopa; PD, Parkinson's disease.

Society of Japan conference held in Kyoto, the most commonly used daily dose of levodopa ranged from 300 mg to 400 mg.[8] For many Japanese providers, the highest daily dose of levodopa was 300 mg, even for patients with advanced PD. Consistent with this, about 17% of patients who were interviewed stated that they had been informed by their physician that their medication could no longer be increased, despite the suggestion of increasing motor disability.

Discussion

Despite being the most effective treatment for PD, the higher possibility of motor complications associated with levodopa may result in potential underdosing.[5] Although dyskinesias are often regarded as one of the most important complications of levodopa therapy,[9] this project suggests that dyskinesias were not a primary concern for patients surveyed in either the US or Japan. In the US, patients were more concerned about wearing-off, whereas other adverse effects, such as hallucinations, were of greater concern to Japanese patients. Interestingly, Japanese patients who had not yet experienced dyskinesia were more concerned about this adverse effect than those with a prior history of dyskinesia, possibly due to concern regarding the mental burden and hardship of the condition. Although primary care providers in the US recognized the importance of wearing-off, specialists considered dyskinesias to be of equal, if not greater, concern for patients. This suggests that patient concerns about dyskinesia may, in some cases, be overestimated by physicians, and may cause some hesitation when prescribing levodopa.

Patient perspectives on treatment options are, among other things, influenced by disease stage, symptom severity, and experience of adverse effects. Understanding patient attitudes towards PD therapies and the associated complications may help physicians devise individualized treatment strategies. There is currently a multitude of therapeutic options for patients with PD, and individual benefit varies significantly among patients. The benefit of efficient communication between the patient and the doctor in any culture cannot be overestimated, particularly when individualizing treatment. However, improved patient education and awareness is paramount for effective patient–physician communication. Patients need to understand the symptoms of PD, and be aware of the implications of certain therapies in order to be familiar with signs of disease progression or treatment complications.

The results of our US survey highlight a further discrepancy between physicians and patients as to reasons for initiation of levodopa-carbidopa therapy: while the majority of patients believed levodopa-carbidopa therapy was initiated because of progressive worsening of PD symptoms, 50% of family physicians and nearly a third of specialists initiated levodopa-carbidopa therapy at diagnosis. Furthermore, more than half of the US patients said they were at least somewhat concerned about taking levodopa-carbidopa, as a result of information obtained on the Internet or from physicians.

It is interesting to note that while US patients were most concerned about long-term side effects of their medication, such as dyskinesia and wearing-off, Japanese patients worried more about experiencing hallucinations. This is possibly due to the fact that the majority of Japanese patients in this study received dopamine agonist therapy. Hallucinations are more likely to occur with dopamine agonists than with levodopa,[6] and, in Japan, it is common clinical practice for patients with PD to be initiated on low-dose levodopa combined with dopamine agonists or amantadine. The higher use of dopamine agonists in Japan is also reflected in Japanese clinical trials compared with those conducted in the West.[10,11] Studies have reported a higher incidence of hallucinations in Japanese patients compared with Western patients, which is attributable to the higher doses of dopamine agonists used in the Japanese PD population.[12–14] Therefore, because hallucinations can impact on the quality of life of both patients and their caregivers,[15] it would seem pertinent for physicians in Japan to know how to avoid these adverse

effects and how to manage drug-induced psychotic symptoms should they arise.[15]

Regarding attitudes towards drug intake and dose increases, it is noteworthy that while almost all US physicians believe patients would rather reduce their pill burden, US patients themselves consider their biggest challenge to be wearing-off. In contrast, patients in Japan would rather increase their dose or dosing frequency in order to ameliorate their symptoms. Indeed, patients in Japan expressed a preference for obtaining symptomatic relief, even if that required an increase in medication dosing. This observation is strengthened further by the fact that this preference for symptomatic relief was similar between patients with or without wearing-off. In addition, one major discrepancy between patients and physicians, in both the US and Japan, related to dose increases. In the US, patients feared wearing-off, yet physicians were under the impression that patients wanted to restrict medication intake; However, in Japan, patients seek symptomatic relief, even if that results in an increase in medication. Despite this, the conference survey results indicated that physicians in Japan are reluctant to increase doses. This is supported by results of Japanese studies advocating the use of low doses of levodopa to avoid the development of motor complications.[12] Therefore, the findings demonstrate a need for improved communication between doctors and patients in both countries regarding dose increases, taking into account patient perspectives of adverse effects.

The difference between patient perspectives among Japanese and US patients is likely to stem from differences in medical practice for the management of PD. However, the underlying reasons for this difference are unclear. One possibility is that availability of certain antiparkinsonian therapeutic agents in the two countries may differ. For example, the triple combination therapy levodopa/carbidopa/entacapone is not yet available in Japan, whereas certain dopamine agonists, such as talipexole and droxidopa, are only marketed in Japan. Monotherapy with selegiline is not covered by Japanese health insurance, because it has not been approved by the local authorities.[16] Another possible difference that may influence decisions on therapy is the cost of the drug in the respective countries. In Japan, the cost of antiparkinsonian therapies is largely covered by government-funded Japanese health insurance. In the US, the cost of the drugs depends on the specific health care insurance scheme in which the patient in enrolled. However, given that the cost of levodopa is much lower than that of dopamine agonists, it is unlikely to play a significant role in determining whether to introduce levodopa or whether increases in its dosage or dosing frequency are required.[17] In fact, in Japan, the cost of levodopa and dopamine agonists will be covered by national insurance (at least for patients with Hoehn and Yahr stage III or higher), and is unlikely to be a driving factor for the choice of therapy used in this region. Therefore, the reason why the doses of levodopa used in Japan tend to be lower than in the West is unclear. Results from a retrospective study based at the Sapporo Azabu Neurosurgical Hospital in Japan suggested that lower doses of levodopa may be sufficient to achieve symptom control and may reduce or delay the appearance of motor complications compared with the higher doses of levodopa required to achieve symptom control in multinational, randomized, controlled trials.[12,18–20] The authors of the former study proposed that Japanese patients with PD may respond better to levodopa compared with their Caucasian counterparts, and speculated that variations in genetic background, pharmacokinetics, and lifestyle choices may contribute to this difference.[12] It is also likely that physicians in Japan are concerned about dyskinesias, which tend to be associated with levodopa, and try as much as possible to avoid the development of this complication.[12] Finally, a long-term anti-levodopa campaign, which focused on the potential neurotoxicity of levodopa, and interpretation of the 2002 Japanese practice guidelines for PD, may play a role in influencing attitudes in Japan.[16,21] Although, the seminal ELLDOPA (Earlier vs Later L-DOPA) study of levodopa in early PD patients has dispelled the notion that levodopa is neurotoxic,[22] concerns may still resonate with many Japanese physicians. However, underdosing with levodopa can be associated with a reduction in symptom control and, consequently, may impact patient quality of life.[5] In addition, the observations that dyskinesia is not a major concern for patients in this study and that patients in Japan prefer increasing the dose of medication to improve symptom control, suggests that physicians should not limit the dose of levodopa to avoid the development of dyskinesia.

This study set out to elucidate the perspectives of patients towards PD and antiparkinsonian therapy and to understand whether such views and concerns differ between patients in the US and those in Japan. Although in some cases (eg, those with cognitive or physical difficulties), the patient's caregiver may have completed the Japanese survey on behalf of the patient, this is unlikely to have affected the study results significantly. However, it should be noted that the way in which the two surveys were conducted varied slightly, and the results between the two countries may not be directly comparable. As such, some caution must be exercised when interpreting these results. Nevertheless, the study highlights some interesting similarities and differences between the

two populations, as well as differences between patient and physician perspectives in both countries.

Conclusion

In conclusion, this study suggests that patient perceptions about PD therapy may differ from the views of their physicians. Heightened understanding of patient concerns and attitudes towards PD treatments and their associated complications may help physicians to individualize optimal treatment strategies. Improving patient education and awareness about PD and medical therapy will be instrumental in enhancing patient–physician communication and, consequently, patient care and treatment outcomes.

Disclosure

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Citation Classic

Parkin and Parkinson Disease

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Featured Article: Shimura H, Hattori N, Kubo S, Mizuno Y, Asakawa S, Minoshima S, et al. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet 2000;25:302–5.[5]

Since the 1970s, Japanese neurologists have described patients with autosomal recessive forms of familial Parkinson disease (PD),[6] which have been termed "autosomal recessive juvenile parkinsonism" and "early-onset parkinsonism with diurnal fluctuation," both of which have become known as "PARK2" *(1)*. We attempted to identify the gene responsible for autosomal recessive familial PD. In 1997, we identified, along with our collaborators, an autosomal recessive familial PD gene between D6S437 and D6S264 *(2)*, and in 1998 we found that mutations in that gene were linked to autosomal recessive familial PD. We designated the gene, formerly known as *parkin*, as *PARK2*[7] [parkinson protein 2, E3 ubiquitin protein ligase (parkin)] *(3)*. Parkin is a 465-amino-acid protein containing an N-terminal ubiquitin-like domain linked to a C-terminal RING box. A year later, we demonstrated that parkin was produced in the substantia nigra and localized in Lewy bodies *(4)*. The function of parkin remained unknown, however. In 2000, in collaboration with Keiji Tanaka, Toshiaki Suzuki, Tomoaki Chiba, Shin-ichiro Kubo, Kazuhiro Iwai, Shuichi Asakawa, Shinsei Minoshima, and Nobuyoshi Shimizu, we were able to identify parkin as a ubiquitin-protein ligase that facilitates the degradation of proteins that interact with ubiquitin-conjugating enzyme UbcH7. We reported our results in the *Nature Genetics* article featured here. Ubiquitin is an interesting protein because it is localized in Lewy bodies, which are the pathologic hallmarks of PD. Ubiquitin is a small covalent modifier that forms a polyubiquitin chain on proteins. The polyubiquitin chain, which becomes a degradation signal for proteasome or lysosomal degradation or a signal for other processes, is synthesized by a cascade reaction involving the 3 enzymes ubiquitin-activating enzyme, ubiquitin-conjugating enzyme, and ubiquitin-ligating enzyme, which act as substrate-recognition molecules. We showed that (*a*) parkin has ubiquitin ligase activity with UbcH7, (*b*) the mutations in parkin that cause PD cause a loss of its ubiquitin ligase activity, and (*c*) proteasome inhibition leads to an accumulation of unknown parkin substrates in SH-SY5Y cells, indicating that the part of parkin linked to ubiquitination is a recognition signal for proteasomal degradation. Thus, our *Nature Genetics* article presented the important finding that impairment in the protein-degradation system causes dopaminergic cell death in PD. We speculated that substrates of parkin accumulate in parkin-deficient brains because of insufficient ubiquitination by mutant parkin. The accumulation of substrates may cause neuronal death in PD. We also suggested that unknown substrates of parkin might play important roles in PD pathogenesis.

To date, >100 parkin mutations have been identified. Various reported substrates of parkin include CDC-rel-1, *O*-glycosylated α-synuclein, the parkin-associated endothelin-like receptor, the α-synuclein–binding protein synphilin-1, actin filaments, the poly(Q)-expanded mutant of ataxin-3, Huntington disease polyglutamine proteins, the amyloidogenic Alzheimer disease Aβ 1–42 peptide (amyloid-β peptide 1–42), and aβ-tubulin. In support of these findings, parkin-linked animal models have shown a dysregulation of dopaminergic cells. Additionally, parkin activity is decreased in sporadic PD. Parkin is considered to play an important role in familial PD and other neurodegenerative disorders. Parkin is a broad neuroprotective agent that acts against a wide range of toxic insults, including those that are not part of the ubiquitin-proteasome system. Parkin also associates with mitochondrial membranes and interacts with the phosphatase and tensin homolog–induced putative kinase gene to protect mitochondrial function. Clarifying the relationships between parkin, ubiquitination, and mitochondria may provide insights into PD pathogenesis.

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[5] This article has been cited more than 950 times since publication.
[6] Nonstandard abbreviations: PD, Parkinson disease; Aβ 1–42 peptide, amyloid-β peptide 1–42.
[7] Human genes: *PARK2*, parkinson protein 2, E3 ubiquitin protein ligase (parkin).

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REVIEW

Molecular pathogenesis of Parkinson's disease: update

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ABSTRACT

Parkinson disease (PD) is a neurodegenerative disease characterised by progressive disturbances in motor, autonomic and psychiatric functions. Much has been learnt since the disease entity was established in 1817. Although there are well established treatments that can alleviate the symptoms of PD, a pressing need exists to improve our understanding of the pathogenesis to enable development of disease modifying treatments. Ten responsible genes for PD have been identified and recent progress in molecular research on the protein functions of the genes provides new insights into the pathogenesis of hereditary as well as sporadic PD. Also, genome wide association studies, a powerful approach to identify weak effects of common genetic variants in common diseases, have identified a number of new possible PD associated genes, including PD genes previously detected. However, there is still much to learn about the interactions of the gene products, and important insights may come from chemical and genetic screens. In this review, an overview is provided of the molecular pathogenesis and genetics of PD, focusing particularly on the functions of the PD related gene products with marked research progress.

INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease, named after James Parkinson's who provided a classic account of the condition in 1817. Affecting 1–2% of the population over the age of 65 years, the prevalence of PD increases by approximately 4% in those older than 85 years. Ten genes that contribute to the genetic aetiology of hereditary PD (hPD) were identified, mainly through positional cloning strategies in inherited PD patients and families (table 1).[1 2] Several responsible genes for hPD have been identified, and based on functional studies in vitro and in vivo of gene products, some have been found to interact with each other in various cellular systems for homeostasis, such as synaptic homeostasis (α-synuclein), mitochondrial maintenance (PINK1, parkin, DJ-1, Omi/HtrA2), autophagy–lysosome pathway (α-synuclein, parkin, PINK1, Omi/HtrA2), axonal transport (LRRK2) and ubiquitin proteasome systems (α-synuclein, parkin, DJ-1, UCH-L1). Impairments in a number of cellular systems have been suggested to underlie hPD (figure 1). Also, more recent studies revealed that mutations in the same genes can be involved in familial PD and be risk factors for sporadic PD (sPD), suggesting that inherited and sPD could have common pathological mechanisms.[3] Therefore, understanding the function of the proteins encoded by hPD genes will hopefully further our understanding of the mechanisms leading to inherited and sPD.

In this review, we will summarise the latest research progress in the molecular mechanisms of hPD and genetic association studies of sPD.

HEREDITARY PD

α-Synuclein (PARK1 and PARK4)

Clinicogenetics

SNCA was the first causal PD gene identified in a large Italian family.[4] Mutations (A30P, E46K and A53T), duplications and triplications of the *SNCA* gene have been reported.[2] Clinical features of patients with the E46K mutation are similar to those of dementia with Lewy bodies, while A30P is not associated with severe dementia. Individuals with *SNCA* triplication developed an early onset form of PD with rapid progression and more extended neurodegeneration.[5]

Recent genome wide association studies (GWAS) have demonstrated a strong association between common single nucleotide polymorphism within the *SNCA* locus and PD in European and Japanese population, consistent with the finding that variation at the *SNCA* locus increases PD susceptibility.[6–9] Although the *SNCA* single nucleotide polymorphism associated with sPD show a low OR (1.2–1.4), these findings are consistent with α-synuclein aggregation pathology.

Molecular biology

α-Synuclein is mainly expressed in the presynaptic terminal of the CNS. The protein binds with lipids and unfolds in the steady state. Although the exact function remains unclear, it regulates dopamine homeostasis in presynaptic vesicle cycling.[5] The phenotype of α-synuclein knockout mice is unremarkable and only shows a mild decrease in dopamine levels in the striatum and a mild decrease in synaptic vesicles in the hippocampus. Compared with the wild-type α-synuclein, mutant forms easily aggregate in neuronal cells in vitro and in vivo.[10 11] Transgenic mice with wild or mutant α-synuclein under various promoters have shown neuronal inclusions, mitochondrial abnormalities and neurodegeneration.[12–14] Which type of α-synuclein species is the most toxic to cells remains unclear but some studies assert that mature aggregates are not themselves the toxic moiety but rather an attempt by the cell to clear small toxic oligomers.[15] Hsp90 modulates the assembly of α-synuclein in an ATP

Table 1 Genetic and clinical characteristics of hereditary Parkinson's disease

Locus	Inheritance	Gene	Type of mutation	Clinical features
PARK1/PARK4	AD	SNCA	Missense, duplication, triplication	A30P: late onset, L-dopa responded parkinsonism; A53T: typical parkinsonism with rapid progression; E64K: DLB-like symptoms; duplication: typical parkinsonism; triplication: early onset parkinsonism with rapid progression
PARK2	AR	PRKN	Nonsense, frameshift, missense	Early onset, symmetric, slowly progressed parkinsonism with spasticity and sleep benefits
PARK3	AD	Unknown	—	—
PARK5	AD	UCH-L1	Missense	Similar to sporadic PD
PARK6	AR	PINK1	Nonsense, frameshift, missense	Early onset typical parkinsonism with psychiatric symptoms and L-dopa associated dyskinesia
PARK7	AR	DJ-1	Missense	Early onset parkinsonism with psychiatric symptoms, occasionally with scoliosis and blephalospasm
PARK8	AD	LRRK2	Missense	Middle to late onset typical parkinsonism with response to L-dopa
PARK9	AR	ATP13A2	Missense, deletion, insertion, duplication	Rapidly progressed parkinsonism with dementia and pyramidal features
PARK10	Sporadic	Unknown	—	—
PARK11	AD	Unknown	—	—
PARK12	Sporadic	Unknown	—	—
PARK13	AD	Omi/HtrA2	Missense	Typical parkinsonism
PARK14	AR	PLA2G6	Missense	Early onset parkinsonism with rapid progression, cognitive decline and brain atrophy (cerebellum and cerebrum)
PARK15	AR	FBXO7	Missense, frameshift	Early onset parkinsonism with spasticity and response to L-dopa
PARK16	Sporadic	Unknown	—	—

AD, autosomal dominant; AR, autosomal recessive; DLB, dementia with Lewy bodies; PD, Parkinson's disease.

dependent manner by restricting conformational fluctuations of α-synuclein.[16] Recent advances in research on the protein degradation system associated with PD revealed the importance of ubiquitin proteasome and the autophagy–lysosome pathway in disease pathogenesis.[17] Wild-type α-synuclein is degraded by both chaperone mediated autophagy and macroautophagy, while A30P and A53T are degraded mainly by the latter.[17–19] Furthermore, macroautophagy itself is blocked by α-synuclein via Rap1a dysregulation.[20]

Several lines of evidence have shown that permeabilised α-synuclein from a neuron may be toxic to neurons and/or glias they are next to. Actually, grafted healthy neurons can gradually develop the same pathology as host neurons in PD brains.[21] These findings have suggested that non-cell autonomous cell death as well as cell autonomous cell death may have an important role in disease pathogenesis.

Parkin (PARK2)

Clinicogenetics

The first genetic locus for autosomal recessive juvenile parkinsonism was mapped to chromosome 6, and the disease gene named parkin (*PRKN*) was identified in consanguineous families.[22–24] Mutations in the *PRKN* gene are most common in autosomal recessive juvenile parkinsonism and many mutations have been reported.[3] The clinical picture is similar to that of sPD except for earlier onset, dystonic features, brisk reflexes and sleep benefit. Pathologically, no Lewy bodies were seen in most cases.[25–27] Whether or not heterozygous *PRKN* mutations may cause or increase the susceptibility to late onset typical PD remains controversial. [18F]Fluorodopa uptake by positron emission tomography was reduced in heterozygous carriers without symptoms.[28 29] In addition, heterozygous carriers of *PRKN* mutations have been reported to have either minor motor signs or present with late onset parkinsonism, suggesting a link between heterozygous mutations and disease pathogenesis.[27 30 31] On the other hand, screening for *PRKN* mutations in late onset PD and healthy controls revealed similar frequencies of genetic variants.[32 33]

Molecular biology

Parkin is associated with the ubiquitin proteasome system as an E3 ubiquitin ligase.[34] The C terminal binds with ubiquitin E2 enzymes and recognises a substrate whereas the N terminal interacts with the 19S subunit of proteasome. A nonsense mutation lacking the rear RING finger motif had no E3 activity and sole IBR-RING2 retained E3 activity, and thus most parkin mutations do not lead to loss of kinase activity.[35] α-Synuclein and synphilin-1 were identified as parkin substrates and consist of Lewy bodies.[36 37] Parkin mainly localises in the cytoplasm as well as in plasma membranes and partly in mitochondria. Under physiological or pathological conditions, parkin is involved in mitochondrial maintenance and recent evidence revealed that parkin with PINK1 physically associate and functionally cooperate to identify and label damaged mitochondria for selective degradation via autophagy (mitophagy).[38–42] Protein–protein interactions between parkin and other PD related genes are detailed in each gene section.

PINK1 (PARK6)

Clinicogenetics

PARK6 was first identified on chromosome 1p36.[43] The disease gene was identified as *PINK1* (PTEN induced kinase 1) containing eight exons.[44] The clinical characteristics are autosomal recessive, early onset, slow disease progression and L-dopa responsive parkinsonism. Most mutations were missense mutations, but whole gene deletions were also reported.[45 46] Many putative pathogenic mutations were also observed in a heterozygous state in familial and sPD patients as well as in healthy controls. However, most of the studies have not checked the copy number variants, causing the mutation pathogenicity to remain controversial.[2] Lewy bodies, neuronal loss and astrocytic gliosis in the substantia nigra were detected in a patient with *PINK1* compound heterozygous mutations.[47]

Molecular biology

PINK1 has eight exons encoding 581 amino acids, including a mitochondrial targeting sequence, transmembrane domain and

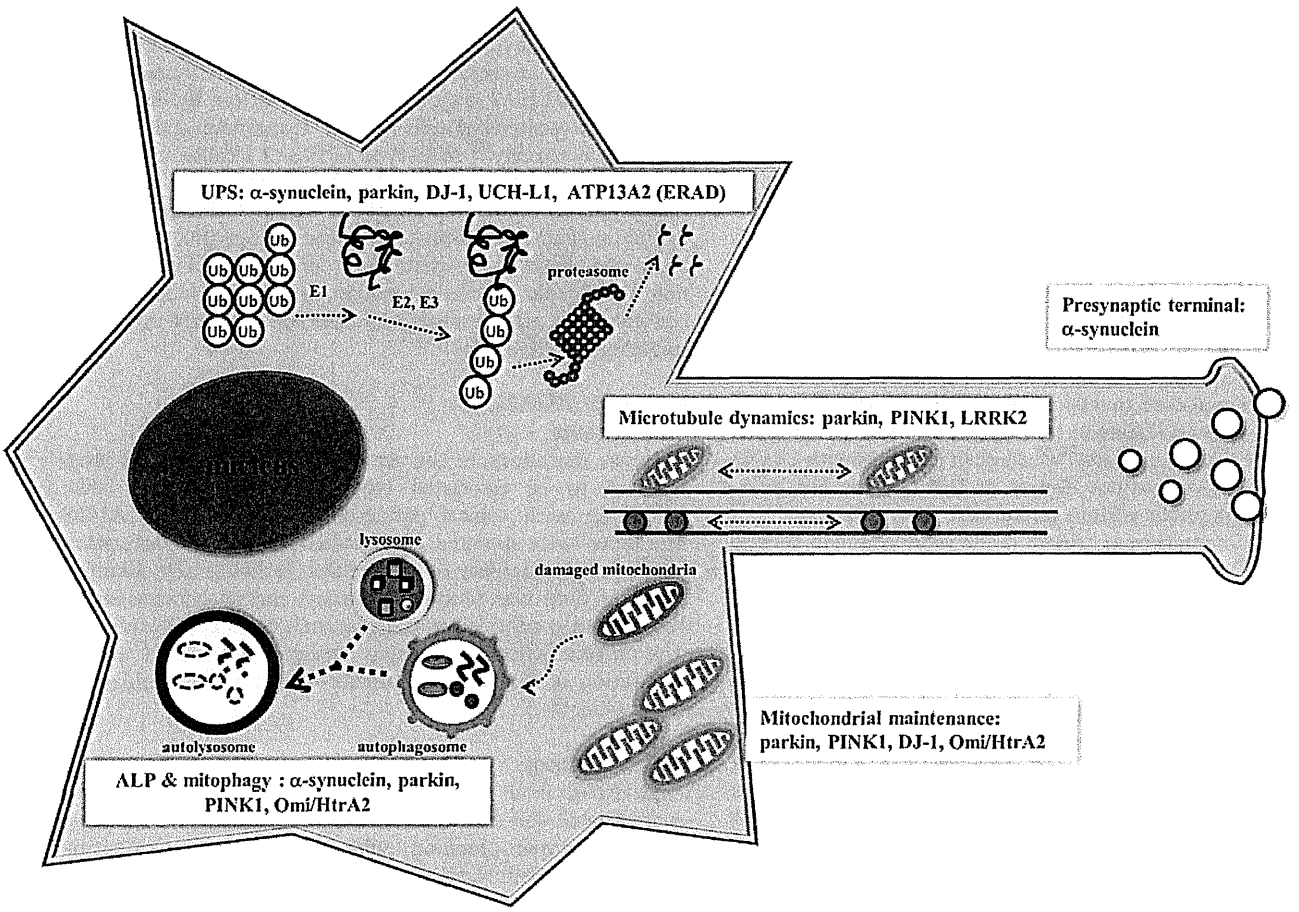

Figure 1 Schematic representation of the possible pathogenesis in hereditary Parkinson's disease. ALP, autophagy—lysosome pathway; ERAD, endoplasmic reticulum associated degradation; Ub, ubiquitin; UPS, ubiquitin proteasome system.

kinase domain.[48] The gene product is ubiquitously expressed in the brain and systemic organs. The protein mainly localises in mitochondria, especially in the outer membrane. PINK1 is a serine—threonine kinase and several pathological mutations in PINK1 have been reported to change their kinase activities.[49–52] In addition, Rictor (a component of mTORC2),[53] tumour necrosis factor receptor associated protein 1 (TRAP1; a mitochondrial chaperone),[50] Omi (PARK13 gene product) and parkin (PARK2 gene product) were identified as substrates for PINK1.[54 55]

PINK1 regulates mitochondrial dynamics and respiratory functions.[38 53 56–58] Mitochondrial fission is accelerated by PINK1 overexpression accompanied by parkin.[59 60] PINK1 ablation with siRNA in neurons reduces resistance against oxidative stress while its overexpression provides resistance.[61] Using genetically modified Drosophila models, we see that PINK1 deficiency causes the same phenotype as parkin deficiency and the PINK1 deficiency phenotype is rescued by parkin complementation, suggesting that parkin is downstream of PINK1.[62–64] Several lines of evidence have provided new aspects of the PINK1/parkin pathway associated with mitochondrial elimination via macroautophagy (mitophagy). When mitochondrial membrane potentials are lost, endogenous PINK1 is accumulated followed by parkin recruitment, and subsequently the depolarised mitochondria were eliminated by mitophagy.[40 41 65 66] Mitochondrial targeting sequence, kinase activity of PINK1 and the linker domain of parkin are indispensable for the PINK1/parkin mediated mitophagy.

DJ-1 (PARK7)

Clinicogenetics

Clinical features of *PARK7* are characterised by early onset parkinsonism with scoliosis, blephalospasm and psychiatric symptoms, similar to those of *PARK2* and *PARK6*. The disease gene was identified as *DJ-1*, which has eight exons encoding 189 amino acids. Three missense mutations (L166P, M26I, E64D) in exons 1—5 of the gene have been identified in Italian, Dutch and Uruguayan families. *DJ-1* protein was detected around Lewy bodies, suggesting *DJ-1* is not in the main structure of Lewy bodies. However, the protein was detected in astrocytes and in a part of the cytoplasmic inclusions positive to tau in brains with corticobasal degeneration, progressive supranuclear palsy and multiple system atrophy.[67–69]

Molecular biology

DJ-1 is almost ubiquitously expressed in organs, including the brain. Endogenous DJ-1 is present in synaptic terminals, mitochondria and membranous organelles.[70 71] DJ-1 with the L166P mutation lost more stability compared with the wild-type and mutant DJ-1 (M26I, E64D).[72] In DJ-1 knockout mice, no significant loss of dopaminergic neurons and decreased susceptibility to oxidative stress were noted.[73] DJ-1 is a multifunctional redox sensitive protein regulating mitochondrial oxidative stress and increases expression levels of SOD1 in an Erk1/2-Elk1 pathway dependent manner,[74] and facilitates prosurvival factor Akt, leading to suppression of apoptosis.[75] Also, the protein

inhibits TRAIL induced apoptosis by blocking Fas associated protein death domain mediated pro-caspase-8 activation.[76] Along with parkin and PINK1, DJ-1 has various cellular functions such as regulation of mitochondrial morphology as well as misfolded protein degradation by forming an E3 ligase complex with those proteins.[77]

LRRK2 (PARK8)

Clinicogenetics

Clinical features of PARK8 are essentially similar to those of sPD except for earlier onset age. The disease gene was identified as the leucine rich repeat kinase 2 gene (*LRRK2*) linked to autosomal dominant inherited PD encoding 2517 amino acids.[78–80] PARK8 is the most common form of hPD in the world. Until now, 20 missense or nonsense mutations have been reported.[81] *LRRK2* mutations were also found in some sPD cases; neuropathological findings were heterogeneous.[82 83] Most of the cases with *LRRK2* mutations showed various degrees of Lewy bodies but intraneuronal aggregations positive to tau were rarely detected.[79 84 85] The G2019S mutation in *LRRK2* is the most common genetic cause of PD, accounting for a significant proportion of both autosomal dominant and sPD cases.

Molecular biology

LRRK2 protein, containing a GTPase domain, a Ras of complex domain, a C terminal of Ras complex domain and a mitogen activated kinase domain, is highly expressed in the brain, and mRNA levels are rich in the striatum and hippocampus compared with other regions.[86] Intracellular LRRK2 is mainly distributed in the plasma membrane and vesicular structures.[87 88] Immunoprecipitation techniques have revealed that LRRK2 interacts with parkin.[89] In transgenic flies, neurodegeneration by LRRK2 with or without a mutation is modified by overexpression or siRNA knockdown of parkin, PINK1 or DJ-1, suggesting genetic interaction between them.[90 91] Activity changes of LRRK2 kinase and GTPase have been suspected as a key factor in LRRK pathogenesis. Changes in LRRK2 activity cause alterations in mitogen activated protein kinase, translational control, tumour necrosis factor α/Fas ligand and Wnt signalling pathways with the cell biological functions of LRRK2 such as vesicle trafficking.[80] The most common pathological mutation in LRRK2, G2019S LRRK2, causes neurite retraction by activation of Rac1 small GTPase.[92] LRRK2 mutations inhibit an endogenous peroxidase by phosphorylation promoting dysregulation of mitochondrial function and oxidative damage.[93] G2019S human LRRK2 transgenic rat models specifically expressed in the nigrostriatal system have shown progressive degeneration of nigral dopaminergic neurons.[94] In terms of LRRK2 control, PKA has been identified as a potential upstream kinase of LRRK2 at S935, on which binding of 14-3-3 with LRRK2 depends.[95] However, the exact biological function of LRRK2 remains largely unclear because no physiological substrates have been identified to date.

ATP13A2 (PARK9)

Clinicogenetics

PARK9, also known as Kufor–Rakeb syndrome, is an autosomal recessive parkinsonian disorder characterised by early onset (14–16 years old), good response to L-dopa treatment, pyramidal feature, supranuclear gaze palsy and dementia.[96] The gene locus was mapped to 1p36 and the disease gene was identified as *ATP13A2*, which localises in lysosomal membranes.[97] Various types of mutations in the *ATP13A2* have been reported.

Molecular biology

ATP13A2 is predicted to be a lysosomal P5-type ATPase that plays important roles in regulating cation homeostasis. Although ATP13A2 function remains unclear, it might be involved in protecting cells against manganese and mutant α-synuclein toxicity.[98] Wild-type ATP13A2 localises mainly in lysosomes whereas three separate mutants with a mutation involved in PD cause retention of the protein in the endoplasmic reticulum, and are eliminated by the endoplasmic reticulum associated degradation pathway.[99] Wild-type ATP13A2, but not pathogenic mutants, reduced intracellular manganese concentration and prevented cytochrome C release from the mitochondria.[100]

Omi/HtrA2 (PARK13)

Clinicogenetics

Missense mutations in the gene coding for Omi/HtrA2 were reported to be associated with four patients with sPD, presenting with typical parkinsonism.[55] G399S and A141S mutations were detected and resulted in defective activation of the protease activity of Omi/HtrA2. Pathologically, accumulation of Omi was found in neuronal and glial inclusions in brains with α-synucleinopathies as well as in Lewy bodies.[101] The largest association study revealed no overall strong association of Omi/HtrA2 variants with sPD in populations worldwide.[102]

Molecular biology

Omi/HtrA2 is a nuclearly encoded mitochondrial protein consisting of 458 amino acids, originally identified as a proapoptotic protein binding with an apoptosis inhibiting protein.[103 104] Omi knockout mice presented with neuronal loss in the striatum and died within 30 days of birth.[105] Cells overexpressing Omi mutant with G399S have shown mitochondrial morphological changes followed by dysfunction and increased susceptibility against oxidative stress.[55] Interestingly, wild-type Omi/HtrA2, not protease defective mutant, activates autophagy through digestion of Hax-1, a Bcl-2 family related protein that represses autophagy via Beclin-1 inhibition, suggesting an insufficient protein degradation system may play a key role.[106]

PLA2G6 (PARK14)

Clinicogenetics

PARK14 is an autosomal recessive parkinsonian syndrome characterised by early onset rapidly progressive parkinsonism, dystonia, cognitive decline, and cerebral and cerebellar atrophy. Through homozygosity mapping and direct sequencing, two different homozygous mutations in *PLA2G6*, which also causes infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation, were identified.[107 108] Cranial MRI did not detect iron accumulation in the basal ganglia in most cases with this disorder.[108 109]

Molecular biology

The PLA2G6 gene encodes a group VIA calcium independent phospholipase A2, also known as calcium independent phospholipase A2 β, which hydrolyses the sn-2 acyl chain of phospholipids, generating free fatty acids and lysophospholipids. In an in vitro assay, wild-type PLA2G6 associated with infantile neuroaxonal dystrophy/neurodegeneration with brain iron accumulation failed to catalyse fatty acid release from phospholipids, while PARK14 associated mutations ((R741Q, R747W and R632W) did not, implying that other functions of PLA2G6

include interactions with calmodulin and that PLA2G6 might also be associated with calcium/calmodulin dependent protein kinase II-β.[110 111]

FBXO7 (PARK15)

Clinicogenetics

Only three families with mutations in *FBXO7* have been reported.[112 113] Affected individuals had juvenile onset (10–19 years old) of progressive parkinsonism associated with spasticity, and variable response to L-dopa. No pathological studies have been reported.

Molecular biology

Fbox7 is a member of the F box containing protein (FBP) family with an F box domain. F box containing proteins are expected to function as molecular scaffolds in the formation of the protein complex; however, the exact function of FBXO7 remains unclear.

OTHER GENES ASSOCIATED WITH PARKINSON'S DISEASE

GWAS have uncovered a number of candidate genes involved in PD in European and Japanese populations, indicating a substantial contribution of genetics underlying susceptibility to both early onset and late onset PD.[6 7 114–119] These studies have shown repeatedly a common variation in *SNCA* and an inversion of the region containing the *MAPT*. Recent genetic studies revealed mutations in the *GBA* gene, the most widespread genetic risk factor for parkinsonism identified to date.[120–124] In this section, we summarise the molecular mechanisms of the two genes, MAPT and GBA.

MAPT

Mutations in *MAPT*, encoding microtubule associated tau, result in tauopathies, including progressive supuranuclear palsy, corticobasal degeneration and frontotemporal lobar degeneration.[125] Tau is a soluble protein, but insoluble aggregates are produced during the formation of neurofibrillary tangles which disrupts microtubule associated dynamics and neuronal functions. Considering the interplay between α-synuclein and tau reported previously,[126] it is interesting that there would be a common pathogenesis associated with aggregation formations.

GBA

Early observed patients with Gaucher disease and their heterozygous relatives present with parkinsonism.[127] In addition, autopsy studies have shown the presence of mutant glucocerebrosidase (GCase) in α-synuclein positive Lewy bodies in Gaucher disease patients and carriers with α-synucleinopathies.[128] GCase is a lysosomal hydrolase with 497 amino acids that catalyses the metabolism of the glycolipid glucosylceramide to ceramide and glucose. Cells overexpressing mutant GCase promoted α-synuclein accumulation in a dose and time dependent manner.[129] α-Synuclein GCase interacts selectively under lysosomal solution conditions (pH 5.5) and the interaction site was mapped to the α-synuclein C terminal residues 118–137.[130] Insufficient functions of the lysosomes may have an effect on chaperone mediated autophagy or macroautophagy.

CONCLUDING REMARKS

In the 14 years since the first causative gene (α-synuclein) in PD was discovered, great advances have been made in understanding the biology of the disease. Recent evidence shows that the environment plays no role in the aetiology of PD.[131] In addition, GWAS suggest that a number of genes influence susceptibility.[3] The PD associated genes provide valuable clues regarding the molecular pathogenesis of PD because the pathomechanism for sPD would have certain pathways in common with those of hPD. Importantly, basic biological studies in PD have led to numerous potential therapeutic strategies. For example, a specific inhibitor for LRRK2 phosphorylations at Ser910 and Ser935 was recently developed.[132] In the future, it becomes more important to translate laboratory data, including molecular pathogenesis as well as genetic associations, into clinical treatments, leading to disease modifying therapies to conquer the disease onset and/or progression.

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