PD GENEration, launched in partnership with the Parkinson Study Group (PSG) in September 2019, is a multi-center, observational study in North America, designed to offer genetic counseling, in English and Spanish, and Clinical Laboratory Improvement Amendments (CLIA)-certified genetic testing to people with Parkinson’s disease (PWP). The PD GENEration test panel, performed by Fulgent Genetics, includes next generation sequencing (NGS) of 7 genes: LRRK2, GBA1, SNCA, PRKN, PINK1, PARK7, VPS35. The broad objectives of the study are to facilitate access to genetic testing to PWP, and their clinicians, and offer educational materials to clinicians on PD genetics, in order to help accelerate clinical trials in PD, improve PD care and research, and empower PWP and their care teams.

Participants receive genetic test results of variants classified as pathogenic or likely pathogenic based on the American College of Medical Genetics (ACMG) criteria. In addition, the E365K GBA1 risk allele is returned as it was considered actionable, i.e. eligible for clinical trial enrollment. Variants of unknown significance (VUS) are not reported but are catalogued for research use and shared among a global consortium of PD genetics panel and clinicians to centralize discussions of VUS identified across multiple cohorts (ClinGen Parkinson’s Gene Curation Expert Panel: https://clinvar.genome.org/affiliation/40079). De-identified data is shared with researchers who are advancing the PD genetics field, such as the Global Parkinson’s Genetics Program (GP2). Curated gene variants will be deposited in the National Institute of Health (NIH) ClinGen and ClinVar repositories.

Three phases of PD GENEration:
1) Pilot study- launched in Sept. 2019 and aimed at feasibility
2) Clinical study- launched in Nov. 2020- continuation of the Pilot study at a larger scale, aimed at frequency and characterization of clinical phenotypes
3) Registry study- launched in Jan. 2021 and aims to make genetic counseling and testing accessible to 15,000 participants

Enrollment

The PD GENEration study has, as of June 1, 2023, enrolled 10,510 participants, showing a 7x increase in recruitment since the start of the Registry study.

Study Enrollment Per Country
United States (US): 10,117
Puerto Rico (PR): 33
Dominican Republic (DR): 305
Canada: 60

58%:42% genetic sex of Male:Female
69 years average age at enrollment
62 years average age at diagnosis
58% diagnosed in the last 5 years

Methodology

PD GENEration Registry Study Pipeline For Participants and Researchers

Reizers

Participants

Clinical Study

Pilot Study

Registry Study

Day 1

Day 20-25

Day 30

Day 60+ s

Reizers

PD GENEration Panell

Genetic Counseling via telemedicine or site-based

Data Collection:

Enrollment Goals Cumulative CLIA Approved, CAP Certified Testing NGS of 7 Genes (del/dip) Bank DNA for Future Research Use Post-Test Genetic Counseling Family History Demographics MDS-UPDRS MOCA Patient and Provider Surveys

Results

The PD GENEration study has, as of June 1, 2023, enrolled 10,510 participants, showing a 7x increase in recruitment since the start of the Registry study.

Study Enrollment Per Country
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58%:42% genetic sex of Male:Female
69 years average age at enrollment
62 years average age at diagnosis
58% diagnosed in the last 5 years

74% New to Clinical Research

Have you participated in research before? # of responses: 8,785

No 74% 6,473

Positive Genetic Makeup in Cohort (n=4,506 completed testing)

Gene
Heterozygotes Homozygotes compound heterozygotes

GBA1 622 (7.3%) 23 (0.3%)
LRRK2 196 (2.3%) 2 (0.02%)
PRKN 120 (1.4%) 57 (0.7%)
SNCA 9 (0.1%) 0 Duplication, A3ST LRRK2 10.2%
VPS35 5 (0.06%) 0
PINK1 3 (0.04%) 4 (0.05%) 4.97%
PARK7 3 (0.04%) 2 (0.02%)
Multiple Genes 35 (0.4%)

PD GENEration makes genetic testing and counseling accessible for PWP and their clinicians. The Parkinson’s Foundation plans to continue to recruit beyond 15,000 participants based on the needs of the patient and research community. By “opening the door” for genetic testing to all those interested and from all backgrounds, the study helps inform care, diversify the data, engage people in research, and quality more for enrollment in precision medicine clinical trials for PD. Data generated from this study will be openly accessible to the research community.

More about PD GENEration

Conclusion

Characterizing the Frequency of Clinically Reportable Variants in Major Genes Established in Parkinson’s Disease in a Large American Cohort

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Genetics

LRRK2
VPS35
PINK1
PRKN
PARK7

2.1% Overall
2.1% Overall
4.4%
6.4%
6.4%
9.4%
14.7%
14.7%
22%
30%
12%
17%
19%
20%
21%
6.4%
4.4%
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30%
12%
17%
Curation of Parkinson’s Disease Genes Performed by an International Expert Panel: A ClinGen Initiative

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1. Parkinson’s Foundation, USA  2. Phenotypes, Canada 3. University of North Carolina, USA 4. University of Liége, Germany 5. Illumina Inc., USA 6. Tel Aviv Sourasky Medical Center, Israel 7. Columbia University Irving Medical Center, USA

Introduction

There has been a great emphasis on the importance genetics plays in PD, with genetic testing for PD becoming more widely used because of observational studies such as PD GENERation and ROPAD (ClinicalTrials.gov Identifiers: NCT04994015 and NCT03866603, respectively). In addition, precision medicine clinical trials for PD require genetic testing prior to enrollment. However, we and others have shown that the definition of PD-related genes and the content of PD panels in the diagnostic setting vary in the number of genes targeted and in variant interpretations. Based on the National Institutes of Health (NIH) Genetic Testing Registry (GTR), there are 502 uniquely commercially available clinical genetic tests for PD, from 28 Clinical Laboratory Improvement Amendments (CLIA)-approved clinical laboratories (reported as of December 2020). Importantly, the size of these panels range anywhere from 5 to 62 genes. Given these differences, and the start of precision medicine trials being offered for PD, we collaborated with the ongoing gene and variant curation efforts lead by MDG Gene (www.mdsgene.org), to develop a Parkinson’s disease Gene Curation Expert Panel (PD-GCEP) under ClinGen, a centralized resource across diseases that applies defined criteria to establish gene-disease validity, and whose findings are recognized by the FDA. The overall objective of this work is to enable variant curation based on ClinGen gene curation to generate consensus for the interpretation of variants for inclusion in precision medicine clinical trials for PD.

Methodology

To close this gap in the field, we formed the Parkinson’s Disease Gene Curation Expert Panel (PD-GCEP) to recognize the need of defining the clinical validity of gene-disease relationships for PD and atypical parkinsonism.

We first targeted the curation of seven well-established PD genes following the ClinGen protocol and using its curation interface.

ClinGen provides a framework in which there are 5 clinical validity classifications (no known disease relationship, limited, moderate, strong, and definitive).

Figure 1 shows the purpose PD-GCEP will have in bettering PD patient care and Figure 2 shows a screenshot of the PD GCEP website landing page that describes the overview and goals of gene curation.

Results

The PD GCEP panel was formally approved in August 2020 consisting of 62 leaders worldwide representing different disciplines such as clinical neurology, genetics, and molecular genomics. Figure 3 depicts the global representation of PD-GCEP members.

As of 2022, the PD GCEP is now affiliated with the recently formed Neurodegenerative Clinical Domain Working Group (CDWG) within the ClinGen infrastructure. The PD-GCEP has curated and published the clinical validity of LRRK2, GBA1, PRKN, PINK1, SNCA, VPS35, and PARK7, as there is reasonable consensus in the field as to them playing a role in the causality of PD. The PD-GCEP found that all these genes are classified as “definitive”, elucidating that certain variants in these genes are causative for PD as shown in Table 1.

We provided a QR code to the PD-GCEP ClinGen website where the evidence criteria applied to confirm definitive gene-disease relationship according to ClinGen’s Gene Validity Evaluation Criteria (SOP8, SOP9) and the full curation conducted by the PD-GCEP is listed and accessible.

Conclusion

We have demonstrated the feasibility of establishing consensus by a leadership curation team using the ClinGen framework. Next, we plan to curate more controversial PD genes that are not necessarily found in all commercial PD panels, e.g., GCH1, as well as genes linked to atypical parkinsonism. Our expert panel curations via the ClinGen pathogenicity framework will help guide precision medicine efforts in PD and enable informed FDA decision-making in future therapeutic trials.

In parallel with gene curation efforts, plans to develop a Variant Curation Expert Panel (VCEP) to begin curation of variants among GBA, LRRK2 and PRKN are underway to address the fieldwide needs of generating consensus on the variants that have clinical implications. Variant interpretation is not black and white because of two main reasons: lack of sharing a standard protocol to interpret the variants, and lack of communication between experts and laboratories, creating multiple interpretations. There are four application parts and we currently are awaiting approval for Part I. For more information about VCEPs and joining please use the following QR code.

Acknowledgements

We would like to acknowledge the commitment and work done by our fellow PD-GCEP members. We also would like to acknowledge the ClinGen group and funding: U24HG009650
Building a Coalition to Advance Engagement of Black and African American Communities in Parkinson’s Disease Research Using Best Practices in Diversity, Equity and Inclusion and Patient Engagement

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1) Parkinson’s Foundation Research Advocate/Volunteer, 2) Parkinson’s Foundation, 3) Emory University, 4) Morehouse School of Medicine, 5) Atrium Health, 6) Adena Medical Center and Kittanning Medical Center, 7) John Hopkins Medicine, 8) Stanford University School of Medicine, 9) Columbia University, 10) Northwestern University, 11) Jefferson Health

Background

• Black and African American communities are underrepresented in Parkinson’s research.1,2

• Not considering the lived experiences of Black and African American communities hinders drug development and improved understanding of Parkinson’s, leading to health inequities with these communities excluded from the benefits of research participation.

• The Parkinson’s Foundation Learning Institute has the potential to mitigate these health inequities through targeted and tailored training in research advocacy for Black and African American people with Parkinson’s and care partners and improve enrollment in research studies, such as PD GENERation.

Methods: Building a Coalition

• The Parkinson’s Foundation built a coalition in 2020 led by Black and African American people with Parkinson’s and their care partners. The coalition is a special interest group (SIG) in Black Diaspora.

• Black and African American clinicians, social workers, nurses and researchers were invited to join the coalition as key partners to driving systemic change among organizations and communities.

The goal of the coalition is to redesign and execute the Parkinson’s Foundation Learning Institute in a culturally responsive way for Black and African American communities and improve enrollment in PD GENERation.

Results: Progress towards Goal

LOGISTICS

• Coalition meets biweekly for planning; the location and date was finalized – Atlanta, GA in Sept 2023

• Refined recruitment process to reduce potential barriers (e.g., modified application)

• Utilized recruitment cohorts for support and sustainability - participants can continue research advocacy with support from Parkinson’s Foundation staff, care network and partners

CURRICULUM & EVALUATION

• Redesigned curriculum to align with the unique needs of the Black and African American community (e.g., greater representation among speakers, less content and more discussion, culturally relevant pedagogy)2

• Expanded metrics to include pre and post measures of self-efficacy, experiences and attitudes towards research, acceptability, feasibility and sustainability

OUTREACH AND SUSTAINABILITY

• Collaboration with Morehouse School of Medicine to advance equitable research

• Added a community day to the Learning Institute to engage community, health and faith-based organizations in partnerships and to provide information and enroll eligible individuals in PD GENERation

• Open House webinar was added before the Learning Institute to promote early rapport and to establish trust

Conclusions: Looking Ahead

• The upcoming Learning Institute will result in 30 people living with the Black and African American community trained in research advocacy, including the tools and resources to advocate in their communities about PD GENERation.

• This cohort of Black and African American people living with Parkinson’s and care partners will be positioned to drive research agendas and partner with researchers and government agencies on improving quality of life for the Parkinson’s community.

Made possible by support from Robert W. Woodruff Foundation and Genentech, a member of the Roche Group
Involving people with Parkinson’s disease (PD) and care partners in research design and execution alongside researchers has gained traction with implementation resources increasing¹. However, research teams still seek tailored trainings on methods and best practices for this work. A landscape review of the PD community and a survey of staff at academic research centers (Parkinson’s Foundation Centers of Excellence- COE) indicated a strong interest in patient engagement opportunities and training. To respond to this, the Parkinson’s Foundation initiated a pilot project to create a replicable, sustainable model of patient engagement (PE) in 5 of its COE. Using a patient advisory board (PAB) model, the goal was for participating COE staff, people with PD and care partners to complete the PAB training and work towards developing a comparative effectiveness research (CER) question through ongoing PAB meetings.

Methods

1. **A National Collaborative**: A national collaborative was established of experts from the Parkinson’s Foundation and the COE network to lead the development of this pilot PAB model. People with PD, patient advocates from other disease areas, researchers, clinicians, social workers, and members of the Parkinson’s Foundation’s patient engagement team came together to help set the priorities and structure of the model and PE training.

2. **Virtual Training**: The National Collaborative developed a training for COE staff, people with Parkinson’s and care partners. This training was delivered as eight, twice-weekly, hour-long sessions over four weeks and provided online sessions on PE topics, including best practices in PE and community based participatory research, research basics, how to run a PAB and developing a research question.

3. **Toolkit and Ongoing Coaching**: A toolkit was created to provide templates and resources for planning and running PAB meetings, including example roles and responsibilities, meeting planning checklists and agendas, and meeting facilitation and discussion guides. The Parkinson’s Foundation patient engagement staff and patient advisors were available to work with PABs throughout the project. Ad hoc phone calls occurred as needed when PAB challenges arose.

After completing the training and receiving the toolkit, COE conducted PABs with the goal of developing a research question. Baseline and follow-up surveys were administered to measure knowledge, attitudes, intent and behavior towards PE, the training, and PABs.

Results

On average, participating COE held 3.3 PAB meetings over the course of a year. Additional results from COE staff are highlighted below.

![Staff Responses on PAB Training and Implementation](chart)

<table>
<thead>
<tr>
<th>Training covered all topics that came up in PAB meetings</th>
<th>Training improved their ability to work with PAB members</th>
<th>Yes, PAB was beneficial to the organization’s research mission and will continue meetings</th>
<th>Used Zoom for PAB Meetings</th>
<th>Felt that patient engagement was important to the research process</th>
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<tbody>
<tr>
<td>100%</td>
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**Strongly Agree** ■ **Somewhat Agree**

Conclusion

This pilot project was effective in engaging and bringing together people with Parkinson’s, care partners and COE staff to advance CER. Overall, COE staff found the training to be comprehensive and effective for preparing them to lead PABs at their center. Limitations of this project included COVID-19 and adapting the PAB training to an online format. Ongoing commitment of COE to this work indicates a successful and satisfactory model is in place, and the overall success of this pilot highlights the quality and short-term impact of PABs at academic centers. Future research will explore long term impact, including sustainability of PABs and implementation of CER.

Acknowledgements

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References