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Short communication

The commercial genetic testing landscape for Parkinson's disease

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ABSTRACT

Introduction: There have been no specific guidelines regarding which genes should be tested in the clinical setting for Parkinson's disease (PD) or parkinsonism. We evaluated the types of clinical genetic testing offered for PD as the first step of our gene curation.
Methods: The National Institutes of Health (NIH) Genetic Testing Registry (GTR) was queried on 12/7/2020 to identify current commercial PD genetic test offerings by clinical laboratories, internationally.
Results: We identified 502 unique clinical genetic tests for PD, from 28 Clinical Laboratory Improvement Amendments (CLIA)-approved clinical laboratories. These included 11 diagnostic PD panels. The panels were notable for their differences in size, ranging from 5 to 62 genes. Five genes for variant query were included in all panels (*SNCA, PRKN, PINK-1, PARK7 (DJ1),* and *LRRK2*). Notably, the addition of the *VPS35* and *GBA* genes was variable. Panel size differences stemmed from inclusion of genes linked to atypical parkinsonism and dystonia disorders, and genes in which the link to PD causation is controversial.
Conclusion: There is an urgent need for expert opinion regarding which genes should be included in a commercial laboratory multi-gene panel for PD.

1. Introduction

The role that genetics plays in Parkinson's disease (PD) etiology is increasingly acknowledged. In the last few decades, we have learned that pathogenic variants in certain genes such as *LRRK2*, *GBA*, and *PRKN* can be important contributing factors. For most forms of PD, other genetic factors, environmental agents and aging also play a role [1]. At least one major pathogenic variant in a PD-associated gene is identified in approximately 10% of patients with PD, depending on the testing used and population studied [1,2]. Parkinson's disease, when inherited, can be autosomal dominant, related to variants in the genes *SNCA*, *LRRK2*, *VPS35*, or autosomal recessive caused by variants in *PRKN*, *PINK1*, or *PARK7* (*DJ1*) [3] (Fig. 1). Variants in the *GBA* gene are believed to be major risk factors for Parkinson's disease, when present in heterozygous or homozygous state [4]. Other genes linked to monogenic atypical forms of parkinsonism have also been described [5,6]. Recently, over 90 genetic variants that appear to be associated with an increased risk of PD have been identified in genome-wide association (GWAS) studies [7]. Individually, these variants are common in the general population and are not associated with a definable PD risk, and they are

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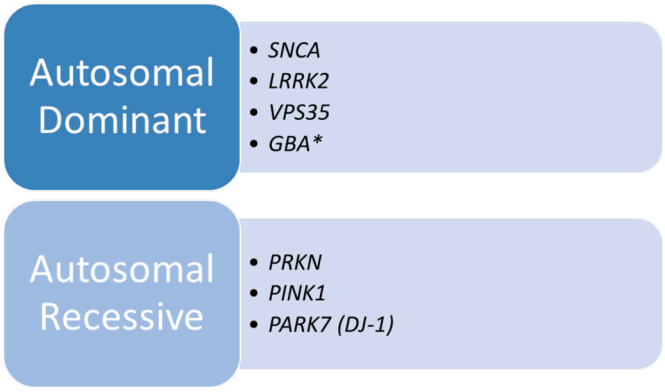

Fig. 1. Monogenic causes of typical Parkinson's disease.

not typically included -on commercially-available testing panels.

Genetic testing options have rapidly increased for movement disorders including PD, driven by new technology such as next generation sequencing (NGS), the interest in precision medicine, demand, and lower costs. This information obtained from testing can be integrated into clinical care allowing for better disease prognostication, management and qualification for clinical trials [8]. On a personal level, information from genetic testing can be useful for people with PD allowing for understanding about their disease etiology, improved risk assessment for family members, and life planning.

As of 2018, it was estimated that there were 75,000 genetic tests (single gene, multigene panel, whole exome, and other complex genetic testing products) marketed by Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories in the United States [9]. Commercial panels and gene tests for a disorder are not necessarily created according to clinical validity and utility. Furthermore, test selection does not always mirror reimbursement or insurance coverage for a condition. Recognizing the wide variation in gene panels, the American College of Medical Genetics and Genomics (ACMG) recently published a technical guideline for clinical laboratories regarding the design of gene panels [10].

Multi-gene panel tests are often selected by clinicians, because of their perceived efficiency, completeness, and cost-effectiveness. However, there are no guidelines to direct the physician in test selection for PD; some groups have provided guidance and algorithms based on family history of PD, clinical features, and ethnicity [11,12]. The limited availability of genotype-phenotype correlations can make it difficult for the health care provider (HCP) to choose the right test. Ultimately, it can be very difficult to navigate the genetic testing menus for PD that feature clinical and genetic heterogeneity [13], due to the lack of uniform testing and inclusion of genes linked to monogenic parkinsonism and other forms of parkinsonism.

The objective of this study is to describe the current landscape of PD genetic testing offered by clinical laboratories and to compare test offerings, as we begin to determine gene-disease validity for PD.

2. Methods

This past year, the ClinGen (Clinical Genome Resource) Parkinson's Disease Gene Curation Expert Panel (GCEP) (https://clinicalgenome.org/affiliation/40079/) formed to create a consensus about the gene-disease validity of specific PD genes. All gene-disease validity curations for this GCEP can be accessed from clinicalgenome.org. The findings from this panel aim to guide key stakeholders, including patients, payers, clinicians, scientists, and clinical laboratory directors. The panel is composed of international, multidisciplinary experts: molecular geneticists, clinicians with genetic research focus, PD-specific genetic counselors, and experts in biocuration. In order to construct a preliminary gene list for curation, the GCEP ascertained and compared current commercial PD genetic testing offerings. We used the Genetic Test Registry (GTR, www.ncbi.nlm.nih.gov/gtr), a database of orderable genetic tests supported by the National Institutes of Health (NIH), to identify current commercial PD genetic test offerings in the United States and internationally [14]. (This database, one of several available test information resources on the web, is a commonly used, self-reported, genetic testing resource for genetic counselors and physicians that is open access.) The search string "Parkinson" was used with the following filters: "Clinical testing/Confirmation of Mutations Identified Previously" and "CLIA Certified". Returns were reviewed and categorized by test type and laboratory. Testing offered was further confirmed by the company websites. Laboratories currently offering multi-gene panels that were labeled as "Parkinson's disease" were chosen for further descriptive analysis. Laboratories that did not clearly offer a multi-gene, diagnostic panel for PD were excluded. In addition, companies whose PD test offerings were not located on their website were excluded.

We reviewed the selected panels, comparing the selection of genes across panels, observing where there was agreement or not. We also noted the disease category representing a gene that was included on a panel, such as if they were linked to differential diagnoses of PD (e.g., Wilson's disease or dystonia) or to atypical parkinsonism (e.g., Kufor-Rakeb disease).

3. Results

A final GTR query to inform curation was performed on 12/7/2020 and returned the following: 502 unique clinical genetic tests were offered from 28 CLIA-approved labs in the United States and internationally. PD gene test offerings were not located for 13 companies upon additional searching of their websites. Four companies did not have obvious diagnostic PD multi-gene panels listed on their websites and were excluded. We observed many types of panels for PD (up to 22 different test choices) offered by individual companies, to evaluate by specific genes, overall clinical features (atypical/parkinsonism); unique clinical features (e.g., dystonia or dementia); age of onset, and inheritance.

From this original test list, 11 company test offerings were chosen for further analysis. All offered a general, diagnostic, multi-gene panel for Parkinson's disease that included 3 or more genes. General diagnostic PD panels were notable for their differences, especially including size, from small (5 genes) to very large (62 genes). There were 71 unique genes queried by the laboratories in total (Table 1). All panels offered by companies in the analysis included 5 genes consistently linked to major PD risk in multiple studies (*SNCA, PRKN, PINK1, PARK7, and LRRK2*). Beyond this consensus, panels varied in inclusion of other genes, most notably *GBA* and *VPS35* (Fig. 2); and some companies offered an enzyme assay for *GBA* as well. All PD panels except one included genes linked with juvenile or atypical parkinsonism, genes linked with diseases in the differential diagnosis of PD (i.e. Wilson's disease or dystonia), and less well-established genes according to published literature: *DNAJC13, TMEM230, GIGYF2, HTRA2, RIC3, EIF4G1, UCHL1,* and *CHCHD2* [15]. Of the analyzed companies, seven originated from the United States and four from Europe; there was a trend for European companies to offer larger gene panels.

None of the analyzed panels were designated for a particular geographic or ancestral population. Although among the 502 unique tests originally returned, at least one population-based panel was identified, specifically for Ashkenazi Jewish ancestry as part of broader disease screening. Among the 11 panels, additional variability was observed in the testing methodology listed by the laboratory on GTR; testing in some cases was referred to as targeted sequencing and in others, the testing/sequencing was more complete. Although all laboratory panels included some type of sequencing, three laboratories did not explicitly offer additional analysis of copy number variation for genes like *PRKN* or *SNCA*, known to have deletions and duplications.

Table 1
Genes on selected PD panels[a].

Gene	Lab (total # of genes on Parkinson's disease panel)										
	Asper Biogene (40)	Athena (5)	Blueprint Genetics (62[a])	CeGaT (30)	Centogene (36)	Fulgent (26)	GeneDx (29)	Invitae (16)	Knight Diagnostic (19)	Prevention Genetics (24)	U of W NCG Lab (45)
ADH1C	●										
AFG3L2							●				
ATP1A3	●		●	●	●	●			●		●
ATP13A2	●		●	●	●	●	●	●	●	●	
ATP6AP2	●				●		●				●
ATP7B					●			●			
ATXN2	●										
C10orf2							●				
C19orf12				●			●				
C9orf12					●						
CHCHD2	●			●						●	
COASY							●				
COMT											●
CP							●				
CSF1R						●			●		●
CYP27A1							●				●
DCTN1	●			●	●	●		●	●		●
DJ1/ PARK7	●	●	●	●	●	●	●	●	●	●	●
DNAJC5							●				
DNAJC6	●		●	●	●	●	●	●		●	●
DNAJC13	●										●
EIF4G1	●					●				●	●
FBX07	●		●	●	●	●	●	●	●	●	●
FTL	●			●	●						●
FUS					●						
GBA	●		●[b]	●	●	●	●		●	●	●
GCH1	●		●	●	●	●		●		●	●
GIGYF2	●									●	●
GNAL											●
GRN				●	●						
HTRA2	●				●	●				●	●
LMNB1											●
LRRK2	●	●	●	●	●	●	●	●	●	●	●
MAPT	●		●	●	●	●			●	●	
NOTCH3						●					
OPA1											●
PANK2				●	●						
PDGFB			●								●
PDGFRB			●								●
PINK1	●	●	●	●	●	●	●	●	●	●	●
PLA2G6	●		●	●	●	●	●		●	●	●
PODXL	●										
POLG						●	●		●		●
PRKN	●	●	●	●	●	●	●	●	●	●	●
PRKRA	●		●		●	●	●	●			●
PRNP						●					
PSEN1											●
PTRHD1	●										
RAB29											●
RAB39B	●				●					●	●
SLC6A3	●		●	●	●	●	●	●	●	●	●
SLC16A2							●				
SLC20A2			●		●		●				●
SLC30A10	●			●	●						
SLC39A14			●	●							
SMPD1							●				
SNCA	●	●	●	●	●	●	●	●	●	●	●
SNCB	●				●						
SPG11	●			●							
SPR	●		●	●	●			●		●	●
SYNJ1	●		●	●	●		●			●	●
TAF1	●					●			●	●	●
TBP	●										
TH	●		●	●	●	●		●	●		●
TMEM230	●				●						●
UCHL1	●				●	●				●	●
VPS13A			●		●		●				
VPS13C	●		●	●						●	●
VPS35	●		●	●	●	●	●	●	●	●	●
WDR45					●		●				
XPR1			●				●				

[1] Based on data pulled from the GTR on 12/7/2020 and should not be used to base clinical test decisions as this information quickly changes over time.
[a] Includes 37 mitochondrial genes.
[b] Available by request with reflex testing.

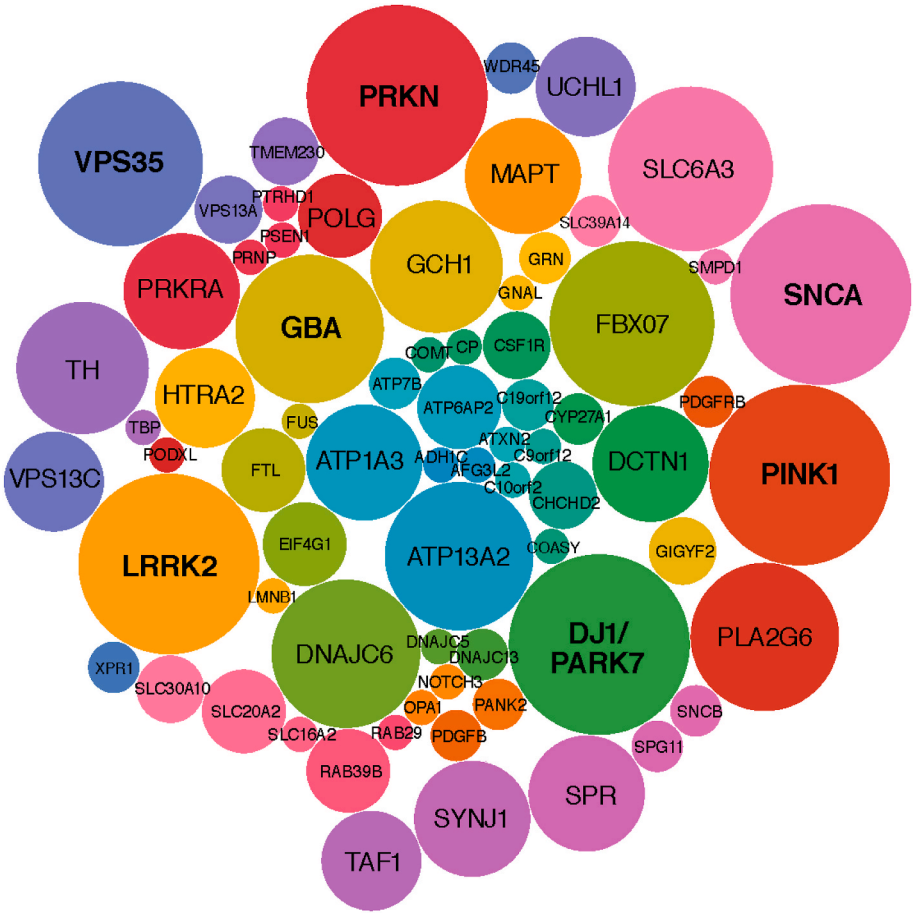

Fig. 2. Genes offered on PD panels.
Legend: Bubble plot of genes offered on general diagnostic panels of the 11 companies analyzed. Bubble size corresponds to the frequency a particular gene appears across panels. The genes *SNCA, PRKN, PINK1, PARK7* and *LRRK2* were most common and offered across all panels. *GBA*, a gene carrying significant risk for PD, was not consistently offered and only appeared on 8 panels, whereas other genes, *FBOX07* (atypical parkinsonism) and *SLC6A3* (infantile parkinsonism-dystonia), appear more frequently.

4. Discussion

We have documented marked differences in diagnostic, multi-gene panels for PD offered by laboratories in the United States and internationally. In addition, we observed a remarkable array of PD gene panel options, even by the same company. Genes considered in the literature to be established as linked with monogenic PD or a major risk factor such as *GBA*, were not always included on a panel. Monogenic, atypical forms of parkinsonism were represented on the panels to a variable degree with the majority of labs including *ATP13A2, DNAJC6, FBX07, SYNJ1*, and *DCTN1* (Table 1).

We believe that this diverse and unstandardized state of PD testing has consequences for test ordering, usefulness of the genetic information, and interpretation. Recent work has found that movement disorder specialists are not widely offering genetic testing to their patients with PD. A key reason cited by neurologists for this reduced utilization was the confusion surrounding genetic testing [16]. Further, the impact of negative results on test utility and interpretation for genetic counseling are markedly different if five versus more than 60 genes are tested. For instance, if only five major genes are tested – and then incompletely – the scope of testing may be too narrow to rule out a major genetic cause. The implications of testing that is too narrow for PD are very clear. Currently, precision medicine clinical trials for *GBA* mutation carriers are widely available for pathogenic variants carriers. However, some panels do not include *GBA*, (Table 1), or may not perform full sequencing of the gene. There also can be a difference as to which variants are reported out by laboratories.

Variants that are of uncertain significant (VUS) present a unique challenge as they do not fit into a benign or pathogenic category based on available data and, what is a particular difficulty, is that they may be reclassified later. Multigene and especially larger panels will have a potentially high rate of VUS—with commercial multigene panels approaching 10% for some neurologic disorders [17]. As a result, the large number of VUS likely to be discovered/revealed, combined with lack of consistency in reporting and classification, has the potential to further complicate test interpretation and counseling of patients.

To overcome these issues surrounding genetic testing, we suggest that physicians should have panel options for PD that are based on overall clinical features (typical versus atypical) with all genes included that are likely associated with monogenic PD. Additional options to include on the panel would be genes whose variants are associated with atypical parkinsonism and others associated with similar presentation, recognizing that there will be a cost/benefit analysis required for these larger panels. The technology used for PD panels will also be important to clarify, including the type of sequencing employed. In addition, laboratories should make clear to the physician if deletion/duplication testing will be performed since the majority of variants in the *PRKN* and *SNCA* gene involve copy number variation [2,12,18]. Another consideration for panel design and interpretation of results is the awareness about ethnic and population differences in PD, as we begin to better understand genetic diversity among populations and generate more supporting data through large research initiatives. There are indications

that there are different genetic risks and clinical expressions of PD among population groups [19].

Future work by the ClinGen PD GCEP will aim to create consensus on casual genes for PD and reveal those that have an uncertain or disputed relationship. The preliminary information obtained from the commonly used GTR will inform the process of creating a PD gene list for curation. In addition, the GCEP will review evidence from the Movement Disorder Society Genetic mutation database (MDSGene) as well as from published literature to further refine the gene list. We have ongoing curation of the following seven genes defined as Tier 1 for PD (not necessarily in this order): *SNCA, PRKN, PINK1, PARK7, LRRK2, and VPS35*. Ideally, this consensus will guide key stakeholders with the ultimate aim to improve the use of genetic information in the care of people with PD and improve patient outcomes.

5. Conclusion

We have identified marked heterogeneity in commercial gene tests offered for PD, specifically for multigene panels. This may create obstacles to test ordering and unnecessarily complicate genetic testing, interpretation, and counseling by HCPs. Our findings highlight the urgent need for expert opinion on which genes and variants commercial laboratory services should consider for general PD panels and other PD-related panels.

Author contributions

Lola Cook – Organized and executed research project; designed, executed, reviewed and critiqued data for analysis; writing, reviewing and critique of all drafts of manuscript; designed figure.

Jenny verbrugge – review and critique of all drafts of manuscript

Jeanine Schulze - Reviewed and critiqued data analysis, designed table.

James C. Beck - Review and critique of manuscript, designed figure.

Karen S. Marder - Review and critique of manuscript.

Rachel Saunders-Pullman - Review and critique of manuscript.

Christine Klein - Review and critique of manuscript.

Anna Naito - Review and critique of manuscript, organized research project.

Roy N. Alcalay – Research project conception and oversight, review and critique of manuscript.

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Declaration of competing interest

None.

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