Parkinson's disease among Ashkenazi Jews

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Parkinson disease

- The 2nd most common age-dependent neurodegenerative disorder second to Alzheimer's disease
- ~1% of the population is affected at 65 years, increasing to 4–5% at 85-years
- Mean age of onset : ~70 years, 4% of patients develop early-onset disease, (<50y).
- Familial history of PD: ~20% of the cases

Genetic and environmental factors in PD

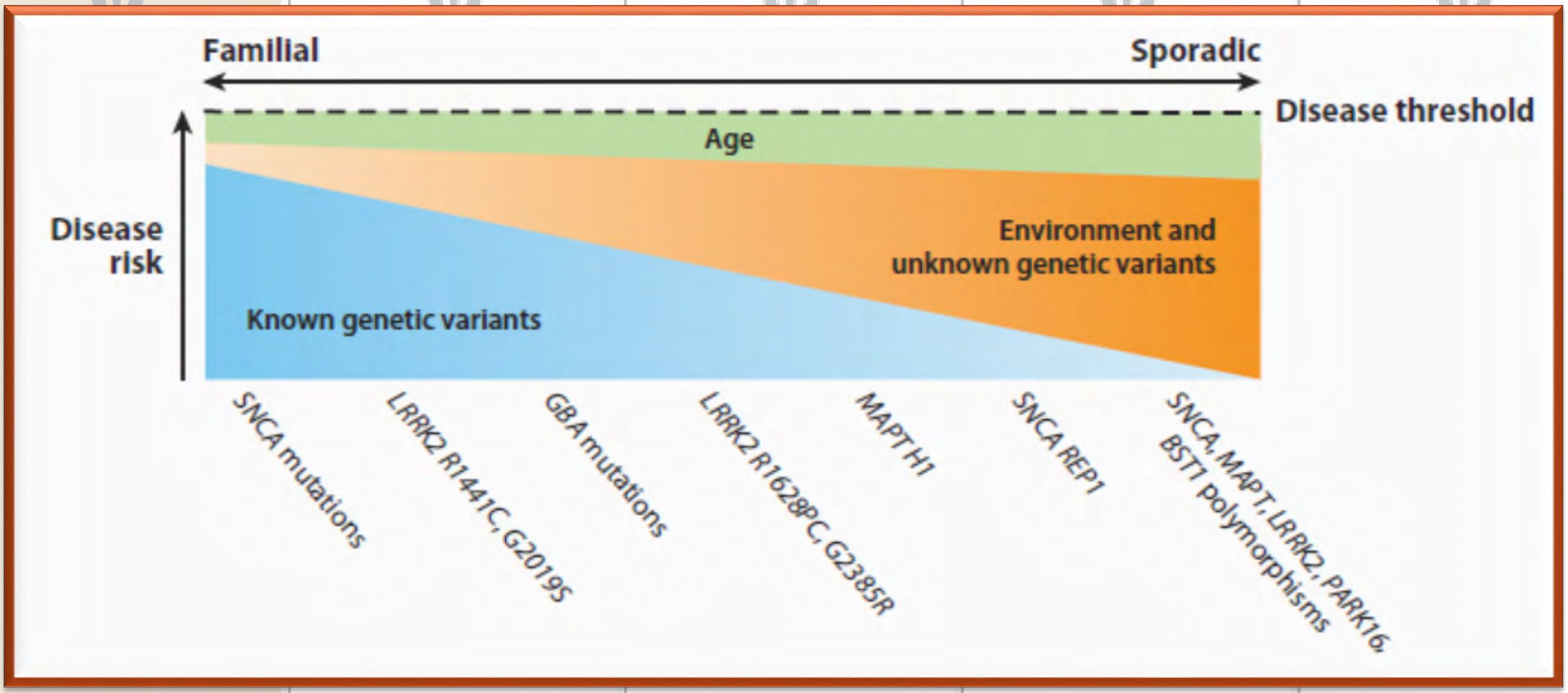
- *Environmental influences* :
  - Industri… …anide, carbon disulfide
  - plant-de… …ctions
  - Mild to …
  - Protective effects: cigarette smoking, coffee and tea drinking, NSAIDs.

PD is generally considered a multifactorial disorder that arises owing to a combination of genes and environmental factors.

(There are conflicting outcomes between individual human studies)

Parkinson's disease is a complex genetic disorder

- ***The genetic portion of PD is ascribed to 2 (non-mutually exclusive) contributions:***
  - **Common disease rare variant (CDRV):** rare DNA sequence variations (mutations), each with relatively high penetrance, contribute to genetic susceptibility of disease. These present the monogenic forms of PD.
  - **Common disease common variant (CDCV):** a large number of CV that each exert relatively small effects on disease risk but that cumulatively confer substantial risk; particularly pronounced in late-onset diseases such as genetically complex PD.
  - *Both GWAS and candidate gene association studies continuously validate that the most statistically significant signals associated with PD are* **common variants** *located close to* ***SNCA, LRRK2,*** *and* ***MAPT*** *as well as low-frequency coding variants in* ***GBA****.*


Familial
Sporadic
Disease threshold
Age
Disease risk
Environment and unknown genetic variants
Known genetic variants
SNCA mutations
LRRK2 R1441C, G2019S
GBA mutations
LRRK2 R1628PC, G2385R
MAPT H1
SNCA REP1
SNCA, MAPT, LRRK2, PARK16, BST1 polymorphisms

Parkinson disease

- Familial history of PD: ~20% of the cases
- 5–10% of patients have a recognized pathogenic Mendelian cause, yet large multi-incident Mendelian pedigrees are rare
- Common variants only contribute <5% of the genetic heritability .
- Thus the majority of genetic inheritance is unexplained.

List of monogenic PD and parkinsonism

Designation	Previous locus symbol	Inheritance	Main clinical features
Classical PD			
PARK-*SNCA*	PARK1	AD	Clinically typical PD or EO with dementia
PARK-*LRRK2*	PARK8	AD	Clinically typical PD
PAR-*VPS35*	PARK17	AD	Clinically typical PD
Early-onset PD			
PARK-*Parkin*	PARK2	AR	EO with dystonia
PARK-*PINK1*	PARK6	AR	EO with psychiatric features
PARK-*DJ1*	PARK7	AR	
Parkinsonism			
PARK-*ATP13A2*	PARK9	AR	Parkinsonism +dystonia, pyramidal, supranuclear gaze palsy and more
PARK-*FBXO7*	PARK15	AR	EO parkinsonism +pyramidal signs
PARK-*DNAJC6*	PARK19	AR	Parkinsonism +mental retardation, seizures
PARK-*SYNJ1*	PARK20	AR	Parkinsonism +cognitive decline, dystonia

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PARK-*LRRK2*	PARK8	AD	
PAR-*VPS35*	PARK17		
Early-onset PD			
PARK-*Parkin*			
PARK-*PINK*			atures
P		AR	Parkinsonism +dystonia, pyramidal, supranuclear gaze palsy and more
PAR	ARK15	AR	EO parkinsonism +pyramidal signs
PARK	PARK19	AR	Parkinsonism +mental retardation, seizures
PARK-*SYNJ1*	PARK20	AR	Parkinsonism +cognitive decline, dystonia

To date, PD causing mutations have been identified in 15 genes responsible for monogenic forms. , explaining only ~30% of monogenic and 3–5% of genetically complex cases

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

2014

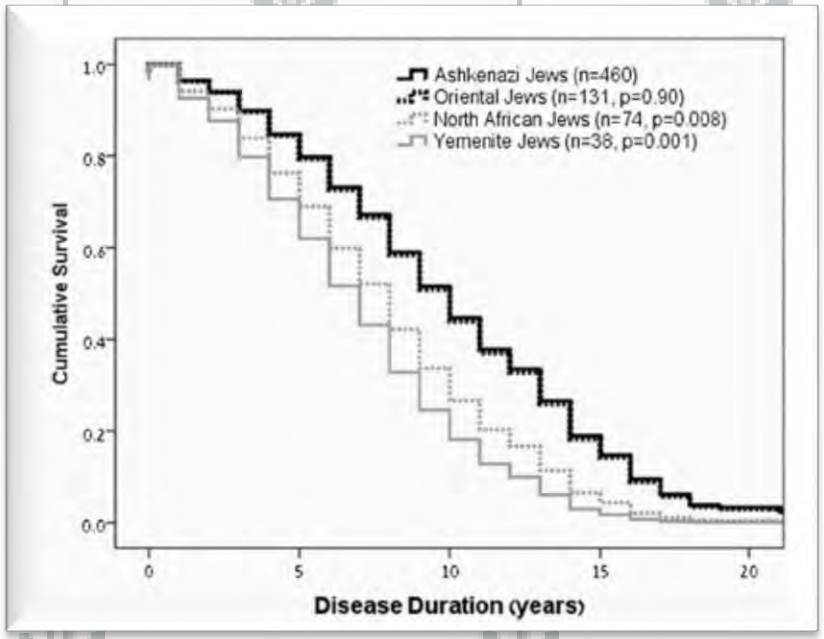
Exploring determinants of progression in Parkinson's disease. Is there a difference among Jewish ethnic groups?

Y. Orlev [a, b, 1], G. Yahalom [a, c, 1], O.S. Cohen [a, c], S. Elincx-Benizri [a], E. Kozlova [a], R. Inzelberg [a, c], U. Goldbourt [b], S. Hassin-Baer [a, c, *]

Survival curves : time from onset until reaching H&Y stage III

707 PD patients [AJ: 458, YJ: 37, NAJ: 75 and OJ: 137], 343 had reached HY3.

Jewish PD patients of Yemenite and North African origin may have a more rapid disease progression, compared to those of Ashkenazi and Oriental origin, suggesting distinctive genetic influences.



Who are *Ashkenazi Jews?*

- Jewish origins trace to the indigenous Israelite tribes of Canaan living in the Middle East more than 3 millennia ago, who later generated the ethnic Ashkenazi, Sephardi, and Yemenite Jewish groups.
- The Ashkenazim represent a distinct Jewish subpopulation characterized by well-described patterns of migration and settlement in **Europe,** first appearing in the 10th century AD in the **German Rhineland region** and subsequently migrating to other Central and Eastern Europe
- The Ashkenazim show evidence of low intra-population variability and a genetic profile that is distinctly different from other populations
- AJ constitute the majority (80%) of the present-day Jewish population , over 10 million AJ around the world, including ~3 million in Israel.

SCIENCE NOW | SCIENCE

Los Angeles Times

DNA ties Ashkenazi Jews to group of just 330 people from Middle Ages

By KAREN KAPLAN | SEP 09, 2014 | 3:00 PM

Albert Einstein and all other Ashkenazi Jews can trace their roots to a group of about 330 people who lived during the Middle Ages, a new study finds. (Associated Press)

nature COMMUNICATIONS

2014

ARTICLE

Received 24 Jun 2014 | Accepted 28 Jul 2014 | Published 9 Sep 2014

DOI: 10.1038/ncomms5835 OPEN

Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins

Shai Carmi[1], Ken Y. Hui[2], Ethan Kochav[1], Xinmin Liu[3], James Xue[1], Fillan Grady[1], Saurav Guha[4,5,6], Kinnari Upadhyay[7], Dan Ben-Avraham[7,8], Semanti Mukherjee[4,5], B. Monica Bowen[2], Tinu Thomas[9,10], Joseph Vijai[9,10], Marc Cruts[11], Guy Froyen[12], Diether Lambrechts[13], Stéphane Plaisance[14], Christine Van Broeckhoven[11], Philip Van Damme[13,15], Herwig Van Marck[14], Nir Barzilai[7,8], Ariel Darvasi[16], Kenneth Offit[9,10], Susan Bressman[17], Laurie J. Ozelius[6], Inga Peter[6], Judy H. Cho[2], Harry Ostrer[7,18], Gil Atzmon[7,8], Lorraine N. Clark[3,19], Todd Lencz[4,5,20] & Itsik Pe'er[1,21]

- Compared results of high-depth sequencing of 128 healthy AJ with each other, as well as with DNA of 26 Flemish people from Belgium.
- Their analysis allowed them to trace the genetic roots of this population to a founding group of 330 people who lived 600 to 800 years ago.
- Those ancient people had split off from the ancestors of today's Middle Easterners more than 20,000 years ago, with a founding group of about 3,500 to 3,900 people, and no more than half of their DNA comes from ancient Europeans .

Genetic Diseases in *Ashkenazi Jews*

- The long migration history, geographical isolation and narrow population bottlenecks of just a few hundred Ashkenazi individuals resulted in high frequencies of founder mutations and deleterious mutation load that is reflected in high incidences of certain Mendelian disorders, e.g Familial dysautonomia, Gaucher disease and Tay-Sachs disease.
- These gene mutations have been maintained because of religious and societal restrictions against marriage outside of the group.
- The individual mutations in each of these disease genes are presumed to have occurred many generations ago as haplotypes of polymorphic markers surrounding individual mutations are largely the same in apparently unrelated families
- A mutation occurred on a particular chromosome point in time and was since transmitted from family to family, accounting for its spread and prevalence in that population.

Genetic Diseases and Testing in Ashkenazi Jews

Gilbert F. Genetic Testing 1997

TABLE 1. DISEASES IN ASHKENAZI JEWS

Disease	*MIM***	*Chromo.*	*Gene*
Abetalipoprotinemia	200100	4q22-q24	Microsomal triglyceride transferase
Bloom syndrome*	210900	15q26.1	helicase
Colorblindness, red–green	303800	Xq28	red–green pigment complex
Factor XI deficiency	264900	4q35	thromboplastin antecedent
Familial dysautonomia	223900	9q31–q33	?
Gaucher disease, Type I adult onset*	230800	1q21	acid beta-glucosidase
Gilles de la Tourette Disease	137580	18q22.1	?
Lactase deficiency	223100	2q21	lactase
Mucolipidoses IV	252650	?	?
Niemann–Pick disease, infantile type*	257200	11p15.4-p15.1	sphingomyelinase
Pentosuria	260800	?	xylitol dehydrogenase
Canavan disease*	271900	17pter-p13	aspartoacylase
Tay-Sachs disease*	272800	15q23-q24	hexosaminidase A
Torsion dystonia	224500	?	?
Cystic fibrosis*	219700	7q31.2	CFTR
Heritable breast cancer*	113705	17q21	BRCA1
	600185	13q1203	BRCA2

Goodman 1979

Genetic Diseases and Testing in Ashkenazi Jews
Gilbert F. Genetic Testing 1997

- **Tay-Sachs: 3 mutations in Hexosaminidase account for ~94% of the chromosomes (Navon et al. 1985)**
- **Gaucher Disease: 5 mutations in GBA account for ~95% of the chromosomes (Beutler et al. 1993);**
- **Cystic fibrosis in: 6 mutations** account for approximately 97% of chromosomes
- **Canavan Disease: 3 mutations account for ~98% of chromosomes (Kaul et al. 1994);**
- **Breast cancer: 3 mutations** in BRCA1/BRCA2 account for virtually all of the risk

Clinical Review & Education

Review

Genetic Movement Disorders in Patients of Jewish Ancestry

Rivka Inzelberg, MD; Sharon Hassin-Baer, MD; Joseph Jankovic, MD

JAMA Neurol. 2014.

About one-third of patients with sporadic Parkinson disease (PD) and more than 40% of patients with familial PD of Ashkenazi Jewish (AJ) descent likely carry

- the G2019S mutation in the *LRRK2* gene
- a mutation in the glucocerebrosidase (*GBA*) gene
- or both.

This finding contrasts with only a 10% frequency of these mutations in patients with PD who are of non-Jewish ancestry.

Clinical Review & Education

Review

Genetic Movement Disorders in Patients of Jewish Ancestry

Rivka Inzelberg, MD; Sharon Hassin-Baer, MD; Joseph Jankovic, MD

JAMA Neurol. 2014.

Figure 1. Mutations in Ashkenazi Jewish Patients With Apparent Sporadic Parkinson Disease (PD)

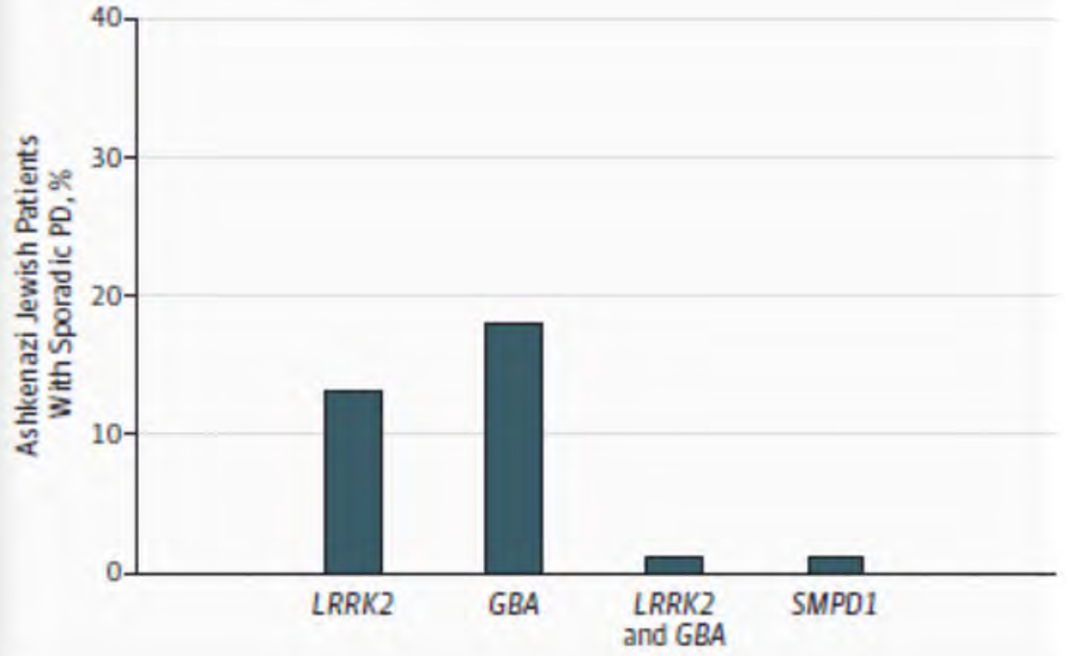
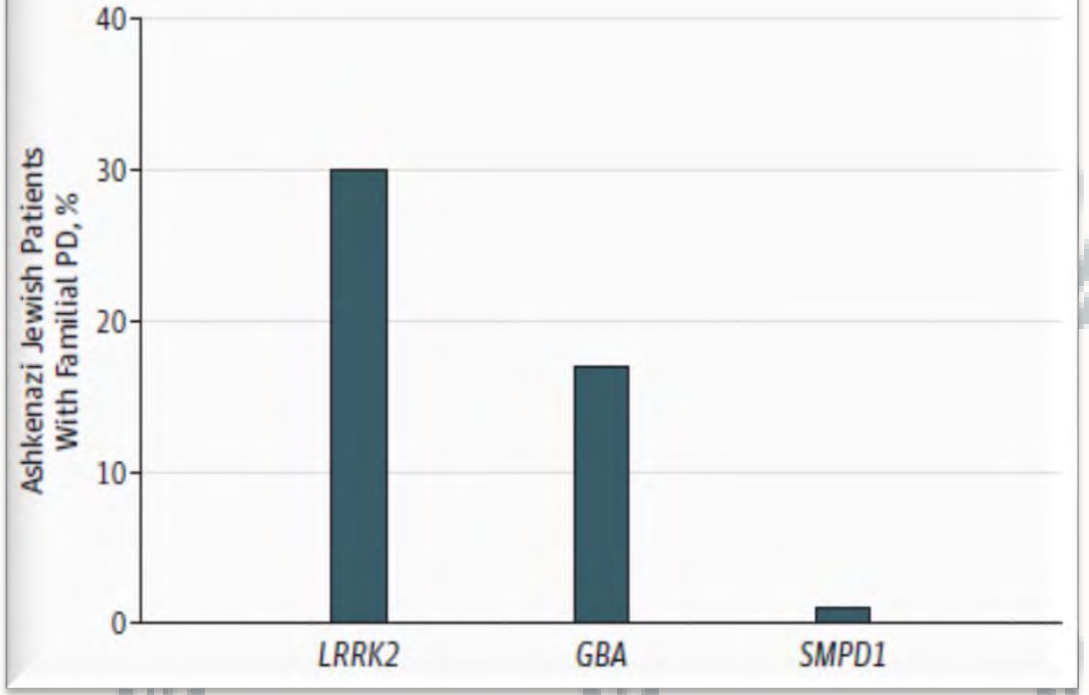


Figure 2. Mutations in Ashkenazi Jewish Patients With Familial Parkinson Disease (PD)



GBA-ASSOCIATED PARKINSON'S DISEASE

Is this the Parkinson's that is associated with more RBD and cognitive impairment, faster progression?

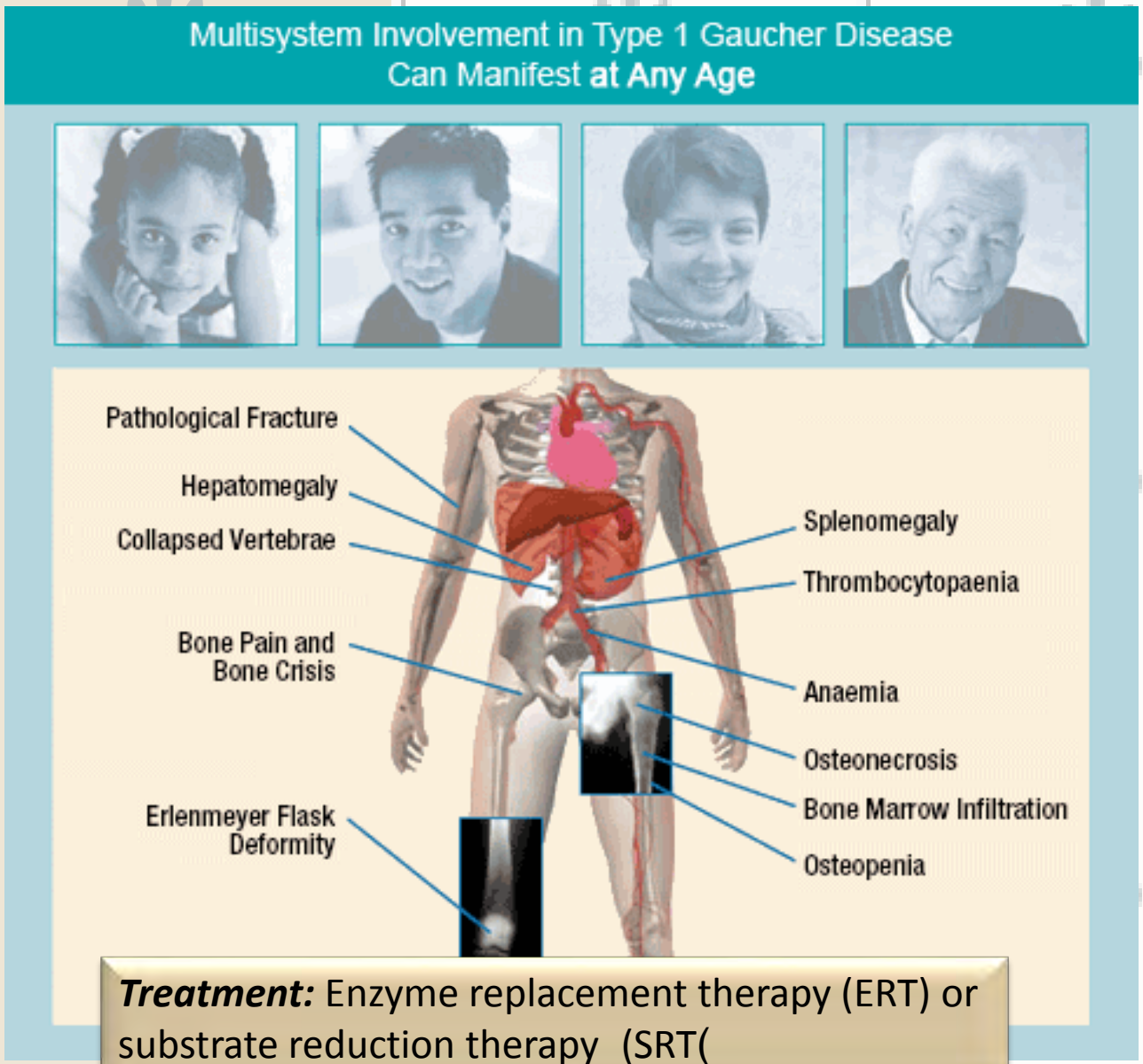
What is the mechanism?

GBA and Gaucher Disease

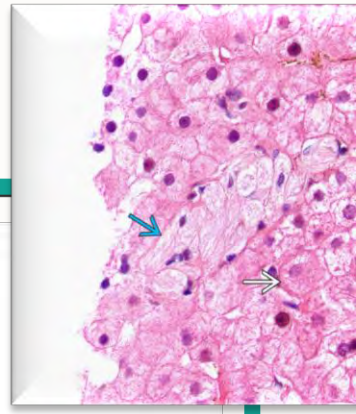
Philippe Gaucher 1882

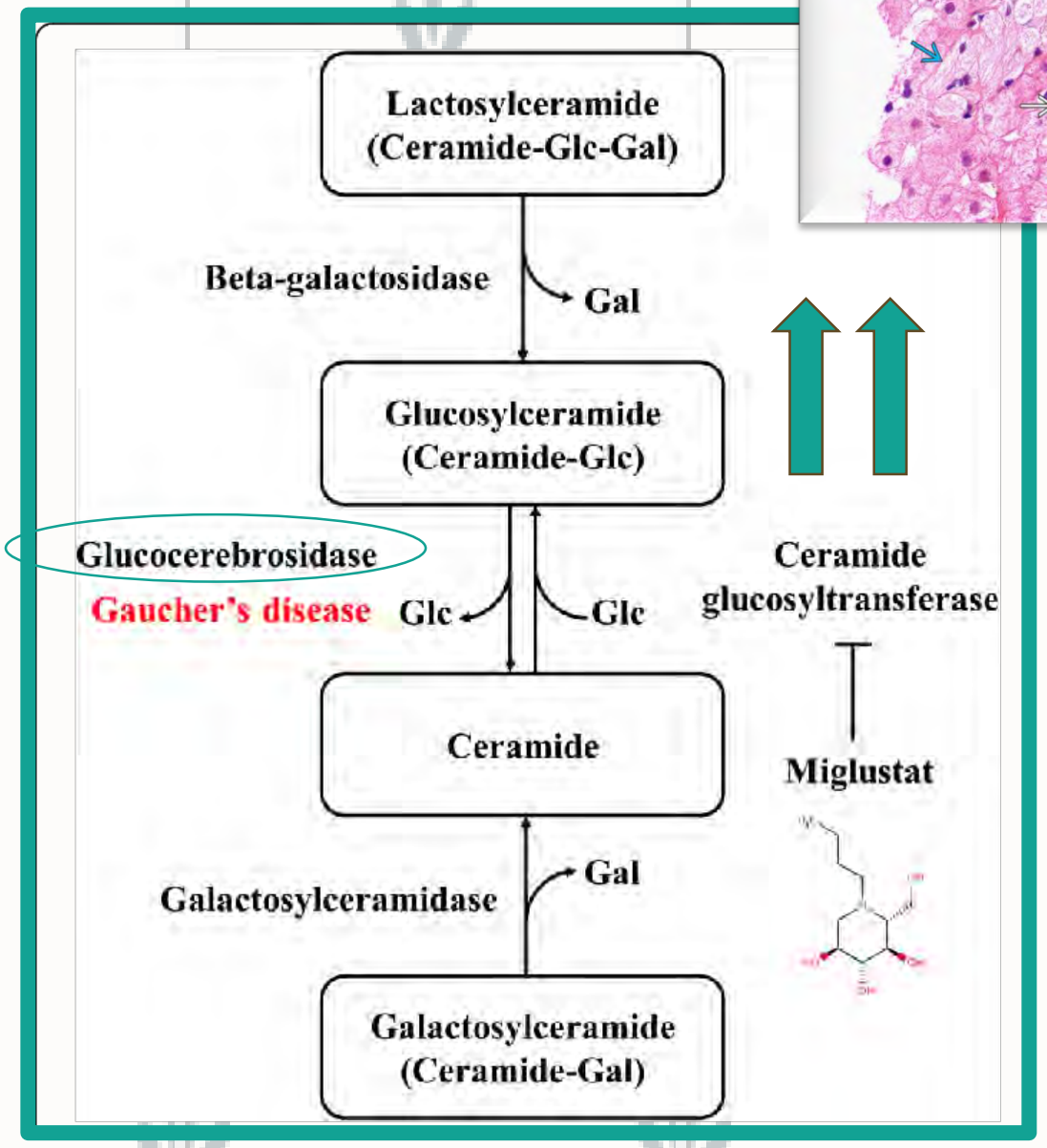
- GBA , (1q21) encodes for glucocerebrosidase (GCase), a lysosomal enzyme involved in the metabolism of glucosylceramide.
- GBA mutations have been classically associated with **Gaucher disease (GD)**, a systemic disorder leading to visceral and hematological signs and symptoms with a variable degree of CNS involvement.
- Traditionally, GD is divided into 3 types according to increasing severity of the disease and the degree of neuronal involvement, where **type 1 is non-neuronopathic**, **type 2 is acute neuronopathic**, and **type 3 is chronic neuronopathic.**
- GD has an estimated frequency of 1:50,000 live births, but the AJ population the mutated **gene frequency is 1 to 15 and GD occurs in 1 out of 850.**

GAUCHER DISEASE



Treatment: Enzyme replacement therapy (ERT) or substrate reduction therapy (SRT(





Parkinson's disease among patients with Gaucher disease

- GBA pathogenic variants can be classified based on their association with GD:
  - **"severe variants"** are those that in homozygous carriers lead to the severe forms of GD, type II and type III
  - **"mild variants"** lead to the mild type I GD
- ***Neudorfer et al. 1996:***
  - *patients with type 1 GD (at least one "mild" mutation) developed an early-onset, aggressive form of PD that in a few patients was also refractory to L-dopa*

GBA, Gaucher Disease, and Parkinson's Disease

- ~15 years ago it was observed that mutations in GBA were associated with an increased incidence of PD, in both Gaucher disease patients as well as asymptomatic GBA mutation carriers.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutations in the Glucocerebrosidase Gene and Parkinson's Disease in Ashkenazi Jews

Judith Aharon-Peretz, M.D., Hanna Rosenbaum, M.D., and Ruth Gershoni-Baruch, M.D.

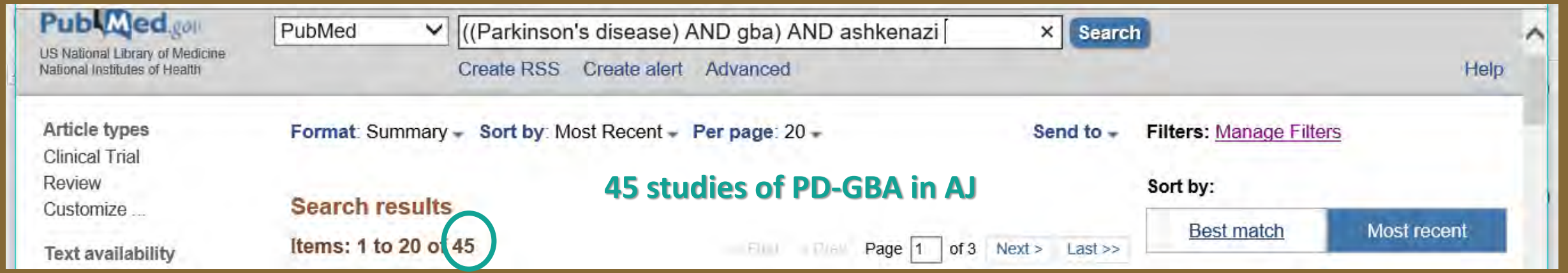
2004

Table 2. Rates of Carriage of Gaucher's Disease among Patients with Parkinson's Disease, Patients with Alzheimer's Disease, and Control Subjects.

Population	No. Tested	No. of Carriers (%)	95% Confidence Interval
Patients with Parkinson's disease	99	31 (31.3)	22.2–40.4
Patients with Alzheimer's disease	74	3 (4.1)	0.0–8.5
Controls	1543	95 (6.2)	5.0–7.4

***6 GBA* mutations**: N370S, L444P, 84GG, IVS+1, V394L, R496H

AJ PD had greater odds of being GBA carriers than did AJ AD or AJ controls (ORs 10.8; 95 %CI 3.0-46.6 and 7.0; 95 %CI 4.2-11.4, respectively; P<0.001).



– The most exciting of all genetic associations with PD !

-Mutations of the GBA gene are the most common and important risk factor yet discovered for PD,

– a relationship first identified in the Ashkenazi Jewish population.

European Journal of Medical Genetics 62 (2019) 65–69

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

January 2019

Increased yield of full *GBA* sequencing in Ashkenazi Jews with Parkinson's disease

Jennifer A. Ruskey[a,b], Lior Greenbaum[c,d,e], Léanne Roncière[f], Armaghan Alam[a], Dan Spiegelman[a,b], Christopher Liong[g], Oren A. Levy[g,h], Cheryl Waters[g], Stanley Fahn[g], Karen S. Marder[g,h], Wendy Chung[i], Gilad Yahalom[e,j,k], Simon Israeli-Korn[j,k], Vered Livneh[j,k], Tsvia Fay-Karmon[j,k], Roy N. Alcalay[g,h], Sharon Hassin-Baer[e,j,k], Ziv Gan-Or[a,b,l,*]

- **Initially genetic studies in AJ PD were based on genotyping of 5- 7 specific GBA variants, all linked to GD.**
- **The contribution of other GBA variants to PD in the AJ population was unknown.**
- **Full GBA sequencing (AJ PD=735, AJ HC=3700) increased the number of variants discovered by 17.4%.**
- **The p.E326K variant (not associated with GD) was found in 1.6% of AJ PD patients, (2nd most common PD-associated GBA variant in AJ after p.N370S).**
- **In large-scale GWASs, the GBA locus was associated with the strongest risk for PD, driven by the p.E326K variant**
- **GBA variants were found in 18% of PD patients and 7.5% of controls (OR=2.7, 95%CI=1.9–3.8, p < 0.0001).**
- **Message: the importance of full sequencing of GBA in studies of PD-GBA, as well as the importance of the p.E326K variant in this population**

GBA–associated Parkinson's disease in Ashkenazi Jews

- **Mild mutation carriers: a 2-3 fold increased risk for developing PD**
- **Severe GBA mutation carriers: the risk for developing PD is significantly higher , up to 10-fold increased risk.**
- **The overall penetrance / lifetime risk of PD for GBA carriers:**
  - **up to 20% at 70 years**
  - **Up to 30% at 80 years**

GBA associations:

- **Positive for dementia with Lewy bodies**

Shiner et al *JAMA Neurol* 2016

- 1 in 3 AJ DLB patients (n=35) were carriers of a GBA mutation, making it the most common genetic mutation identified in association with DLB (or any dementia)
- GBA mutations were associated with more severe motor and cognitive dysfunction.
- **Negative for- MSA, PSP, CBD**

Genotype-phenotype correlations in *GBA*

- **On an individual level, *GBA* htz/ hmz with PD are indistinguishable from iPD patients, but-**
- **Motor symptoms are similar to those of** iPD
- *GBA* mutation carriers are more likely to manifest ***nonmotor symptoms***
  - ***cognitive impairment***
  - ***REM sleep behavior disorder (RBD)***
  - ***hyposmia***
  - ***autonomic dysfunction***

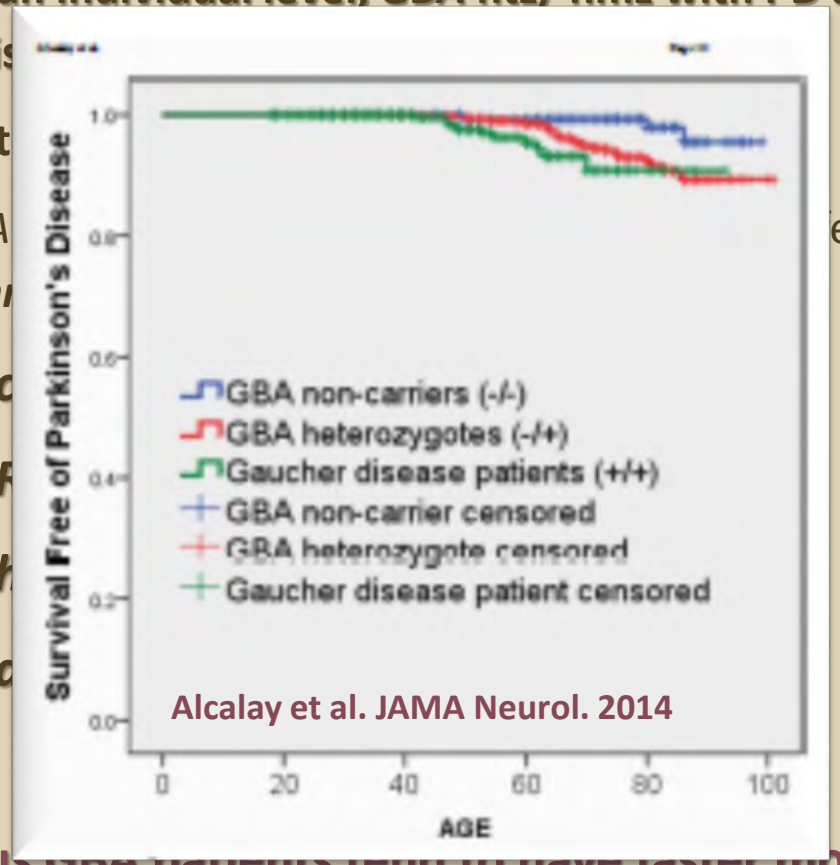
Alcalay et al. JAMA Neurol. 2014

- **Thus GBA patients tend to have faster motor and cognitive progression than iPD**

- **A GBA mutation "dose effect"**
  - **GD-PD** : is associated with earlier age at onset and more cognitive changes than *GBA* PD
  - **Among *GBA* PD cases**
    - PD-GBA who carry severe mutations (e.g., L444P) compared to carriers of mild mutations (e.g., N370S):
      - *faster motor progression as measured by the UPDRS*
      - *faster rate of dementia*
      - *younger age-at-death*

Genotype-phenotype correlations in *GBA*

- **On an individual level, *GBA* htz/ hmz with PD are indis**
- **Mot**
- *GBA* **est**
  - **c**
  - **F**
  - **h**
  - **c**



Alcalay et al. JAMA Neurol. 2014

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    - *faster motor progression as measured by the UPDRS*
    - *faster rate of dementia*
    - *younger age-at-death*

Clinical characteristics of GBA-PD compared to iPD

Age at onset	Younger age at onset	[84••, 85, 86•, 87, 88]
Motor features		
Postural gait instability	Comparable	[84••, 87]
Freezing	Unclear	[84••, 87]
Dysphagia	More	[84••]
Dyskinesia	More	[87]
Response to levodopa	Comparable	[87]
Motor fluctuations	More	[87]
Non-motor features		
Anxiety	Unclear	[87, 89]
Depression	Unclear	[4, 87, 89]
Cognitive impairment/dementia	More	[84••, 87–90, 91•, 92•]
Hallucinations	More	[85, 87, 90]
Autonomic dysfunction		
Orthostatic hypotension	Unclear	[84••, 87, 89]
Constipation	More	[87, 89]
Urinary urgency	More	[89]
Incontinence	Comparable	[87]
Sexual dysfunction	Comparable	[87]
Hyposmia/anosmia	More	[85]
REM sleep behavior disorder	More	[85, 87, 93]
Pathology		
Lewy body density	Comparable	[94]

Gan-Or et al. Current Neurology and Neuroscience Reports (2018)

Clinical characteristics of GBA-PD compared to iPD

Table 2 Longitudinal characteristics of *GBA* PD compared to idiopathic PD

GBA longitudinal phenotype	
More rapid motor progression	[86•, 95]
Earlier and more rapid cognitive decline	[84••, 86•, 91•]
Comparable mood over time	[86•]
Quicker progression to advanced PD therapies (deep brain stimulation, continuous apomorphine, intestinal levodopa)	[84••, 95, 96]
Earlier death	[84••, 86•]

Gan-Or, Liong and Alcalay. Current Neurology and Neuroscience Reports (2018)

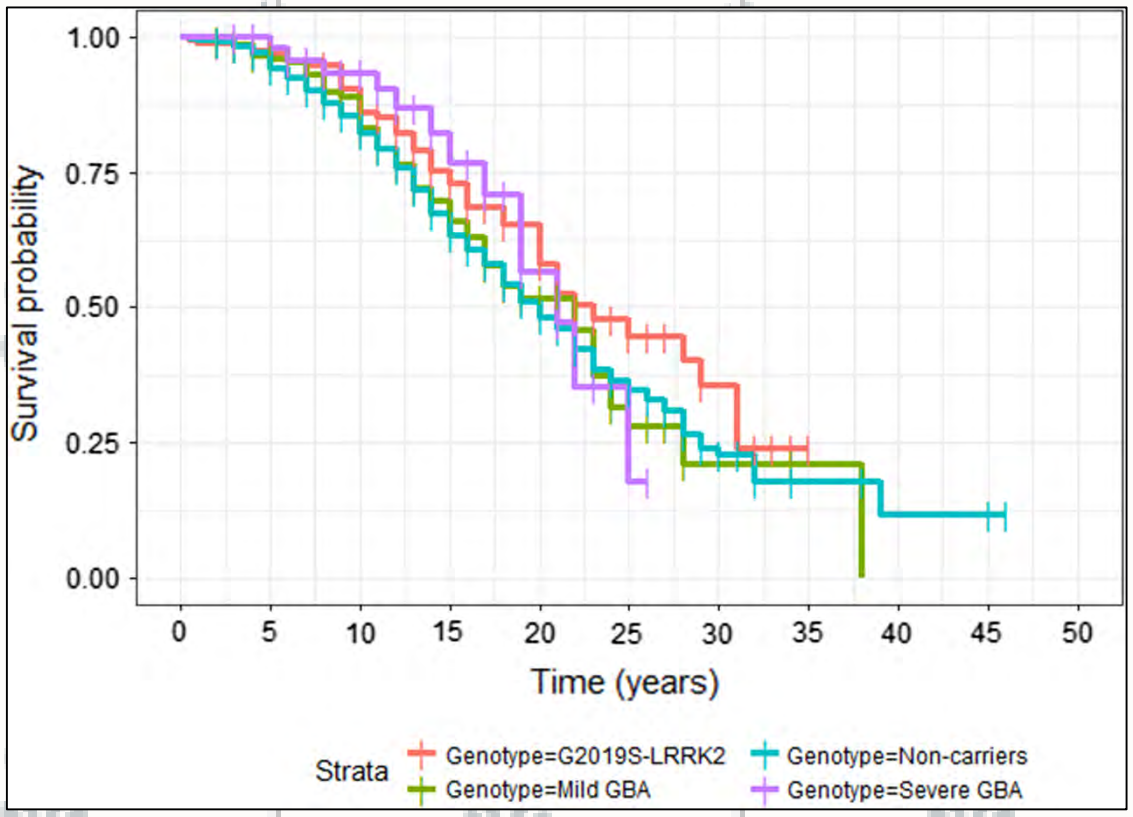
Treatment Issues in GBA-PD

Lyth et al JPD 2017: GBA-PD- progression in a DBS Cohort

- 17 patients GBA+, matched to 17 GBA-
- **Follow-up of ~7.5 years after DBS: GBA+ compared to GBA-**
- **cognitive impairment**
  - ***more prevalent (70% vs 19%)***
  - ***more severe (60% vs 6% were severely impaired).***
- NMS : more severe and QOL more impaired
- Motor symptoms, LED, and stimulation settings - not significantly different.
- **GBA status appears to be an important predictor for non-motor symptom disease progression, after DBS surgery.**

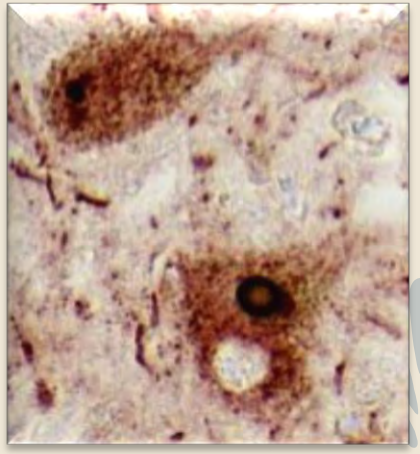
Survival rates among PD patients who carry LRRK2 and GBA mutations

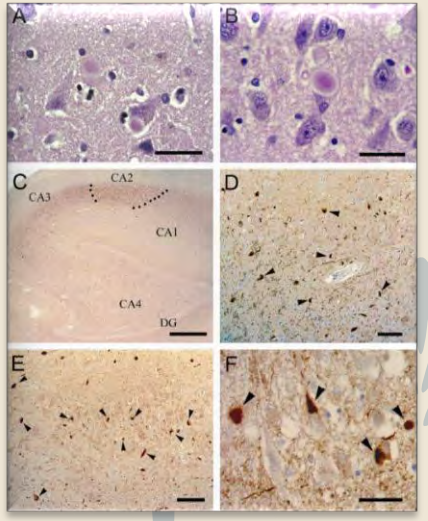
PATIENTS DEAD AT TIME OF ANALYSIS
380 of 1,086 iPD
49 of 159 G2019SLRRK2*-PD**
56 of 148 mGBA-PD, 13 of 49 sGBA-PD



Survival of patients with PD does not seem to be related to *GBA* status, whereas G2019S**LRRK2* might confer higher survival rates

Thaler et al. Movement Disorders, 2018





Wong et al. Molecular Genetics and Metabolism 2004 **(brain pathology in seven subjects with type 1 GD)**

GBA–associated Parkinson's disease Neuropathology and link to α-synuclein

- The pathology of GBA mutation positive PD appears to be identical to that of idiopathic disease.
- GCase has also been found in Lewy bodies, more frequently in those with GBA mutations
- Some studies have suggested that Lewy body deposition is more extensive in GBA mutant positive brains (not universally found)
- Functional studies have proven an interaction between α-synuclein and GBA (inverse correlation).
  - Mutant GBA proteins cause increases in α-synuclein levels, while an inhibition of GBA by α-synuclein has been also demonstrated.

Potential Mechanisms of GBA PD

The substrate of GCase, **glucosylceramide, may lead to α-synuclein accumulation**, and inversely, α-synuclein accumulation may lead to reduced GCase activity.
(but… no study to date has shown elevated concentration of glucosylceramide in GBA Hzs)

Endoplasmic-reticulum-associated protein degradation (ERAD) impairment and ER stress-related cell death. Mutant GCase variants present variable degrees of ER retention and undergo ERAD in the proteasome. α-synuclein accumulation may cause ER stress, impair degradation of ERAD substrates, and inhibit ER to Golgi traffic…

These mechanisms are challenged

- *Null GBA mutations (no protein product!!!) also increase the risk of developing PD….*
- It is also likely that GBA mutations increase susceptibility to PD in more ways than one and that both suggested mechanisms contribute to disease development.

Other mechanisms suggested: involvement of SMPD1, ASAH1, and GALC and thus the ceramide metabolism pathway, contributing to α-synuclein accumulation in GBA PD

Precision Medicine interventions for GBA carriers

The main challenge is the incomplete understanding of the underlying mechanisms governing the role/s of *GBA* mutations in the development of synucleinopathies.

- **Modulating *GBA*-Related Glycosphingolipids (Substrate Reduction Therapy)**
  - Sanofi initiated a double-blind, placebo-controlled study to assess the efficacy and safety of a glucosylceramide synthase inhibitor (GZ/SAR402671, venglustat) in PD patients carrying a *GBA* mutation
- **Increasing Glucocerebrosidase (GCase) Activity**
  - Gene therapy
  - Small molecule activators of GCase activity (Ambroxol)

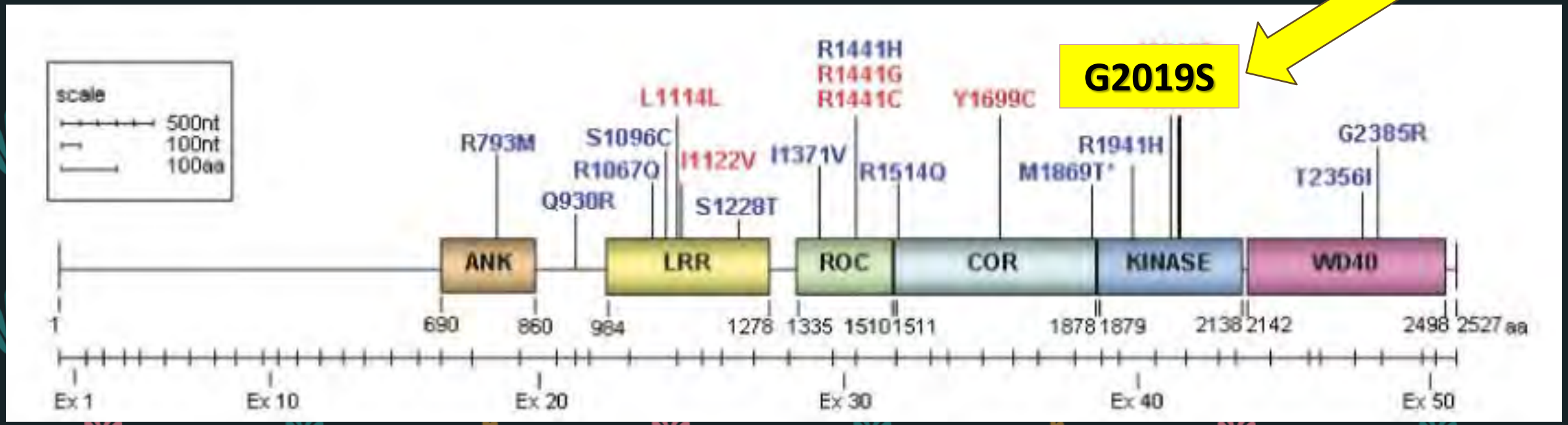
LRRK-2-RELATED PARKINSON'S DISEASE

Is this the 'good' Parkinson's?

The G2019S*LRRK2 gene in Parkinson's disease

- An autosomal dominant form of PD, **PARK8**, has been defined (2004).
- The causative gene encodes for **leucine-rich repeat kinase 2 (*LRRK2*)**, OMIM *609007, chromosome 12q12.
- **A common *LRRK2* (G2019S) mutation was identified across populations in both familial and sporadic PD patients.**
- Early studies: prevalence of G2019S is ~5 to 6% for familial and 1 to 2% for apparently sporadic cases of PD [Di Fonzo et al., 2005; Gilks et al., 2005; Skipper et al., 2005a; Tan et al., 2005d].
- Subsequent studies: ethnicity has a significant influence on the mutation frequency [Zabetian et al., 2005; Lesage et al., 2005, 2006; Ozelius et al., 2006; Tan et al., 2005d; Lu et al., 2005; Fung et al., 2006].

Parkinson Disease and the G2019S**LRRK2* mutation



The *LRRK2* gene product is a large multidomain protein involved in multiple cellular processes, including neurite outgrowth and synaptic morphogenesis, membrane trafficking, autophagy, and protein synthesis.

The G2019S*LRRK2 Mutation in Ashkenazi Jewish Parkinson Disease

- The G2019S has been observed with higher-than-expected frequency in AJ patients (2006).

The highest rates worldwide of the G2019S*mutation are observed among patients with familial PD who are of Ashkenazi Jewish (30%) and North African Arab (40%) origins.

The LRRK2 Ashkenazi Jewish Consortium

Established in 2009

- **Centers:**
  - **Israel** (Tel-Aviv Medical Center)
  - **New York** (Beth Israel Medical Center and Columbia University Medical Center).
- **The aim of the consortium:**
  - To examine the clinical characteristics and genetic modifiers of AAO in families of PD probands with and without LRRK2 G2019S mutations.

- **Participants:**
  - Previously identified LRRK2 G2019S carriers and non-carriers
  - Newly screened participants (the majority)
  - Carriers, a subset of non-carriers, and their first-degree relatives underwent an in-depth evaluation.

G2019S*LRRK2–associated Parkinson's disease in Ashkenazi Jews

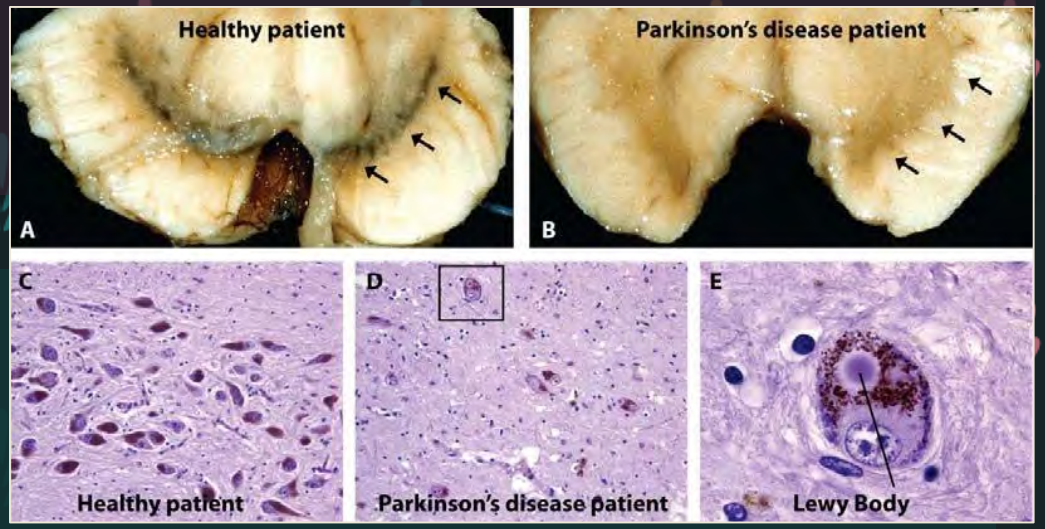
- **Clinical features-** age at onset, PD prodrome, motor symptoms, NMS (cognitive, RBD), response to DRT and other interventions, motor complications, disease progression, survival.
- **Molecular genetics**
- **Imaging and pathological features**
- **Biochemical features**
- **Disease mechanisms**
- ***Precision Medicine interventions for G2019S*LRRK2 carriers:***
  - *Personalized disease modifying therapies???*

Parkinson Disease in Ashkenazi Jewish G2019S*LRRK2 Mutation Carriers

- A common founder of the G2019S**LRRK2* mutation is reported in European, North African, and AJ populations and it is estimated to have occurred between 13th -2nd centuries BC.
- Thus, the common founder may have lived centuries before the most recent G2019S**LRRK2* AJ ancestor , estimated to have lived around 2nd- 5th centuries AD.

- *This does not explain how the G2019S*LRRK2 mutation is so rare in patients of Sephardi Jewish ancestry as the differentiation of ethnic Jewish subgroups occurred after the common era, that is, several centuries after the diverse estimated mutation times.*

PD and the LRRK2 Gene Neuropathology



- **Most *LRRK2* cases exhibit a pattern of features**

  consistent with typical PD, namely Lewy bodies

  in the brainstem and loss of dopaminergic neurons in the substantia nigra.

- **Discordant pathological features :**
  - fulminant plaque and tangle pathology in addition to PD pathology
  - a pure substantia nigra degeneration without Lewy bodies
  - glial cytoplasmic inclusions reminiscent of MSA

- *There have been no large series of genetically defined LRRK2 cases (e.g. G2019S) that have been neuropathology examined.*

Parkinson Disease in G2019S*LRRK2 Mutation Carriers **Healy et al (Lancet Neurol 2008)**

- The largest report comparing PD phenotype between multi-ethnic LRRK2 mutation carriers and non-carriers;
- **6 pathogenic mutations , the most frequent- G2019S (1% of sporadic PD , 4% of hereditary PD.**
- **The mean age of PD onset for all *LRRK2* mutation carriers 58·1 years (14·0 years), slightly younger than other series.**
- **Motor symptoms (eg, disease severity, rate of progression, occurrence of falls, and dyskinesia) and NMS (eg, cognition and olfaction) were more benign in of *LRRK2*-associated PD .**
- **The risk of PD for a *LRRK2* G2019S mutation carrier:**
  - **28% at age 59 years, 51% at 69 years, and 74% at 79 years.**

Parkinson Disease in G2019S*LRRK2 Mutation Carriers **Healy et al (Lancet Neurol 2008)**

- The largest report comparing PD phenotype between multi-ethnic LRRK2 mutation carriers and
- **6 pathogenic**
- **The mean age** **than other series.**
- **Motor sympt** **nesia) and NMS (eg**
- **The risk of PD**
  - **28% at age 59 years, 51% at 69 years, and 74% at 79 years.**

The estimated penetrance of *LRRK2* p.G2019S in AJ and non-AJ carriers:

25% to 42.5% at age 80.

Lee et al Movement Disorders, Vol. 32, No. 10, 2017

Movement Disorders, Vol. 28, No. 14, 2013

Parkinson Disease Phenotype in Ashkenazi Jews With and Without *LRRK2* G2019S Mutations

Roy N. Alcalay, MD, MS,[1,2*] Anat Mirelman, PhD,[3,4] Rachel Saunders-Pullman, MD, MPH,[5,6] Ming-X Tang, PhD,[1] Helen Mejia Santana, MS,[1] Deborah Raymond, MS,[5] Ernest Roos, MD,[1] Martha Orbe-Reilly, MD,[1] Tanya Gurevich, MD,[3,7] Anat Bar Shira, PhD,[8] Mali Gana Weisz, PhD,[8] Kira Yasinovsky, BS,[3] Maayan Zalis, DMD,[3] Avner Thaler, MD,[3] Andres Deik, MD,[5] Matthew James Barrett, MD, MS,[5] Jose Cabassa, MD,[5] Mark Groves, MD,[5] Ann L. Hunt, DO,[5] Naomi Lubarr, MD,[5,6] Marta San Luciano, MD, MS,[5] Joan Miravite, NP,[5] Christina Palmese, PhD,[5,6] Rivka Sachdev, MD,[5,6] Harini Sarva, MD,[5] Lawrence Severt, MD, PhD,[5] Vicki Shanker, MD,[5,6] Matthew Carrington Swan, MD,[5] Jeannie Soto-Valencia, BA,[5] Brooke Johannes, MS,[5] Robert Ortega, MS,[5] Stanley Fahn, MD,[1] Lucien Cote, MD,[1] Cheryl Waters, MD,[1] Pietro Mazzoni, MD, PhD,[1] Blair Ford, MD,[1] Elan Louis, MD, MSc,[1,2] Oren Levy, MD, PhD,[1,2] Llency Rosado, MD,[1] Diana Ruiz, BSc,[1] Tsvyatko Dorovski, MS, MBA,[9] Michael Pauciulo, MBA,[10] William Nichols, PhD,[10] Avi Orr-Urtreger, MD, PhD,[7,8] Laurie Ozelius, PhD,[11] Lorraine Clark, PhD,[12,13] Nir Giladi, MD,[3,7] Susan Bressman, MD,[5] and Karen S. Marder, MD, MPH[1,2,9,14]

Movement Disorders, Vol. 28, No. 14, 2013

Parkinson Disease Phenotype in Ashkenazi Jews With and Without *LRRK2* G2019S Mutations

- 553 AJ PD patients from 3 sites (two in New York and one in Tel-Aviv).
- Evaluation consisted of : MoCA, UPDRS, GDS and the NMS-Q
- G2019S**LRRK2* carriers (n=97) and non-carriers (n=391) similar in age and PD AAO.
- Carriers were more likely to be women (51.5% vs. 37.9%; P=0.015)
- In logistic models (adjusted for age, disease duration, sex, education, and site)
  - Carriers were more likely to have lower extremity onset (P < 0.001), postural instability and gait difficulty (PIGD) (P=0.043), and a persistent levodopa response for >5 years (P=0.042).
  - Performance on the UPDRS, MoCA, GDS, and NMS did not differ by mutation status.
- **PD in AJ G2019S* *LRRK2* mutation carriers is similar to idiopathic PD but is characterized by more frequent lower extremity involvement at onset and PIGD without the associated cognitive impairment.**

RISK FOR PD IN LRRK2 G2019S CARRIERS

- Risk of PD in LRRK2 p.G2019S mutation carriers:
  - Similar penetrance of LRRK2 p.G2019S estimated in Ashkenazi Jewish carriers and non-Ashkenazi Jewish carriers confirms that p.G2019S penetrance is 25% to 42.5% at age 80 in all populations analyzed.

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

The *LRRK2* G2019S mutation status does not affect the outcome of subthalamic stimulation in patients with Parkinson's disease

Lior Greenbaum [a,b], Simon D. Israeli-Korn [a,b], Oren S. Cohen [a,b,c], Sandra Elincx-Benizri [a,b], Gilad Yahalom [a,b,c], Evgenia Kozlova [b], Hanna Strauss [b], Noa Molshatzki [a], Rivka Inzelberg [a,b,c], Roberto Spiegelmann [d], Zvi Israel [e], Sharon Hassin-Baer [a,b,c,*]

- **Population:** 39 AJ PD + bilateral STN-DBS.
  - **G2019S positive:** 13 patients (8 men)
  - **G2019S negative:** 26 patients, matched (2:1) for gender, AAO, PD duration at surgery.
- **Evaluation:** UPDRS score, , LEDD, and clinical global impression of change (motor and psychiatric)
- **Time points:** preoperative and postoperative 6 months, 12 months and 3 yrs.

- **Statistics:** linear mixed model
- **Results:**
  - significant improvement for the whole group concerning reduction in motor UPRDS (off state) and LEDD .
  - No difference in clinical outcome between carriers and matched non-carriers

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  (2[illegible]
  su[illegible]
- **Evaluat[illegible]**
  global ir[illegible]
  psychiat[illegible]
- **Time poi[illegible]** [illegible]operative
  6 months[illegible] months and 3 yrs.

- **Statistics:** linear [illegible]

[illegible]e whole
[illegible]motor
[illegible]e
[illegible]matched non-
carriers

Conclusions:

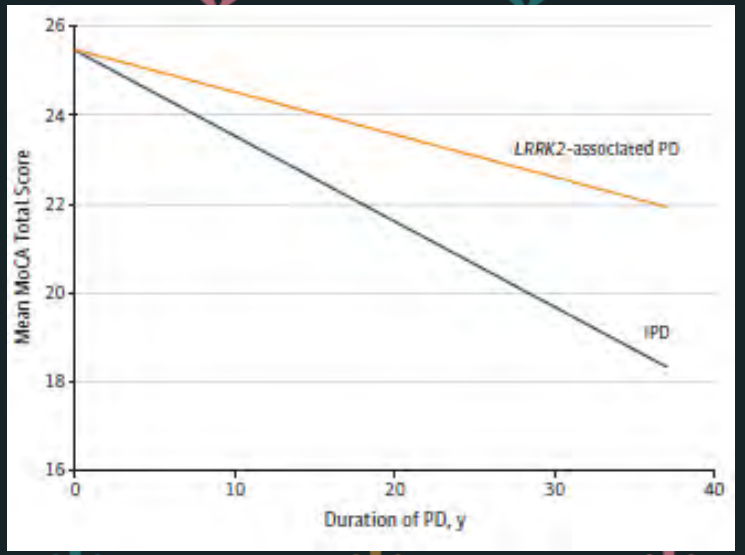
-STN-DBS outcomes were not influenced by the *LRRK2* G2019S mutation

-knowledge of carrier status is not relevant to the considerations of patient selection for surgery.

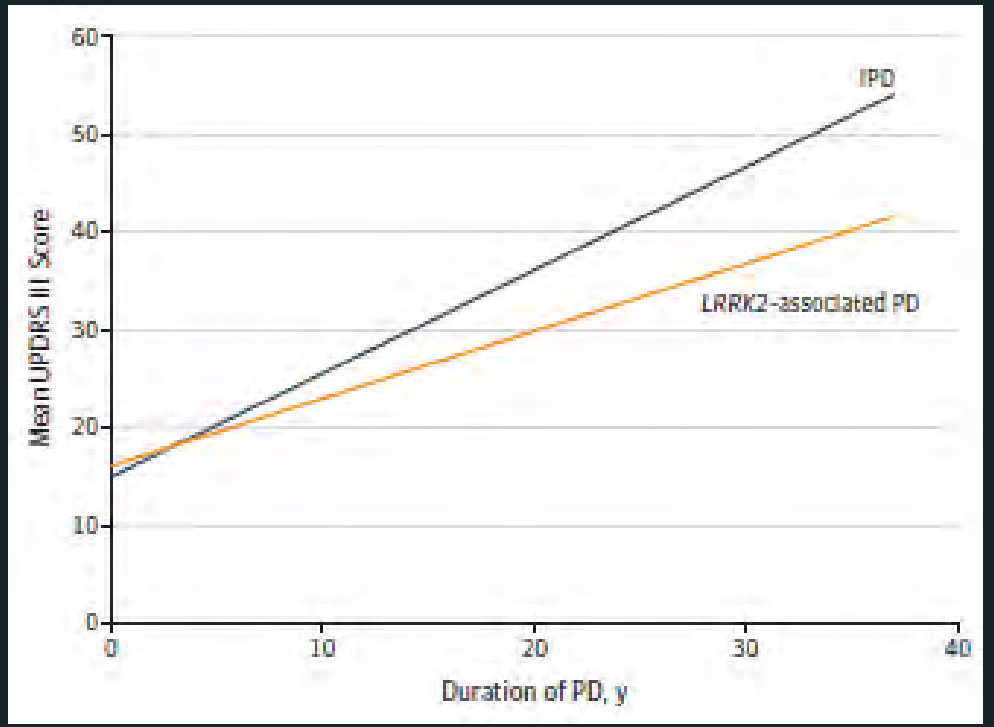
JAMA Neurology | Original Investigation

Progression in the *LRRK2*-Associated Parkinson Disease Population

Rachel Saunders-Pullman, MD, MPH; Anat Mirelman, PhD; Roy N. Alcalay, MD, MS; Cuiling Wang, PhD; Roberto A. Ortega, MS; Deborah Raymond, MS; Helen Mejia-Santana, MS; Martha Orbe-Reilly, MD; Brooke A. Johannes, MS; Avner Thaler, MD; Laurie Ozelius, PhD; Avi Orr-Urtreger, MD, PhD; Karen S. Marder, MD, MPH; Nir Giladi, MD; Susan B. Bressman, MD; for the LRRK2 Ashkenazi Jewish Consortium



- A prospective comprehensive assessment of a large (GBA negative) cohort of patients from 3 sites with AJ PD , G2019S**LRRK2* positive or negative , 2009- 2016.
- Among the 545 participants, 144 patients (26.4%) carried the G2019S**LRRK2* mutation.
- The yearly rate of change in the motor UPDRS was slower in mutation carriers.



G2019S*LRRK2–associated PD in Ashkenazi Jews

Associations

Sharon Hassin-Baer
Yael Laitman
Esther Azizi
Irena Molchadski
Gilli Galore-Haskel
Frida Barak
Oren S. Cohen
Eitan Friedman

The leucine rich repeat kinase 2 (LRRK2) G2019S substitution mutation

Association with Parkinson disease, malignant melanoma and prevalence in ethnic groups in Israel

The *LRRK2* G2019S mutation is associated with Parkinson disease and concomitant non-skin cancers

R. Inzelberg, MD
O.S. Cohen, MD
J. Aharon-Peretz, MD
I. Schlesinger, MD
R. Gershoni-Baruch, MD, PhD
R. Djaldetti, MD
Z. Nisipeanu, MD
L. Ephraty, MD
O. Tunkel, MD
E. Kozlova, RN, MA
L. Inzelberg, BSc
N. Kaplan, BSc
T. Fisher Mehr, BSc
A. Mory, MSc
E. Dagan, PhD
E. Schechtman, PhD
E. Friedman, MD, PhD
S. Hassin-Baer, MD

ABSTRACT

Objective: In view of the fact that cancer patterns in patients with Parkinson disease (PD) differ from the general population, we aimed to verify whether patients with PD with *LRRK2* mutations have an increased risk for particular cancer types.

Methods: In this cross-sectional study, eligible consenting Jewish patients with PD were genotyped for the predominant *LRRK2* G2019S mutation. Oncologic data were obtained by personal interview and reviewing patients' files. Stepwise logistic regression was applied to model the probability of cancer occurrence in carriers vs noncarriers.

Results: Overall, 79/490 (16.1%) genotyped patients carried the G2019S mutation. Seventy-seven (16%) were diagnosed with cancer; of those, 67 (14%) with a non-skin cancer. Eighteen (23%) carriers vs 49 (12%) noncarriers had a non-skin cancer ($p = 0.01$, odds ratio [OR] = 2.18, 95% confidence interval [CI] 1.19–3.99). A significant ethnicity effect was noted ($p = 0.045$, OR = 1.84, 95% CI 1.02–3.34). Among Ashkenazi patients, age and *LRRK2* emerged as significant using stepwise logistic regression including age, gender, and *LRRK2* status as explanatory variables. The OR for *LRRK2* mutation carriers adjusted for age was 3.38 (95% CI 1.64–6.97, $p = 0.0009$).

Conclusions: Ashkenazi Jewish patients with PD who harbor the G2019S *LRRK2* mutation are more likely to have a concomitant non-skin cancer than noncarriers. *Neurology*® 2012;78:1–1

Table 2 Cancer types in all patients with Parkinson disease (n = 490)

Cancer type	LRRK2 carriers (n = 79), n (%)	Noncarriers (n = 411), n (%)
≥1 cancer	18 (23)	59 (15)
Multiple cancers	3 (4)	8 (2)
Lung	1 (1)	0
Breast women	6 (15)	7 (5)
Breast men	1	0
Prostate	3 (8)	12 (5)
Colon	3 (4)	6 (1)
Stomach	1 (1)	0
Hematologic	0	5 (1)
Reproductive	3 (8)	4 (3)
Renal	1 (1)	2 (2)
Other	0	5 (1)
Skin cancers	1 (1)	21 (5)
Melanoma	0	7 (2)
Other skin	1 (1)	14 (3)

G2019S*LRRK2–associated PD in Ashkenazi Jews

Associations

RESEARCH ARTICLE | CROHN'S DISEASE

Functional variants in the *LRRK2* gene confer shared effects on risk for Crohn's disease and Parkinson's disease

Ken Y. Hui[1,2], Heriberto Fernandez-Hernandez[3], Jianzhong Hu[3], Adam Schaffner[4,5], Nathan Pankratz[6], N...
+ See all authors and affiliations

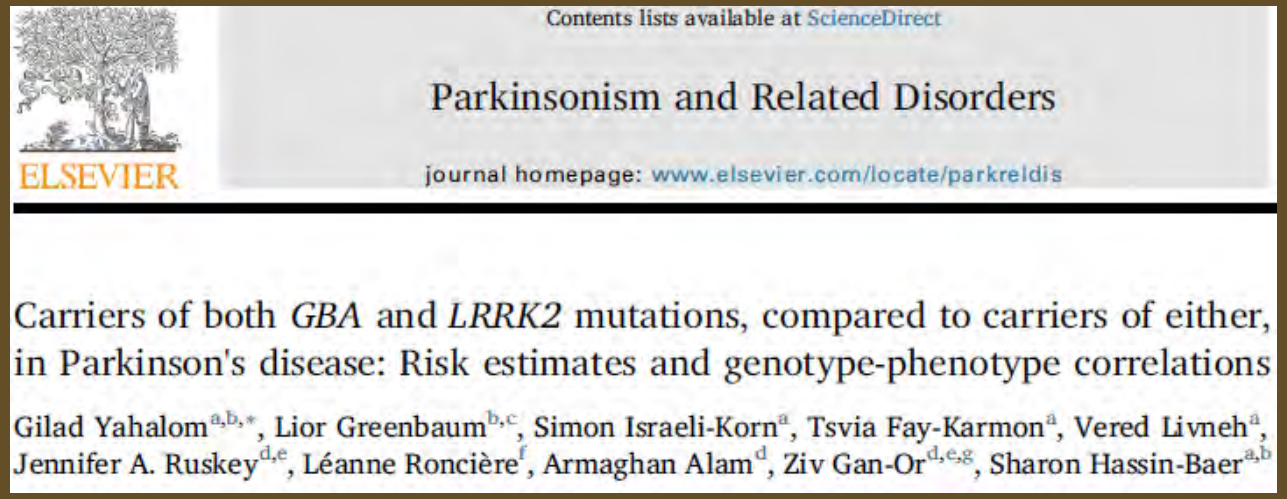
Science Translational Medicine 10 Jan 2018:
Vol. 10, Issue 423, eaai7795
DOI: 10.1126/scitranslmed.aai7795

- **Crohn's disease (CD)**, an IBD, has a ***higher prevalence in AJ*** than in non-Jewish Europeans
- ***2066 AJ CD patients and 3633 HC***
- Association signals in the ***LRRK2 gene*** were detected that conferred risk for CD, variants affected CD age of onset, disease location, LRRK2 activity, and autophagy.
- The *LRRK2* N2081D CD risk allele , located in the ***same kinase domain as G2019S*** was associated with ***increased kinase activity***

Precision Medicine interventions for G2019S*LRRK2 carriers

- The LRRK2 protein is a large kinase containing several conserved regions including several relevant active domains.
- LRRK2 interacts with many key proteins implicated in PD, suggesting that LRRK2 may be a central player in the pathways underlying genetic and also sporadic disease pathogenesis.
- The most frequent LRRK2 mutations that segregate with familial PD , including the G2019S mutation map to its catalytic, GTPase, and kinase domains **contributing to PD pathogenesis via increased kinase activity**

- Several companies are pursuing **LRRK2 inhibitors** for PD, and highly potent, selective, and brain penetrant LRRK2 inhibitors are being evaluated preclinically , one of them clinically.
- The use of **antisense oligonucleotides** to reduce the total levels of LRRK2 represents an alternative strategy to directly reduce the LRRK2 activity in the CNS .



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Carriers of both *GBA* and *LRRK2* mutations, compared to carriers of either, in Parkinson's disease: Risk estimates and genotype-phenotype correlations

Gilad Yahalom[a,b,*], Lior Greenbaum[b,c], Simon Israeli-Korn[a], Tsvia Fay-Karmon[a], Vered Livneh[a], Jennifer A. Ruskey[d,e], Léanne Roncière[f], Armaghan Alam[d], Ziv Gan-Or[d,e,g], Sharon Hassin-Baer[a,b]

A PD cohort consisting of 556 PD patients , 156 (28.1%) : carriers of one or more of the *LRRK2* p.G2019S mutation or a *GBA* variant.

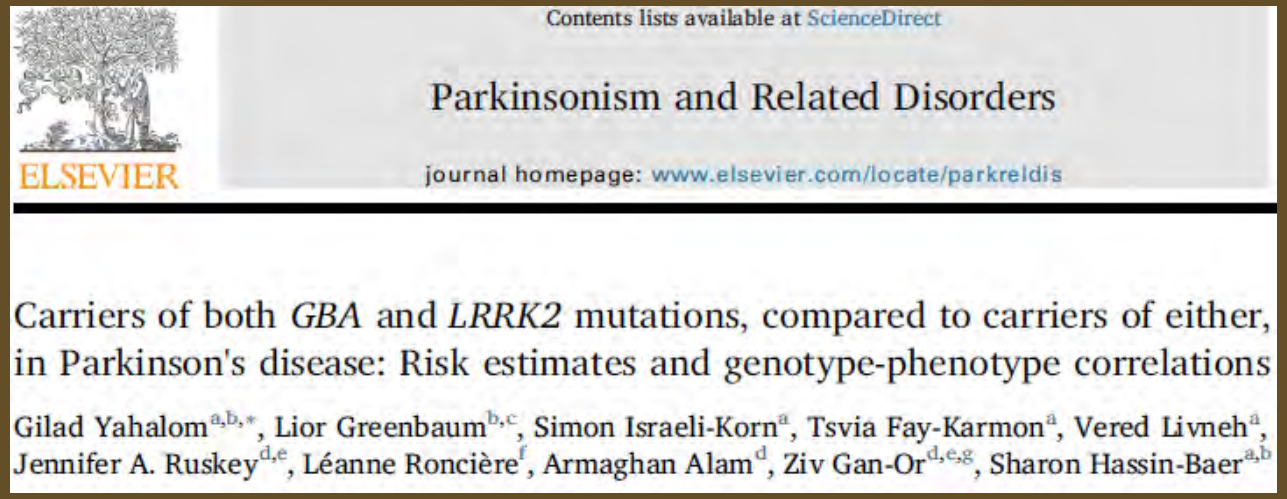
GBA-PD : 78 patients (14.0%

LRRK2-PD : 66 patients (11.8%)

LRRK2-GBA-PD : 12 patients (2%)

Asheknazi Jewish PD
Double mutation carriers
GBA + G2OI9S*LRRK2

G2019S*LRRK2
+



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LRRK2-GBA-PD : 12 patients (2%)

GBA mutation	GBA-PD n (%)	LRRK2-GBA n (%)
All mutations	78 (100)	12 (100)
p.N370S	52 (66.7)	9 (75)
p.E326K	6 (7.7)	2 (16.7)
p.V394L	1 (1.3)	
p.E388K	1 (1.6)	
p.L444P	2 (3.2)	
p.A384D	1 (1.3)	
p.N188S	1 (1.3)	
p.R496H	3 (3.8)	1 (8.3)
p.R44C	1 (1.3)	
c.84dupG	10 (12.8)	

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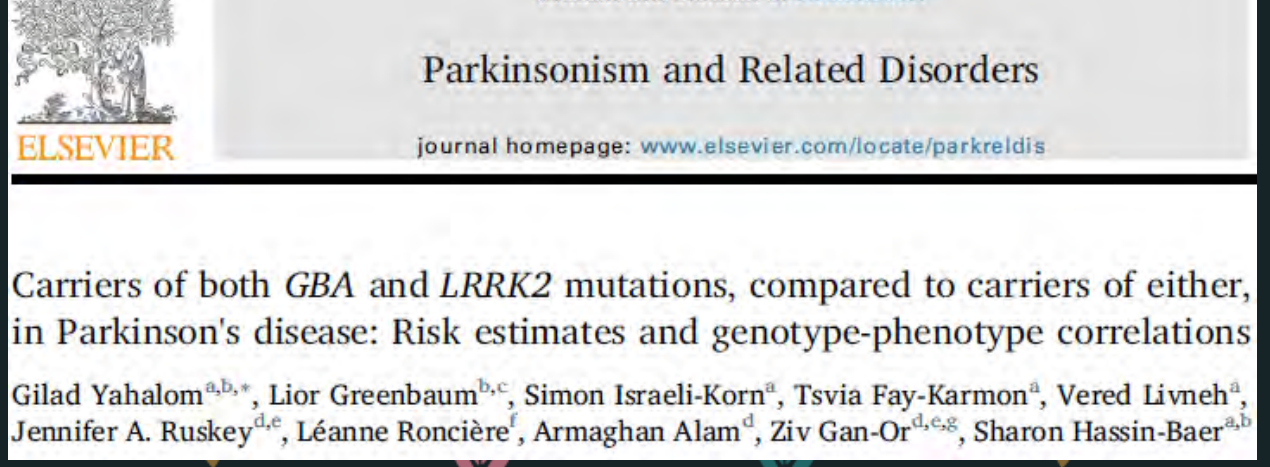
– Estimated ORs for AJ GBA-LRRK2 PD: **15–28 (95% CI 6.7–72.0, p < 0.0001),** compared to AJ controls.

	Total	*LRRK2*-PD	*GBA*-PD	*LRRK-GBA*-PD	MNPD
Number	236	66	78	12	80
Males, % (n)	60.2 (142)	57.6 (38)	60.3 (47)	41.7 (5)	65 (52)
PD duration, years (mean ± SD)	12.2 ± 7.3	14.4 ± 8.3	11.5 ± 7.0	11.8 ± 6.9	11.3 ± 6.5
Age at symptom onset, years (mean ± SD)	59.1 ± 10.9	57.7 ± 10.8	58.6 ± 10.0	54.4 ± 10.5	61.4 ± 11.7
Motor UPDRS, mean ±SD (n)	31.7 ± 15.9	30.9 ± 19.1 (43)	37.3 ± 18.1 (32)	28.4 ± 11.4 (8)	29.6 ± 11.2 (53)

	LRRK2-PD	*GBA*-PD	*LRRK-GBA*-PD	MNPD
Number	66	78	12	80
Tremor as first sign, %	**43.5** (N=62)	**50.6** (N=77)	**25** (N=12)	**57.5** (N=80)
MF, %	**68.3** (N=63)	**64.5** (N=76)	**66.7** (N=12)	**51.3** (N=78)
LID, %	**61.9** (N=63)	**57.9** (N=76)	**66.7** (N=12)	**32.1** (N=78)
Reaching HY3, %	**47.4** (N=38)	**40.8** (N=49)	**71.4** (N=7)	**26.8** (N=56)
FOG, %	**45.0** (N=60)	**33.8** (N=74)	**33.3** (N=12)	**35.9** (N=78)
Probable RBD, %	**16.4** (N=55)	**50.0** (N=60)	**0** (N=11)	**37.5** (N=72)
Psychosis, %	**19.0** (N=63)	**45.9** (N=74)	**8.3** (N=12)	**17.7** (N=79)
Dementia, %	**6.5** (N=62)	**31.6** (N=76)	**8.3** (N=12)	**10.3** (N=78)



- Using logistic regression (while controlling for sex, age at onset and PD duration:
- **probable RBD** was significantly more common for GBA-PD than for LRRK2-PD, while none of the GBA-LRRK2-PD patients reported RBD.
- **Dementia** was significantly more common for GBA-PD than for the LRRK2-PD and MNPD.
- **Psychosis** was the most common for GBA-PD and least common for LRRK2-GBA-PD.

Conclusions:

While GBA-PD is characterized by higher rates of dementia, probable RBD and psychosis, it seems that compared to the other groups, these features are less common for LRRK2-GBA-PD.

This may imply to a possible protective effect of LRRK2 p.G2019S mutation among GBA variant carriers.

LRRK-2–associated PD, and GBA–associated PD
Clinical implications

- Genetic testing for PD gene mutations is not standard practice in care of PD patients
  - *…even though genetic information could inform diagnosis, prognosis, care/treatment decision taking.*
- Despite the research data obtained regarding *the 2 common genes, GBA and LRRK2,*
  - *there is no impact on family planning regarding potential to develop PD in later life.*
- The majority of *GBA* or LRRK2 mutation carriers will never develop PD (or a synucleinopathy),
  - *which complicates genetic counseling for carriers without PD….*
- Family members in the reproductive age should be warned about the potential for having children with GD and genetic consultation is recommended.
- **At the launch of precision medicine clinical trials targeting *GBA* / *LRRK2* mutation carriers, physician and patient interests in obtaining genotype information will increase**

Parkinson's disease among Ashkenazi Jews

Sharon Hassin-Baer

Movement Disorders Institute and Department of Neurology

Chaim Sheba Medical Center, Tel-Hashomer

Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv , Israel