Update On Genetics In Parkinson Disease

Martha Nance MD

Struthers Parkinson's Center

Struthers Parkinson's Center

Parkinson's Foundation
CENTER OF EXCELLENCE

Your next four clinic patients

- Philip: 32 years old, onset of PD 3 years ago, mostly affecting gait (?spastic?dystonic), some tremor, good response to levodopa. His 40 year old brother also has PD. German-English ancestry, he thinks.
- Christine: 63 years old, has had PD for a few years, maybe 5,now developing dementia, family reminds you that grandmother and maybe an uncle had PD or Lewy body disease, they aren't quite sure. 23 and Me test was negative.
- Eli: 65 years old, referred for confirmation of diagnosis, no affected family members, Ashkenazi ancestry on father's side, African-American on mother's side
- Paul: 70 years old, returning for routine followup of levodopa-responsive PD diagnosed 8 years earlier, has heard the buzz about genetic testing and wants to talk about it. No family history of PD, Scandinavian and European ancestry.

Thinking like a neurogeneticist

- Philip—YOUNG (under 30) onset, AFFECTED SIBLING, European ancestry

- Likely genetic!
- Likely inherited in a recessive manner, could be X-linked

- How Parkinson-like is the patient's phenotype
- How Parkinson-like is the sibling's phenotype
- Any other neurologic diseases in the family?

Gene [1]	PD Designation [2]	MOI	% of Adult PD	Comments
GBA [3]	PARK-*GBA*	AD	3%-7% (20% in AJ ancestry)	•Onset age may be <50 yrs. •Higher likelihood of cognitive impairment, atypical motor findings & severe progression •Associated w/dementia w/Lewy bodies •Variable penetrance dependent on age, variant, & ethnicity [4] •Consider if family history of Gaucher disease.
LRRK2	PARK-*LRRK2*	AD	1%-2% (13%-30% in AJ ancestry; 41% in African Berber ancestry)	•Classic manifestations w/less non-motor involvement •Variable penetrance dependent on age, variant, & ethnicity [5]
PARK7 (*DJ1*)	PARK-*DJ1*	AR	Rare	•Phenotype similar to PARK-*Parkin* •ID &/or seizures occasionally •Risk to heterozygotes unknown
PINK1	PARK-*PINK1*	AR	Rare (3.7% of early-onset adult PD)	•Phenotype similar to PARK-*Parkin* •Non-motor manifestations incl psychiatric features more common •Heterozygotes may have ↑ PD risk.
PRKN	PARK-*Parkin*	AR	1% (4.6%-10.5% of early-onset adult PD)	•Slow progression •Can have lower-limb dystonia, dyskinesias, hyperreflexia •Mild non-motor manifestations •Heterozygotes may have ↑ PD risk.
SNCA	PARK-*SNCA*	AD	Rare	•Onset age may be <50 yrs •Cognitive & psychiatric features more likely
VPS13C	Not assigned	AR	Rare	Early-onset PD w/very rapid progression; truncating variants cause severe disease.
VPS35	PARK-*VPS35*	AD	Rare	•Classic PD w/tremor •Fewer non-motor manifestations

GeneReviews "Parkinson disease overview" Shukla et al 2019

Other ”Parkinson’s genes”

- POLG, ATP13A2, FBX07, PLA2G6, DNAJC6, SYNJ1
- (UCHL1, HTRA3, GIGYF2, EIF4G1, DNAJC13, TMEM230, LRP10)

Blauwendraat et al, The genetic architecture of PD, Lancet Neuro Feb 2020

- Genes responsible for conditions that might look a little like PD in a given family member: dopa-responsive dystonia, DYT1 dystonia, spinocerebellar ataxia types 2 and 3, Fragile X (FXTAS), FTD, LBD

Why do a gene test in a Parkinson patient?

- To understand why…
- If/because it impacts on prognosis
- If/because it impacts on treatment
- To clarify risk to other family members

Understanding why

- GBA, LRRK2, SNCA, parkin (DJ1, PINK1) mutations are clearly related to the development of PD
- For the pt, a gene mutation answers the question “why did I get PD?”
- This set of genes provides ample fodder for basic research into the biochemical mechanisms underlying PD
- We think that about 10% of PD patients will turn out to have a monogenic form of PD (which means that 90% won’t)

Impact of genetics on prognosis

- Parkin-related PD is clearly different from “idiopathic PD”:
  - Onset age <30, dystonic gait, no loss of smell, long course, little or no dementia, no Lewy bodies
- GBA-related PD can look different from “idiopathic PD”:
  - More rapid course, more likely to have dementia
- SNCA-related PD certainly looks different from “idiopathic PD”:
  - More of a multisystem process, includes dementia

Impact of genetics on treatment

- No difference in treatment, currently, but…

Clinical trials for GBA-PD

Schneider and Alcalay, J Neurol, Jan 2020

Compound	Venglustat (GZ/SAR402671)		Ambroxol	RTB101	LTI-291	PR001
Admin	Oral		Oral	Oral	Oral	Injections
Sponsor	Sanofi		UCL and Cure PD Trust	Restorbio	LTI/Allergan	Prevail
RCT No	NCT02906020		NCT02941822		(NL7061; NTR7299)[a]	
Mechanism	Glucosylceramide synthase inhibiton; reduction of GBA-related GSLs		GCase activation	TORC1 inhibition	GCase activation	Gene therapy, AAV-based
Status	Completed	Recruiting, estimated primary completion 2021	Estimated completion 04-2018	Ongoing; data expected 2020	Recruiting in Leiden (NL)	Clinical centers initiated
Phase	2		2a	1b/2a	1b	1b

Clinical trials in LRRK2-PD

Compound	DNL-201	No public data	No public data	No public data	BIIB094
Sponsor	Denali	GSK	Pfizer	Genetech	Biogen
RCT No	NCT03710707				NCT03976349
Mechanism	LRRK2 inhibition	LRRK2 inhibition	LRRK2 inhibition	LRRK2 inhibition	Antisense oligomere
Status	Ongoing, recruiting, data expected end of 2019	Planned	Under development	Under development	Ongoing
Phase	1b	N/a	N/a	N/a	Phase 1

Clarifying risk to relatives

- US Caucasian has 3-4% risk of PD by age 80
- That risk doubles to 6-8% in the presence of an affected first degree relative
- But the chance of inheriting a parent's pathogenic dominant gene mutation (SNCA, LRRK2, GBA, VPS35) is 50%
- And if a person has two pathogenic mutations (in both copies of the gene), causing an early onset recessive form of PD (parkin, DJ1, PINK1), then all of that person's children are obligate carriers of a pathogenic mutation
- **** for a currently unaffected individual, the relationship between having a PD gene mutation and developing PD is a) age-related and b) complicated

Back to the clinic

- Philip: 32 years old, onset of PD 3 years ago, mostly affecting gait (?spastic?dystonic), some tremor, good response to levodopa. His 40 year old brother also has PD. German-English ancestry, he thinks.
- Christine: 63 years old, has had PD for a few years, maybe 5,now developing dementia, family reminds you that grandmother and maybe an uncle had PD or Lewy body disease, they aren't quite sure. 23 and Me test was negative.
- Eli: 65 years old, referred for confirmation of diagnosis, no affected family members, Ashkenazi ancestry on father's side, African-American on mother's side
- Paul: 70 years old, returning for routine followup of levodopa-responsive PD diagnosed 8 years earlier, has heard the buzz about genetic testing and wants to talk about it. No family history of PD, Scandinavian and European ancestry.

Genetic testing in the clinic

- Consider which gene(s) to test
  - Laboratories often offer gene test panels
  - Not all tests and test panels are created equal!
- Consider the cost to the patient (insurance often doesn't cover)
- Consider your ability to address family questions, or direct family members to someone who can

- PDGENERATION is an effort funded by Parkinson's Foundation to bring genetic testing to the clinic, get people tested, and get PD neurologists familiar with the genetics of PD

What would a neurogeneticist do next?

- Philip: likely to have parkin-PD, caused by mutations in both copies of the parkin gene (DJ1, PINK1 could look similar).
  - His panel needs to include those three genes, and ideally needs to sequence the parkin gene (there are many reported mutations in that gene)
- Christine: her story is pretty consistent with a dominantly inherited condition, progressing quickly with early dementia. Could be GBA or SNCA. Both are complicated to test, and some PD panels do not include GBA.
- Eli: it is reasonable to test any Ashkenazi Jew with PD for GBA (mutations present in up to 20%) and LRRK2 (present in up to 10%) (which are the conditions for which clinical trials are starting), even without a family history of PD; little is known about the genetics of PD in sub-Saharan Africa

What would a neurogeneticist do next?

- Paul: "there is a 90% chance your test panel will be normal. That won't mean that you don't have PD, just that you don't have PD caused by genes X,Y, and Z."
  - ?if negative, OK for the pt to think that is PD is "more likely environmental"
  - There are additional genetic risk aspects to PD that remain to be understood
    - GWAS meta-analysis involving 37K pts and 1.4M controls suggests up to 90 genes involved in PD risk
  - Laboratories may report only known pathogenic mutations—as more people are tested, we may find additional mutations. Duty to recontact?
- "there is a 10% chance your test panel will show a gene mutation. Your siblings/children may be upset by this result."

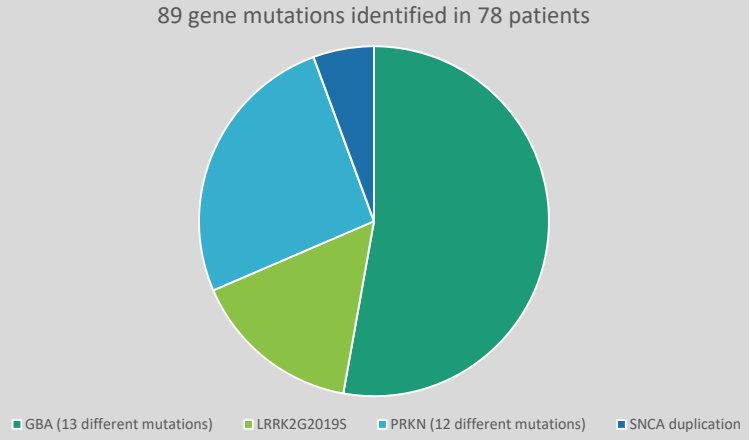
The genetics of PD is complicated

- Paul had mutations in both one copy of the GBA gene and in one copy of the parkin gene

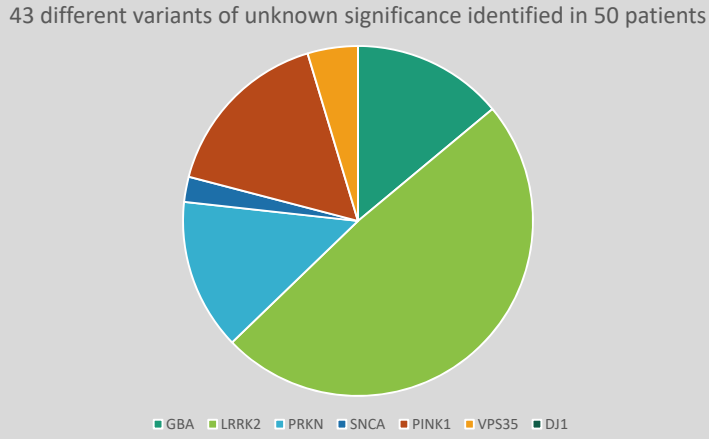
PDGENERATION results to date

- Over 600 enrolled at 6 pilot sites, now opening to multiple additional sites with the goal of enrolling 10,000 people
- Switched from in person to partial or fully telemedicine enrollment
- 525 gene test results reported by end of 2020
- Interest in the PD community is extremely high; sites are overwhelmed

Gene mutations identified in PDGENERATION



Variants of uncertain significance



Resources

- GeneReviews®
- MDSGene (website)
- Clin Gen PD Curation Panel (led by Roy Alcalay), an attempt to reconcile genes and mutations
- GP2—Global Parkinson's Genetics Program (led by Cornelis Blauwendraat)
- Genetic counselors!
- PSG Genetics and Environment Working Group