Supplement

Genome sequencing in the Parkinson's disease clinic

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eTable 1. Parkinson's Disease Gene Panel

The panel considers 5 categories of genes/variant. Categories 1-3 are listed below, based on literature review. Category 4 consists of a published PD genetic risk score consisting of 90 single-nucleotide polymorphisms[1]. Category 5 consists of secondary, medically-actionable findings unrelated to PD, including 59 genes recommended for reporting by the ACMG[2]. PD=Parkinson's disease; YOPD=young-onset PD; LBD=Lewy body dementia; NBIA= neurodegeneration with brain iron accumulation; PSP= progressive supranuclear palsy; FAHN= fatty acid hydrolase associated neurodegeneration; PKAN= pantothenate kinase-associated neurodegeneration; BPAN= beta-propeller protein-associated neurodegeneration; FTD= frontotemporal dementia; AD=autosomal dominant; AR=autosomal recessive; XLR=X-linked recessive; XLD=X-linked dominant

Gene	Phenotype	Inheritance	Reference
Category 1			3
SNCA	YOPD, LBD	AD	
LRRK2	PD	AD	
VPS35	PD	AD	
PARK2	YOPD	AR	
PINK1	YOPD	AR	
Category 2			2,4
GBA	PD, LBD	AD	
SMPD1	PD	AD	
APOE	LBD	AD	
Category 3			
DJ-1	PARK7, parkinsonism, psychiatric symptoms, dystonia	AR	5–7
ATP13A2	PARK9, Kufor-Rakeb syndrome, dystonia parkinsonism, NBIA	AR	8–10
FBXO7	Parkinsonism, pyramidal signs	AR	11–13
SYNJ1	Juvenile parkinsonism dystonia, cognitive decline, seizures	AR	14–16
DNAJC6	Early onset parkinsonism, intellectual disability, seizures	AR	17–19
DNAJC13	Parkinsonism, young or late onset, slow progression	AD	20–22
TAF1	Dystonia parkinsonism (DYT3, Lubag syndrome)	XLR	23,24
SLC30A10	Focal or generalized dystonia, parkinsonism	AR	25–27
PLA2G6	PARK14, dystonia parkinsonism, NBIA	AR	28–30
GCH1	Dopa-responsive dystonia, parkinsonism	AD	31,32
DCTN1	Perry syndrome, parkinsonism with central hypoventilation, PSP	AD	33–36
VPS13C	Parkinsonism, young onset, rapid progression	AR	37–39
ATP1A3	Rapid onset dystonia parkinsonism, alternating hemiplegia of childhood	AD	40–42
PRKRA	Dystonia-parkinsonism	AR	43–45
GLB1	Dystonia-parkinsonism	AR	46–48
RAB39B	Waisman syndrome, early onset parkinsonism, intellectual disability	XLR	49–51
POLG	Progressive external ophthalmoplegia, parkinsonism, ataxia, sensory neuropathy, Alper's syndrome	AR	52–54
CSF1R	Adult onset leukoencephalopathy, frontal lobe syndrome, parkinsonism, seizures	AD	55,56
DNAJC12	Hyperphenylalinemia, developmental delay, dystonia, parkinsonism	AR	57,58
SPG11	Spastic paraplegia, parkinsonism	AR	59–61
TH	Dopa-responsive dystonia	AR	62–64
PTS	Dopa-responsive dystonia	AD	65,66
SPR	Dopa-responsive dystonia	AD	67,68
CP	NBIA, acerulosplasminemia	AR	69–71
FTL	NBIA, neuroferritonopathy	AD	72–74
FA2H	NBIA, FAHN	AR	75–77
PANK2	NBIA, PKAN	AR	78,79
COASY	NBIA, COASY protein-associated neurodegeneration	AR	80,81
DCAF17	NBIA, Woodhouse-Sakati syndrome	AR	82–84
WDR45	NBIA, BPAN	XLD	85–87
C19orf12	NBIA, pallidopyramidal syndrome, dystonia, mitochondrial membrane associated neurodegeneration	AR	88–90
PDGFB	Familial idiopathic basal ganglia calcification	AD	91–93
PDGFRB	Familial idiopathic basal ganglia calcification	AD	94,95
SLC20A2	Familial idiopathic basal ganglia calcification	AD	96,97
XPR1	Familial idiopathic basal ganglia calcification	AD	98–100
VPS13A	Chorea-acanthocytosis	AR	101,102
GRN	FTD, parkinsonism	AD	103–105
MAPT	FTD, parkinsonism	AD	106–108

eTable 2. Sequencing Results with Additional Information

All variants considered as pathogenic in this study were annotated in ClinVar as either "pathogenic" / "likely pathogenic" or in HGMD as "disease causing". In the case of *GBA*, database annotation is largely based on risk for Gaucher disease; however, we additionally considered 2 *GBA* variants, E365K and T408M, with strong literature support for increased risk for PD but which are non-pathogenic for Gaucher. P=pathogenic; LP=likely pathogenic; CIP=conflicting interpretations of pathogenicity; DM=disease causing.

Gene	Transcript	Position	Variant	Subjects	ClinVar	HGMD	References
LRRK2	NM_198578.3	chr12:40252984	c.4937T>C:p.M1646T	5	CIP	DM	109, 110
			c.6055G>A:p.G2019S	1	P	DM	110-112
			c.1256C>T:p.A419V	1	P	DM	109,113,114
PRKN	NM_004562.2	chr12:40320097	c.823C>T:p.R275W	1	P	DM	115–119
GBA	NM_001005741.2	chr1:155236376	c.1093G>A:p.E365K	12	CIP	DM	110,120,122,123
		chr1:155235252	c.1448T>C:p.L483P	1	CIP	DM	124-126,128
		chr1:155240629	c.115+1G>A(IVS2+1)	1	P	DM	127,129
		chr1:155236246	c.1223C>T:p.T408M	3	CIP	DM	110,121,123
		chr1:155235727	c.1342G>C:p.D448H	1	P/LP	DM	126,127
		chr1:155235843	c.1226A>G:p.N409S	2	CIP	DM	110,123,124,128
		chr1:155237458	c.882T>G:p.H294Q	1	CIP	DM	110,127

eTable 3. Variants of Uncertain Significance

Variants of uncertain significance (VUS) are shown for Category 1 genes only. We excluded all variants annotated as "benign" or "likely benign" in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), or any variant with MAF > 5%. CIP=conflicting interpretations of pathogenicity.

Gene (Transcript)	Position	Variant	Subjects (n)	ClinVar
LRRK2 (NM_198578.3)	chr12:40235634	c.356T>C:p.L119P	1	CIP
	chr12:40251346	c.1073C>T:p.T358M	1	CIP
	chr12:40259538	c.1477C>T:p.R493C	1	NA
	chr12:40287559	c.2689+20A>C	1	NA
	chr12:40299212	c.3451G>A:p.A1151T	1	VUS
	chr12:40310461	c.4348G>A:p.V1450I	2	VUS
	chr12:40314114	c.4679A>T:p.N1560I	1	NA
	chr12:40320043	c.4883G>C:p.R1628P	1	CIP
	chr12:40320188	c.5015+13T>A	1	NA
	chr12:40321129	c.5111T>C:p.F1704S	1	NA
	chr12:40323266	c.5616T>A:p.N1872K	1	NA
	chr12:40340439	c.6094T>A:p.S2032T	1	NA
	chr12:40351585	c.6428G>A:p.R2143H	1	VUS
	chr12:40363526	c.7153G>A:p.G2385R	1	CIP
	chr12:40351723	c.6566A>G:p.Y2189C	1	VUS
PRKN (NM_004562.2)	chr6:162262692	c.245C>A:p.A82E	1	CIP
	chr6:162443341	c.140G>A:p.G47E	1	NA
	chr6:161360169	c.1204C>T:p.R402C	1	CIP
	chr6:161785844	c.799T>C:p.Y267H	1	VUS
	chr6:161569358	c.930G>C:p.E310D	1	VUS
	chr6:161350187	c.1310C>T:p.P437L	1	CIP
	chr6:162054183	c.535-9T>A	1	CIP
PINK1 (NM_032409.2)	chr1:20638041	c.587C>T:p.P196L	2	VUS
	chr1:20645615	c.1015G>A:p.A339T	1	CIP
	chr1:20645700	c.1100A>G:p.N367S	1	NA
	chr1:20648612	c.1231G>A:p.G411S	1	CIP
	chr1:20650525	c.1580T>C:p.M527T	1	VUS

eTable 4. Survey Results

Note: Complete survey script with questions immediately follows this Table.

Question	Responses	n (%)
Q1	1	98 (42%)
	2	101 (44%)
	3	30 (13%)
	4	2 (1%)
Q3	1	12 (5%)
	2	32 (14%)
	3	88 (38%)
	4	99 (43%)
Q4	1	190 (82%)
	2	31 (14%)
	3	10 (4%)
Q5	1	2 (1%)
	2	1 (0.5%)
	3	112 (48.5%)
	4	45 (19%)
	5	71 (31%)
Q6	1	3 (1%)
	2	14 (6%)
	3	113 (49%)
	4	44 (19%)
	5	57 (25%)
Q7	1	3 (1%)
	2	26 (12%)
	3	173 (75%)
	4	16 (7%)
	5	12 (5%)
Q8	1	27 (12%)
	2	30 (13%)
	3	65 (28%)
	4	109 (47%)
Q9	1	0 (0%)
	2	7 (3%)
	3	84 (36%)
	4	50 (22%)
	5	90 (39%)
Q10	1	16 (7%)
	2	204 (88%)
	3	11 (5%)
Q11	1	46 (20%)
	2	65 (28%)
	3	44 (19%)
	4	62 (27%)
	Declined	14 (6%)
Q12	1	8 (3%)
	2	67 (29%)
	3	83 (36%)
	4	72 (31%)
	5	1 (<1%)
Q13	1	2 (1%)
	2	3 (1%)
	3	71 (31%
	4	94 (41%)
	5	61 (26%)

eMethods

Survey: Improving Communication About Genetic Testing for Parkinson's Disease

It is possible that you have considered undergoing genetic testing for Parkinson's disease (PD). While genetic testing remains relatively uncommon during routine PD clinical care, this may change as we understand more about how genetics influences disease risk or affects the disease course in individual patients. Our goal is to learn how to better prepare PD patients for genetic testing, and how best to communicate test results. We will discuss four hypothetical "case studies" and answer questionsrelated to genetic testing in PD.

To begin, let's review some common terms related to genetic testing:

- DNA or (**d**eoxyribo**n**ucleic **a**cid) is the genetic code, which is like a blueprint for all living things.
- **Genes** are segments of DNA. Genes give our cells instructions. These instructions lead to individual traits like eye color, hair color, or in some cases, may even affect risk for diseases like PD.
- **Genetic testing** takes DNA from a blood sample and looks for changes that are associated with disease.
- **Variants** are changes that make a gene different, such as the changes that can cause disease.

1. How much do you know about genetics in PD?

1 – nothing
2 – a little
3 – a moderate amount
4 – a lot

Comments:_____

2. Where did you learn what you know about genetics in PD? (please check all that apply)

☐ a doctor
☐ family and friends
☐ book
☐ school
☐ news
☐From the internet (please specify which websites): _____
☐Other (please specify): _____

3. How would you characterize your interest in having genetic testing for PD?

1 – not interested
2 – a little interested
3 – moderately interested
4 – very interested

Vignette 1

Sue is 70 years old and was diagnosed with PD after noticing more difficulty getting dressed and slowed walking. Sue is worried about the risk of PD for her family since her sister recently developed a tremor. Sue has genetic testing and is found to have a *LRRK2* gene variant. Siblings and children have a 50% chance of also having a *LRRK2* variant. People with this variant have a high risk to develop PD; about 85% develop the disease by age 70.

4. If your genetic testing found a *LRRK2* variant, would you tell your family about their risk of PD?

1 – Yes, I would tell all my family
2 – Yes, but I would only tell family members with possible PD symptoms, such as tremor.
3 – No, I would not tell my family members

5. Does the possibility of discovering an increased risk of PD for your family members change your interest in genetic testing?

1 – Much less interested
2 – A little less interested
3 – No change
4 – A little more interested
5- Much more interested

Comments:_____

Vignette 2

Bob is 60 years old, and was diagnosed with PD 6 years ago. He feels his memory is "not what it used to be". He sometimes has hallucinations, but he knows they are not real. During genetic testing, Bob is found to have a glucocerebrosidase (GBA) gene variant. Individuals with *GBA* variants are 5 times more likely to develop PD. Individuals with PD who have a *GBA* variant have an increased risk of dementia and hallucinations. They may also develop PD-related disability more quickly.

6. Does the possibility of discovering an increased risk of dementia change your interest in genetic testing?

1 – Much less interested
2 – A little less interested
3 – No change
4 – A little more interested
5- Much more interested

Comments:_____

Vignette 3

Alice is diagnosed with PD at age 62. She heard about experimental research therapies for patients with GBA variants, and she therefore desires genetic testing. She is initially disappointed to learn that she does not have a GBA variant. For most patients, there is a low likelihood of discovering a high-risk gene variant, such as GBA or LRRK2, on genetic testing. In most cases, therefore, genetic testing results are unlikely to change your treatment plan.

7. Does it change your interest in genetic testing to know that your results are unlikely to change your treatment plan?

1 – Much less interested
2 – A little less interested
3 – No change
4 – A little more interested
5- Much more interested

Comments:_____

Although genetic testing is currently unlikely to identify single, high-risk gene variants in most patients, comprehensive testing of all genes can be used to estimate a "genetic risk score", indicating the overall risk of PD based on your genetic makeup (e.g. low, medium, or high risk).

8. How interested would you be to learn your "genetic risk score"?

1 – not interested
2 – a little interested
3 – moderately interested
4 – very interested

Comments:_____

Vignette 4

Steve is 66 years old and has had PD for 8 years. He is worried about the risk of PD for his sisters and other family, so he undergoes comprehensive genetic testing. He is found to have no high-risk PD gene variants and overall low PD genetic risk score. However, a variant is discovered in the BRCA1 gene. This gene variant increases the risk of breast and ovarian cancer in women (as well as breast cancer and prostate cancer in men). His sisters and children have a 50% chance of also having this variant. If positive, cancer screening may be required.

9. Does it change your interest in genetic testing to know that you may discover results unrelated to PD but with significant implications for you or your family's health?

1 – Much less interested
2 – A little less interested
3 – No change
4 – A little more interested
5- Much more interested

Comments:_____

When having comprehensive genetic testing, you are likely to be offered the choice of only receiving results related to PD, in which case any incidental findings, such as BRCA1, would not be reported to you or your doctors.

10. If you were to have comprehensive genetic testing, what choice would you make?

1 – Receive only results related to PD
2 – Receive all results, including any findings unrelated to PD.
3 – I don't want comprehensive genetic testing

11. Finances can affect the decision to pursue comprehensive genetic testing because it can be expensive and is frequently not covered by insurance. If you are comfortable doing so, please indicate which category describes your household income in the past 12 months?

1 – Less than $50,000
2 – $50,000-100,000
3 – $100,000-150,000
4 – More than $150,000

Feedback

12. We hope these case studies and questions have helped you better understand possible PD genetic testing results. Please tell us how much you learned from this experience

1 – I learned nothing new
2 – I learned a little
3 – I learned a moderate amount
4 – I learned a lot
5 – I am more confused now than before

Comments:_____

13. Overall, how has this experience changed your interest in genetic testing?

1 – Much less interested
2 – A little less interested
3 – No change
4 – A little more interested
5- Much more interested

14. Please tell us anything you think doctors could do better to help people understand genetic testing for PD.

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