Aufzien Center - June 13, 2019

Genetic Modifiers in Parkinson's Disease

Avi Orr-Urtreger, MD PhD

Ashkenazi in Europe

12th Cen ~10-20K

1650 ~ 425,000

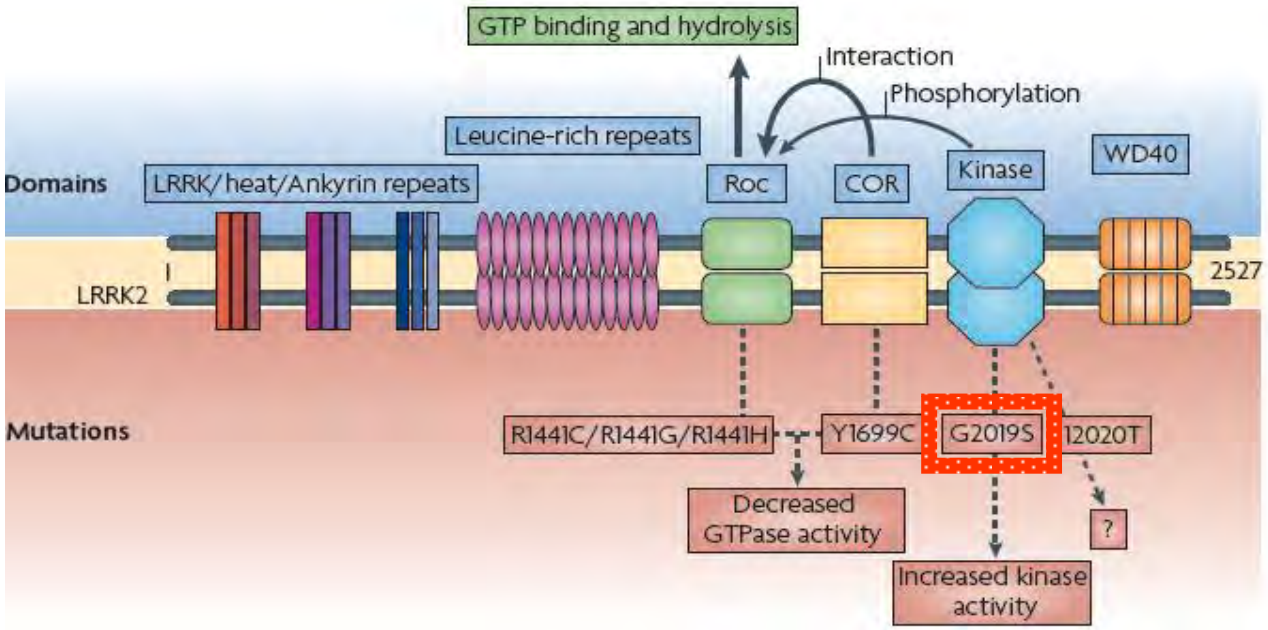
1880 ~6,550,000

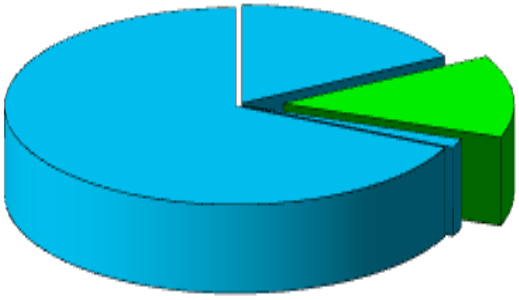
1939~12,000,000

Founder effect: ~ 800 X expansion

From: A historical atlas of the Jewish people, ed. Eli Barnavi

PARK8=Dardarin=LRRK2-Leucine rich kinase 2





~14%

Neurology
69(16) 2007

The *LRRK2* G2019S mutation in Ashkenazi Jews with Parkinson disease

Is there a gender effect?

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ABSTRACT

Background: Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are the most common genetic determinant of Parkinson disease (PD) identified to date, and have been implicated in both familial and sporadic forms of the disease. The G2019S change in *LRRK2* exon 41 has been associated with disease at varying frequencies in Asian, European, North American, and North African populations, and is particularly prevalent among Ashkenazi Jews.

Methods: We assessed the occurrence of the *LRRK2* G2019S, I2012T, I2020T, and R1441G/C/H mutations in our cohort of Jewish Israeli patients with PD, and determined the *LRRK2* haplotypes in 76 G2019S carriers detected and in 50 noncarrier Ashkenazi patients, using six microsatellite markers that span the entire gene.

GBA Gene and Glucocerebrosidase A

ARTICLES

Neurology

70(24): 2008

Genotype–phenotype correlations between *GBA* mutations and Parkinson disease risk and onset

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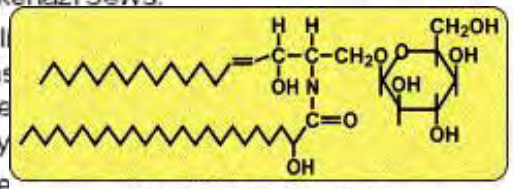
A. Orr-Urtreger, MD, PhD

ABSTRACT

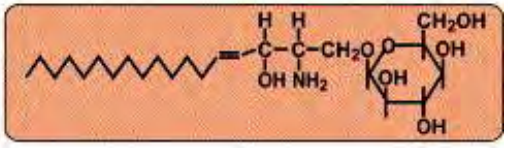
Background: Mutations in *GBA* and *LRRK2* genes have been implicated in Parkinson disease (PD), particularly among Ashkenazi Jews.

Method: An Israeli young controls was R496H and se with PD and elderly

Results: GBA carrie 6.35% in young c



Glucosylceramide (Glucocerebroside)

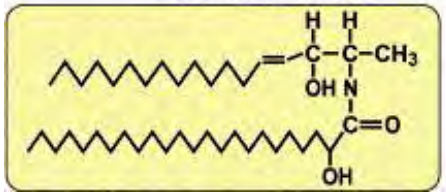


Glucosylsphingosine

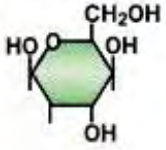
Gluco ebrosidase

GBA gene

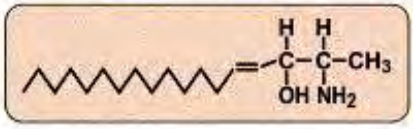
Ceramide



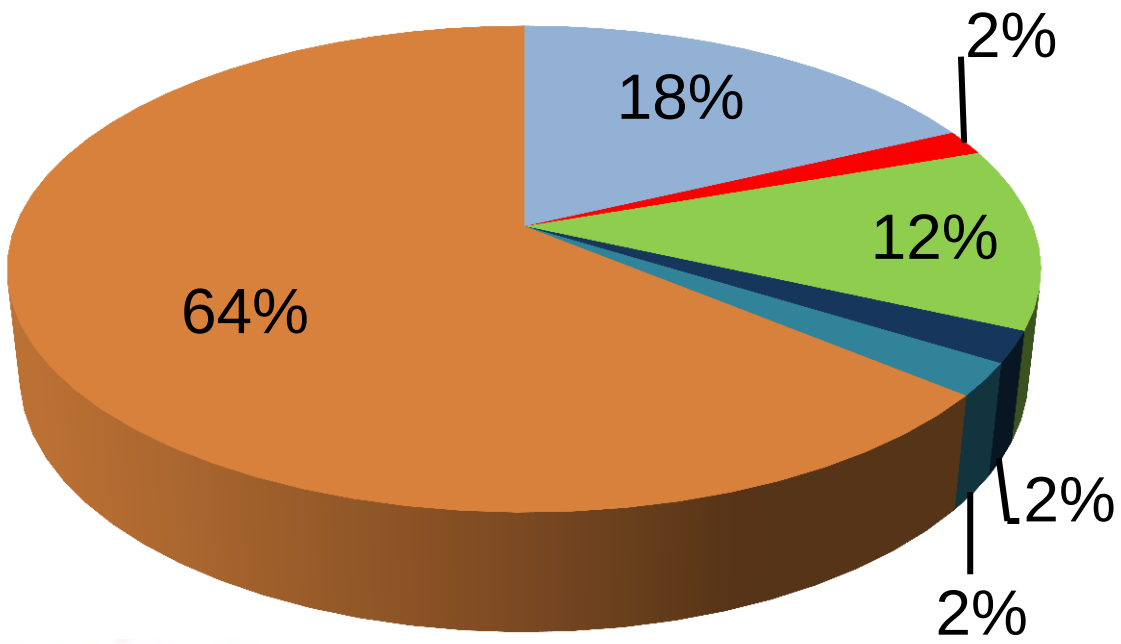
Glucose



Sphingosine



Founder Mutations in Parkinson's Disease Patients of Ashkenazi Origin (1200)



36%

- GBA carriers
- GBA- CH or homozygotes
- LRRK2 carriers
- GBA+LRRK2
- Others
- IPD

Tel-Aviv Sourasky Medical Center

CH, compound heterozygote
Unpublished data,

How Many at Risk?

- Carriers' rate among Ashkenazi in Israel:
  - LRRK2 G2019S ~ 2%
  - GBA ~ 7.8%
- ~ 2.8 X 10^6 X 9.8% = **275,000 at Risk**
- How many will have PD ?
- Depends on: Genetic Background, Partial penetrance, Environment, Epigenetics, Immune system, involvement of additional genes, other….

Neurology
June 2015

Age-specific penetrance of *LRRK2* G2019S in the Michael J. Fox Ashkenazi Jewish LRRK2 Consortium

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Roy N. Alcalay, MD, MSc
Helen Mejia-Santana, MS
Ming-Xin Tang, PhD
Annie Lee, MS
Deborah Raymond, MS
Anat Mirelman, PhD
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For the LRRK2 Ashkenazi Jewish Consortium

ABSTRACT

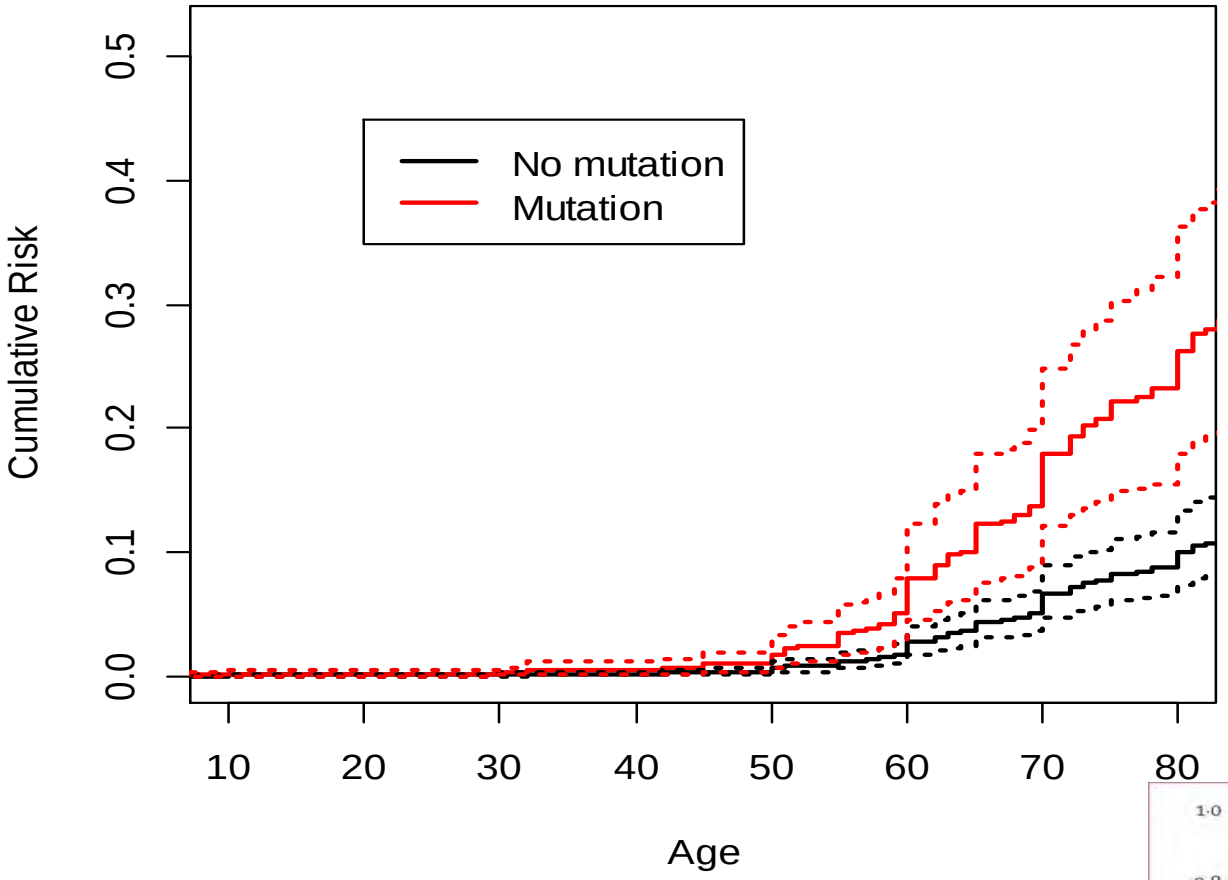
Objective: Estimates of the penetrance of *LRRK2* G2019S vary widely (24%–100%), reflective of differences in ascertainment, age, sex, ethnic group, and genetic and environmental modifiers.

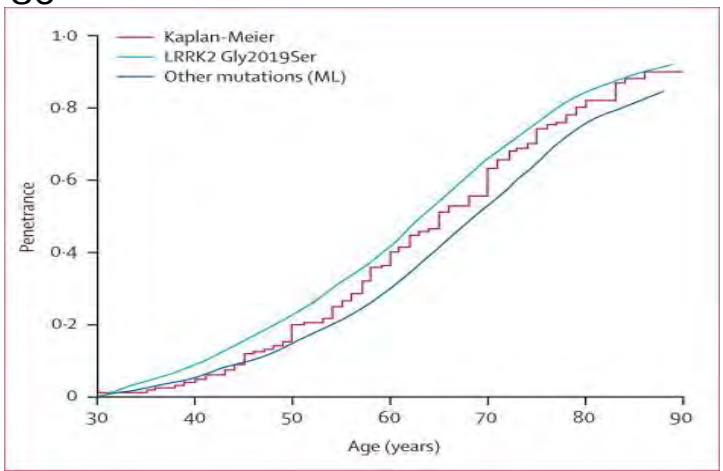
Methods: The kin-cohort method was used to predict penetrance in 2,270 relatives of 474 Ashkenazi Jewish (AJ) Parkinson disease (PD) probands in the Michael J. Fox LRRK2 AJ Consortium in New York and Tel Aviv, Israel. Patients with PD were genotyped for the *LRRK2* G2019S mutation and at least 7 founder *GBA* mutations. *GBA* mutation carriers were excluded. A validated family history interview, including age at onset of PD and current age or age at death for each first-degree relative, was administered. Neurologic examination and *LRRK2* genotype of relatives were included when available.

Results: Risk of PD in relatives predicted to carry an *LRRK2* G2019S mutation was 0.26 (95% confidence interval [CI] 0.18–0.36) to age 80 years, and was almost 3-fold higher than in relatives predicted to be noncarriers (hazard ratio [HR] 2.89, 95% CI 1.73–4.55, $p < 0.001$). The risk among predicted G2019S carrier male relatives (0.22, 95% CI 0.10–0.37) was similar to predicted carrier female relatives (0.29, 95% CI 0.18–0.40; HR male to female: 0.74, 95% CI 0.27–1.63, $p = 0.44$). In contrast, predicted noncarrier male relatives had a higher risk (0.15, 95% CI 0.11–0.20) than predicted noncarrier female relatives (0.07, 95% CI 0.04–0.10; HR male to female: 2.40, 95% CI 1.50–4.15, $p < 0.001$).

Conclusion: Penetrance of *LRRK2* G2019S in AJ is only 26% and lower than reported in other ethnic groups. Further study of the genetic and environmental risk factors that influence G2019S penetrance is warranted. **Neurology® 2015;85:89–95**

Age Specific Penetrance of LRRK2 G2019S Mutation in MJFF Ashkenazi Jewish Consortium



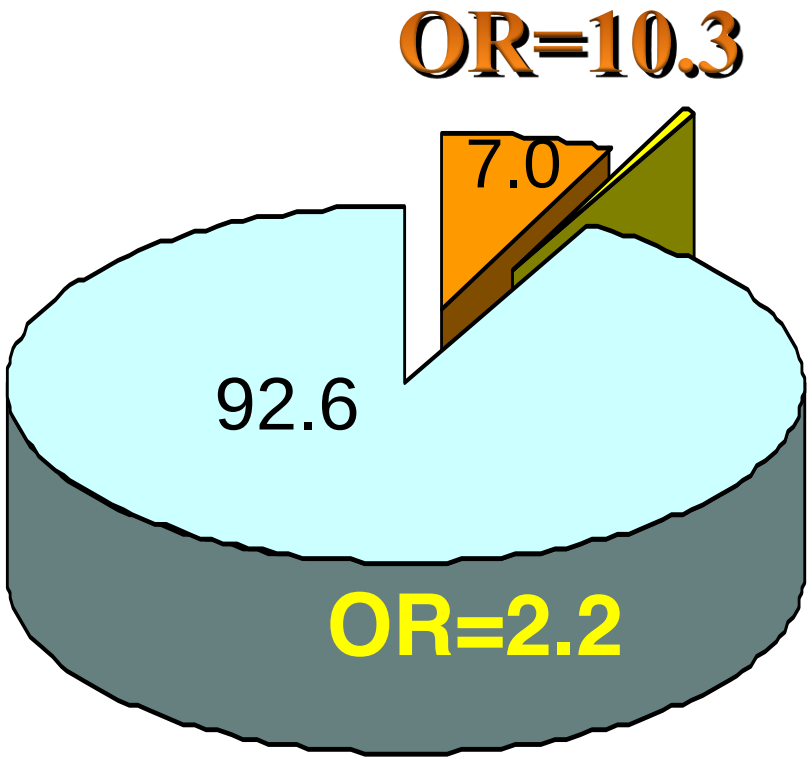


THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

GBA: Genotype-Phenotype Correlation with Type of mutation:

"Mild" mutations:
N370S
R496H

"Severe" mutations:
84GG
L444P
IVS2+1
V394L
RecTL



1000 PD patients

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Neurology 2015

Differential effects of severe vs mild *GBA* mutations on Parkinson disease

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ABSTRACT

Objective: To better define the genotype-phenotype correlations between the type of *GBA* (glucosidase, beta, acid) mutation, severe or mild, and the risk and age at onset (AAO), and potential mechanism of Parkinson disease (PD).

Methods: We analyzed 1,000 patients of Ashkenazi-Jewish descent with PD for 7 founder *GBA* mutations, and conducted a meta-analysis of risk and AAO according to *GBA* genotype (severe or mild mutation). The meta-analysis included 11,453 patients with PD and 14,565 controls from worldwide populations. The statistical analysis was done with and without continuity correction (constant or empirical), considering biases that could potentially affect the results.

EDITORIAL

GBA mutations and Parkinson disease

When genotype meets phenotype

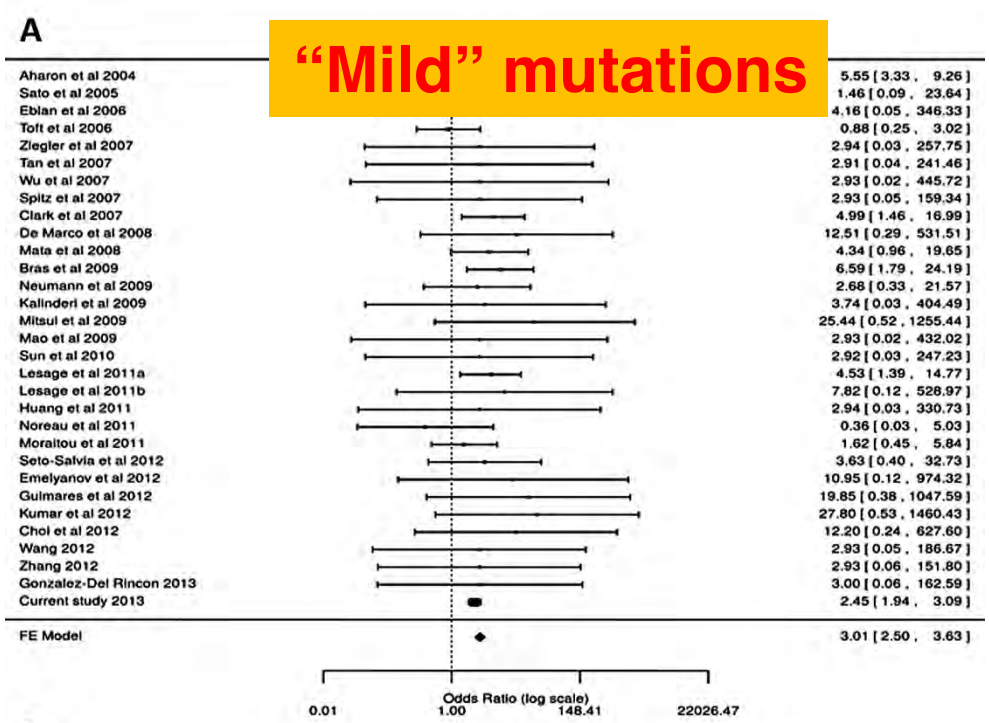
Sonja W. Scholz, MD, PhD
Beom S. Jeon, MD, PhD

The last 2 decades have seen remarkable advances in our understanding of genetic risk factors underlying the pathogenesis of Parkinson disease (PD). One of

cohorts to evaluate mild vs severe *GBA* mutations in multiple different populations. This led to an impressive cohort of 11,453 patients with PD and

Name (year)	Population	Mutations tested	PD patients		Controls		Inclusion
			Total	GBA mutation carriers (%)	Total	GBA mutation carriers (%)	
Aharon-Peretz (2004)[21]	Ashkenazi-Jewish	N370S, L444P, 84GG, IVS2+1, V394L, R496H	99	31 (31.3%)	1,543	95 (6.2%)	R
Sato (2005)[39]	Caucasian	N370S, K178T, 84GG, R329C, RecNciI, IVS2+1, L444P	88	5 (5.7%)	122	1 (0.8%)	R+A
Eblan (2006)[17]	Venezuelan	Whole-gene sequencing	33	4 (12.1%)	31	1 (3.2%)	R+A
Toft (2006)[40]	Norwegian	N370S, L444P	311	7 (2.3%)	474	8 (1.7%)	R+A
Ziegler (2007)[6]	Chinese	Whole-gene sequencing	92	4 (4.3%)	92	1 (1.1%)	R+A
Tan (2007)[4]	Chinese	N370S, L444P	331	8 (2.4%)	347	0 (0%)	R+A
Wu (2007)[5]	Taiwanese	L444P, RecNciI, R120W	518	16 (3.1%)	339	4 (1.2%)	R+A
Spitz (2007)[20]	Brazilian	N370S, L444P, G377S	65	2 (3.1%)	267	0 (0%)	R+A
Clark (2007)[14]	Jewish	Whole-gene sequencing	178	30 (16.9%)	85	6 (7.1%)	R
	Non-Jewish	Whole-gene sequencing	100	8 (8.0%)	94	2 (2.1%)	R
De-Marco (2008)[41]	Italian	N370S, L444P	395	11 (2.8%)	483	1 (0.2%)	R
Mata (2008)[15]	North-American	N370S, L444P	721	21 (2.9%)	504	1 (0.4%)	R+A
Bras (2009)[7]	Portugal	Whole-gene sequencing	230	14 (6.1%)	430	3 (0.7%)	R
Neumann (2009)[11]	British	Whole-gene sequencing	790	33 (4.2%)	257	3 (1.2%)	R+A
Kalinderi (2009)[9]	Greek	Whole-gene sequencing	172	11 (6.4%)	132	4 (3.0%)	R
Mitsui (2009)[3]	Japanese	Whole-gene sequencing	534	50 (9.4%)	544	2 (0.4%)	R
Mao (2010)[42]	Chinese	L444P	616	20 (3.2%)	411	1 (0.2%)	R
Sun (2010)[43]	Chinese	L444P	402	11 (2.7%)	413	0 (0%)	R+A
Lesage (2011)[13]	North-African	Whole-gene sequencing	194	9 (4.6%)	177	1 (0.5%)	R+A
Lesage (2011)[26]	European	Whole-gene sequencing	1,130	76 (6.7%)	391	4 (1.0%)	R
Huang (2011) [44]	Taiwanese	L444P, D409H, R120W, L174P, Q497R	967	36 (3.7%)	780	2 (0.3%)	R
Noreau (2011)[16]	French-Canadian	Whole-gene sequencing	212	22 (10.4%)	189	11 (5.8%)	R
Moraitou (2012)[10]	Greek	N370S, D409H, L444P, IVS10-1, H255Q, R120W, Y108C, IVS6-2	205	21 (10.2%)	206	7 (3.4%)	R+A
Seto-Salvia (2011)[12]	Spanish	Whole-gene sequencing	225	22 (9.8%)	186	1 (0.5%)	R+A
Emelyanov (2012)[8]	Russian	N370S, L444P	330	9 (2.7%)	240	1 (0.4%)	R
Guimarães Bde (2012)[19]	Brazilian	N370S, L444P	347	13 (3.7%)	341	0 (0%)	R
Kumar (2012)[33]	Serbian	Sequence of exons 8-11	360	21 (5.8)	348	5 (1.4%)	R
Choi (2012)[2]	Korean	Whole-gene sequencing	277	9 (3.2%)	291	0 (0%)	R+A
Wang (2012)[45]	Chinese	L444P, N370S, R120W	208	7 (3.4%)	298	1 (0.3%)	R
Zhang (2012)[46]	Chinese	L444P, N370S, R120W	195	6 (3.1%)	443	0 (0%)	R+A
Gonzalez-Del Rincon Mde (2013)[18]	Mexican	L444P, N370S	128	7 (5.5%)	252	0 (0%)	R
Current study	Ashkenazi-Jewish	N370S, R496H, 84GG, IVS2+1, V394L, D409H, L444P, RecTL	1,000	192 (19.2%)	3,805	242 (6.4%)	R+A

31 populations; 11,453 Parkinson patients; 14,565 Controls



Forest plots of:
31 studies
Total of:
11,453 cases
14,565 controls

OR- 3.01
(2.50-3.63, $p<1x10^{-20}$)

OR- 14.59
(10.00-21.31, $p<1x10^{-20}$)

Modifier genes for **Risk** or **Severity** by **Stratification**

MTX1
BIN1
MAPT (TAU)
SEPT14
PARK16

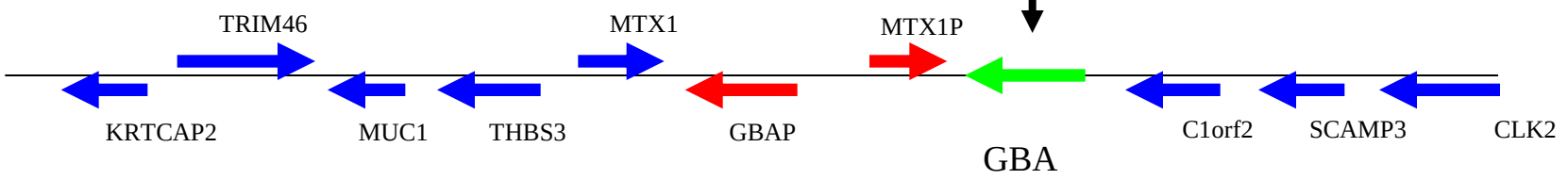
Red – increased risk or severity
Blue – decreased risk or severity

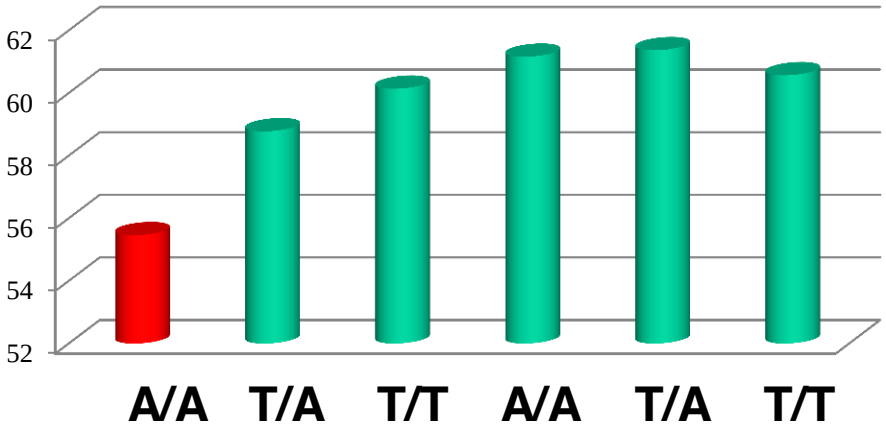
Homozygosity for the *MTX1* c.184T>A (p.S63T) alteration modifies the age of onset in *GBA*-associated Parkinson's disease

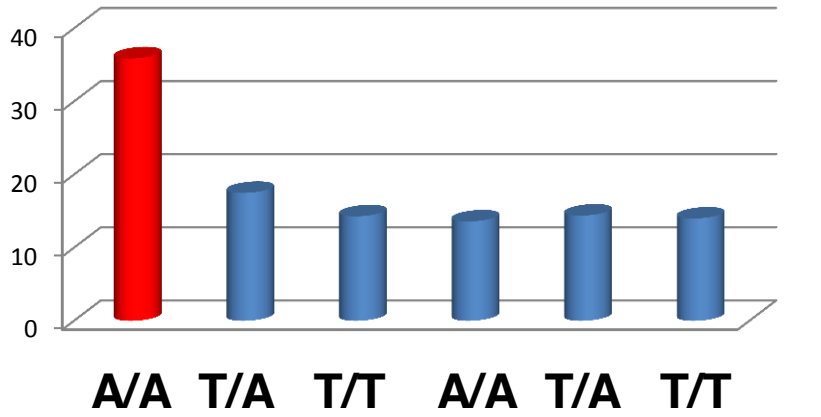
Ziv Gan-Or · Anat Bar-Shira · Tanya Gurevich · Nir Giladi · Avi Orr-Urtreger

Neurogenetics
DOI 10.1007/s10048-011-0293-6

ORIGINAL ARTICLE







AAO Years

EOPD % AAO <50

J Neurol
DOI 10.1007/s00415-015-7868-3

ORIGINAL COMMUNICATION

The Alzheimer disease *BIN1* locus as a modifier of *GBA*-associated Parkinson disease

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SNP (annotated gene)	Genotype	Validation cohort (n=113, mild)			Replication cohort (n=41, severe)			Total		
		N	AAO (±SD)	*p* value	N	AAO (±SD)	*p* value	N	AAO (±SD)	*p* value
rs13403026 (*BIN1*)	GG	105	58.17 (±10.5)	**0.005**	38	54.58 (±9.9)	**0.01**	143	57.2 (±10.4)	**0.0001**
	AG	8	68.88 (±6.8)		3	71.67 (±2.5)		11	69.6 (±5.9)	
rs10898685 (*RAB38*)	AA	99	57.5 (±10.2)	0.001	36	54.7 (±10.4)	0.07	135	56.8 (±10.3)	0.0002
	AG	13	69.0 (±8.3)		5	64.2 (±7.6)		18	67.7 (±8.2)	
	GG	1	67.0 (-)			-		1	67.0 (-)	
rs4263397 (*BST1*)	TT	60	61.4 (±10.2)	0.02	18	55.9 (±11.1)	0.89	78	60.1 (±10.6)	0.055
	GT	45	55.6 (±10.6)		15	56.7 (±10.0)		60	55.9 (±10.4)	
	GG	8	59.0 (±10.3)		8	54.0 (±11.2)		16	56.5 (±10.7)	
rs6860670 (*SV2C*)	GG	28	54.2 (±9.6)	0.002	8	53.3 (±12.4)	0.28	36	54.0 (±10.1)	0.02
	AG	60	58.7 (±10.9)		23	58.1 (±9.3)		83	58.6 (±10.4)	
	AA	25	64.7 (±8.4)		10	52.6 (±11.4)		35	61.2 (±10.7)	
rs7800486 (*CACNA2D1*)	TT	54	54.9 (±9.6)	0.0004	21	54.5 (±9.8)	0.67	75	54.8 (±9.6)	0.001
	CT	43	63.0 (±9.9)		14	58.1 (±10.2)		57	61.8 (±10.1)	
	CC	16	61.7 (±11.1)		6	55.2 (±14.3)		22	59.9 (±12.1)	

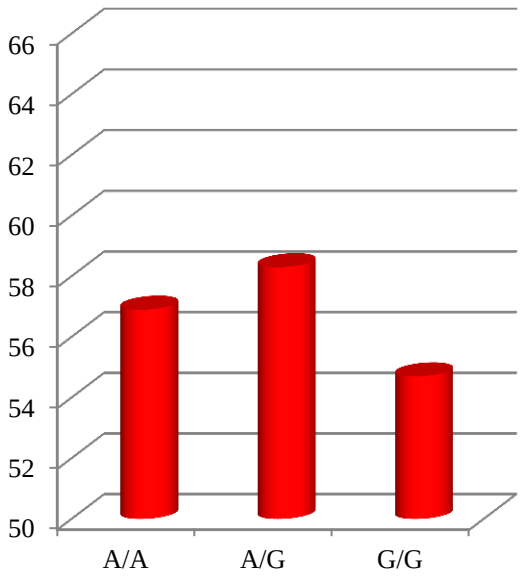
Later AAO; No homozygous AA

***BIN1* - Bridging Integrator 1 is involved in synaptic vesicle endocytosis, interacts with transport & synaptic proteins like dynamin, clathrin**

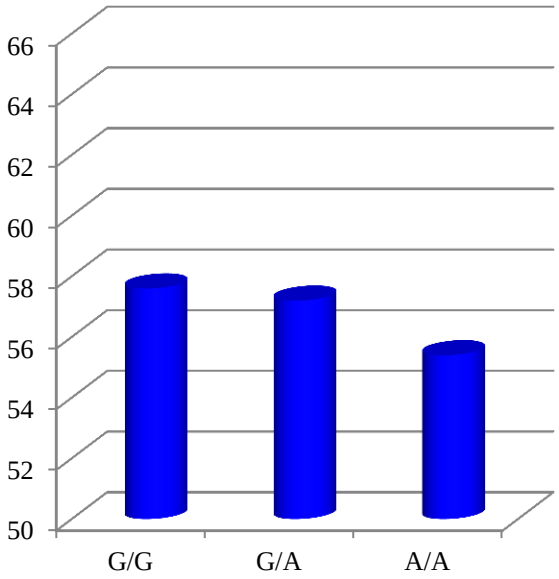
J Mol Neurosci
DOI 10.1007/s12031-011-9641-0

The Age at Motor Symptoms Onset in *LRRK2*-Associated Parkinson's Disease is Affected by a Variation in the *MAPT* Locus: A Possible Interaction

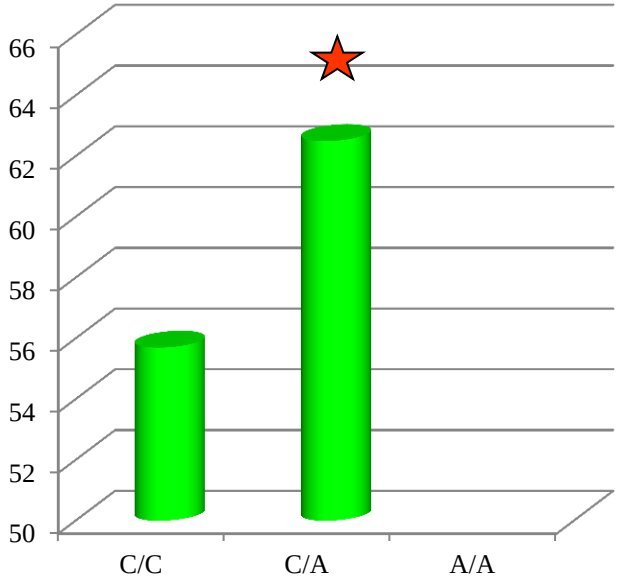
Ziv Gan-Or · Anat Bar-Shira · Anat Mirelman · Tanya Gurevich · Nir Giladi · Avi Orr-Urtreger



rs393152, NS

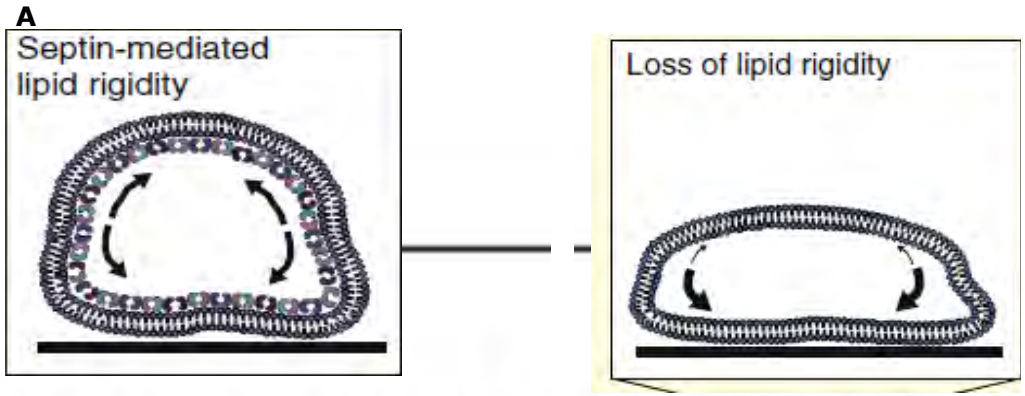


rs2435207, NS



rs2435207, *p*=0.025

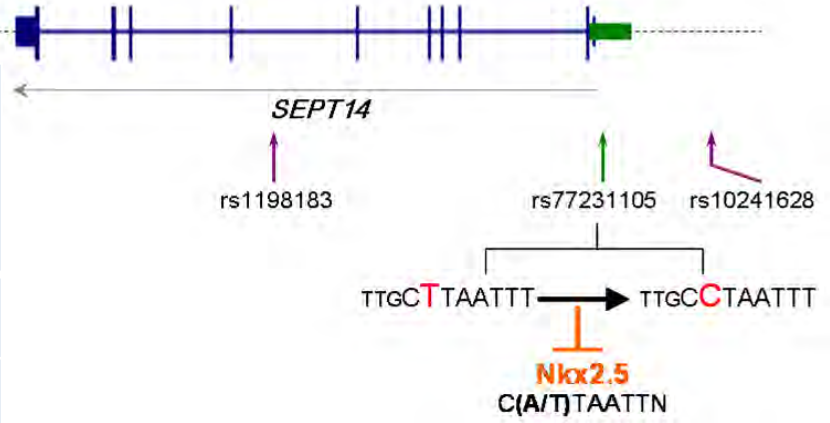
J Mol Neurosci
DOI 10.1007/s12031-016-0738-3



SEPT14 Is Associated with a Reduced Risk for Parkinson's Disease and Expressed in Human Brain

Liron Rozenkrantz[1,2] · Ziv Gan-Or[1,2] · Mali Gana-Weisz[1] · Anat Mirelman[3] · Nir Giladi[2,3] · Anat Bar-Shira[1] · Avi Orr-Urtreger[1,2]

Populati o	Haplotype		Haplotype frequency		OR	95% CI	p value
			Patients	Control			
Entire cohort			N=1440	N=1480			
	A	TAA	0.994	0.977	1.00	0.95-1.05	0.957
	B	GGG	0.005	0.018	0.27	0.12-0.63	0.002
	C	GAG	0.000	0.003	---	---	---
	D	TGG	0.001	0.002	0.34	0.04-3.29	0.353



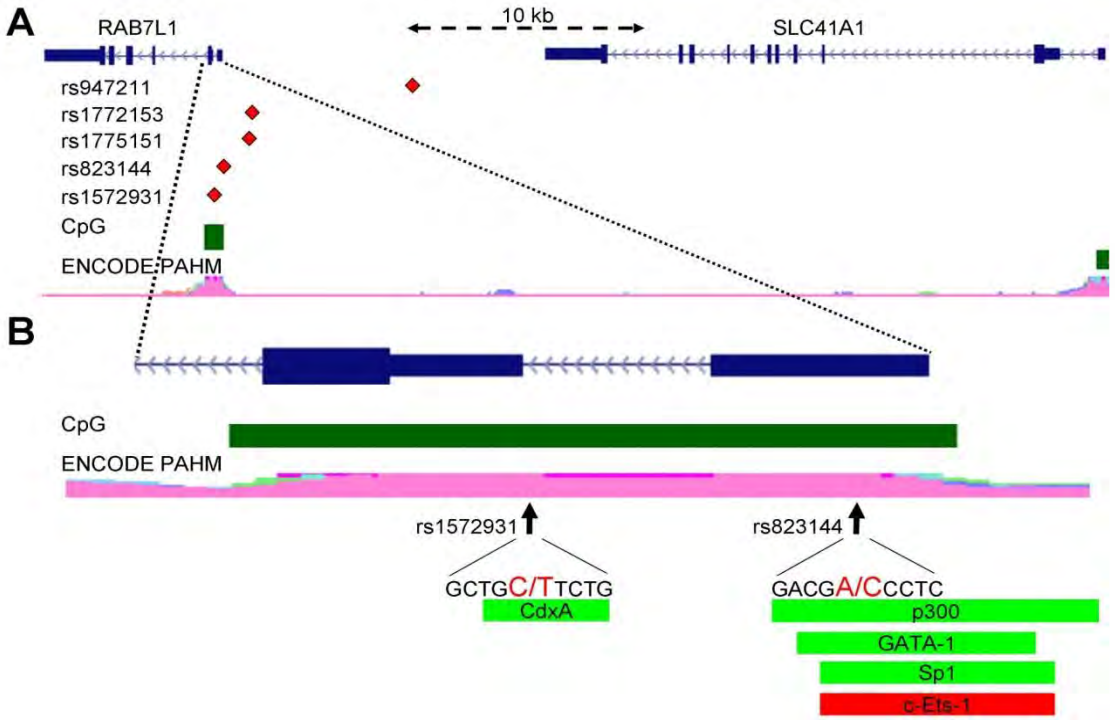
SEPT14 Protective Haplotype in Putative promoter

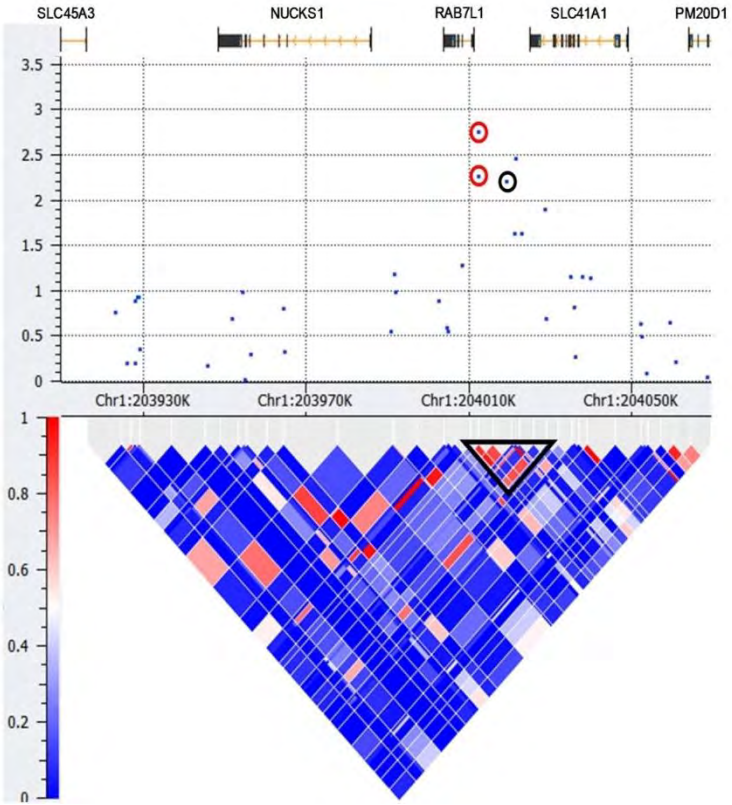
Protection - Ch 1 PARK16 Locus

Association of Sequence Alterations in the Putative Promoter of *RAB7L1* With a Reduced Parkinson Disease Risk

Arch Neurol. 2012;69(1):105-110

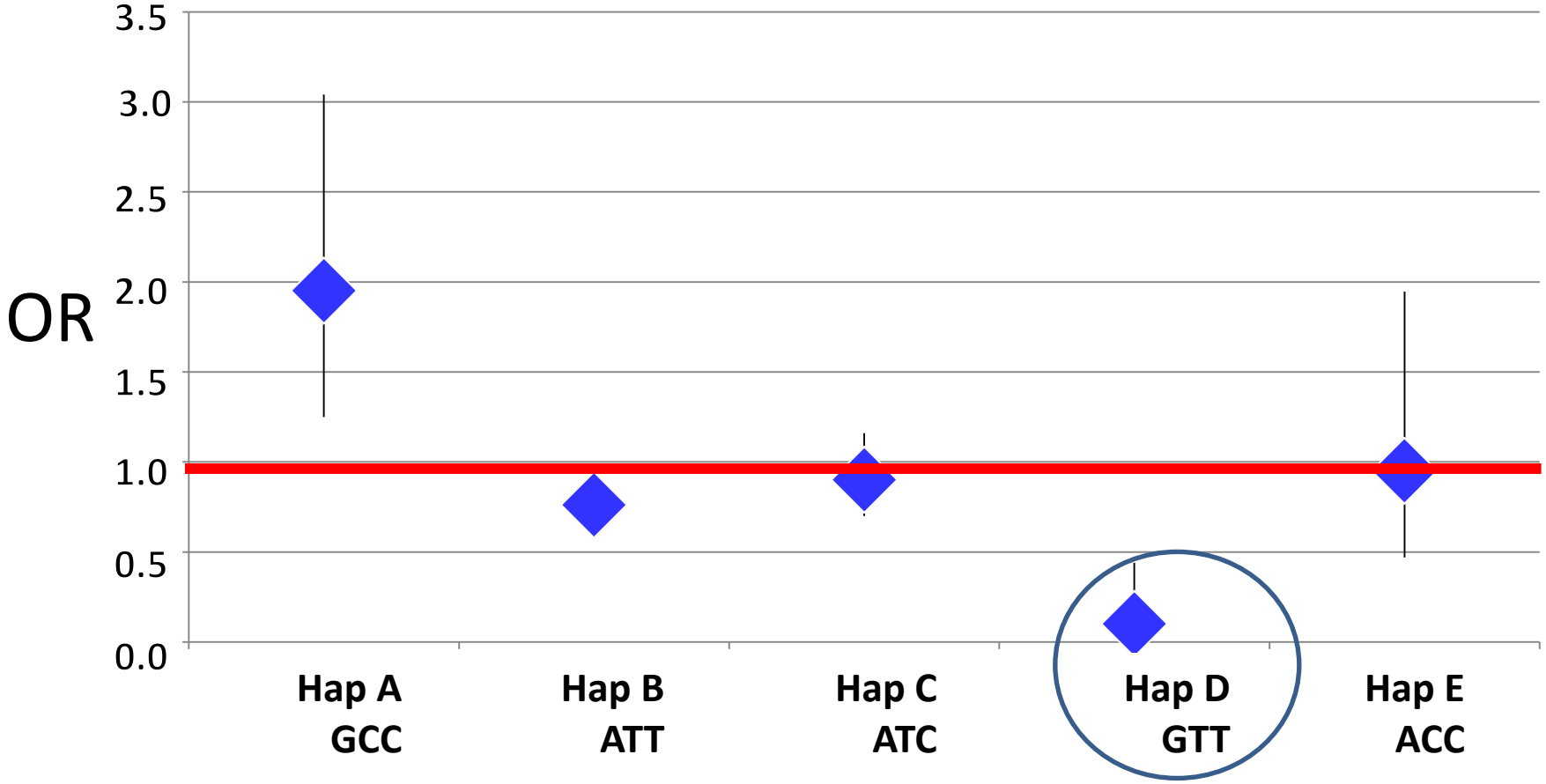
Ziv Gan-Or, BMedSci; Anat Bar-Shira, PhD; Dvir Dahary, MSc; Anat Mirelman, PhD; Merav Kedmi, PhD; Tanya Gurevich, MD; Nir Giladi, MD; Avi Orr-Urtreger, MD, PhD



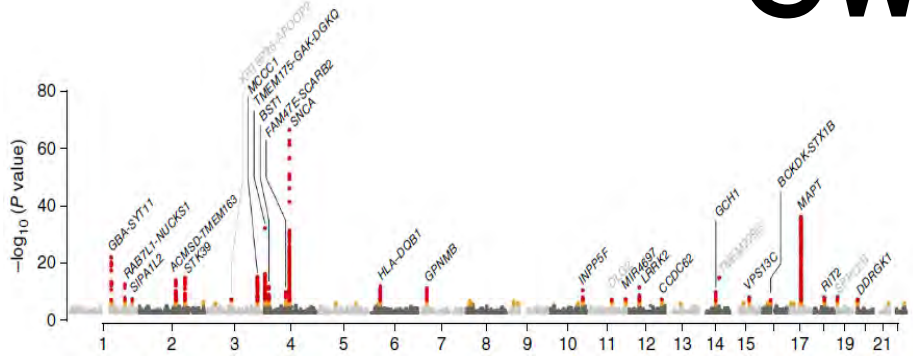


Parkinson's Protection

- *Five RAB7L1 haplotypes for increased- and decreased risk*
- *Hap-D lowers the risk for PD by 10 times*

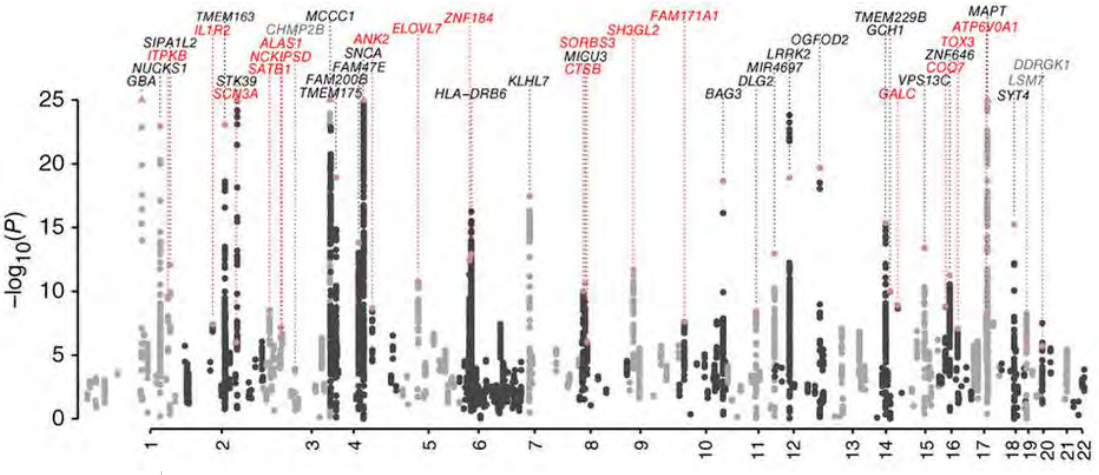


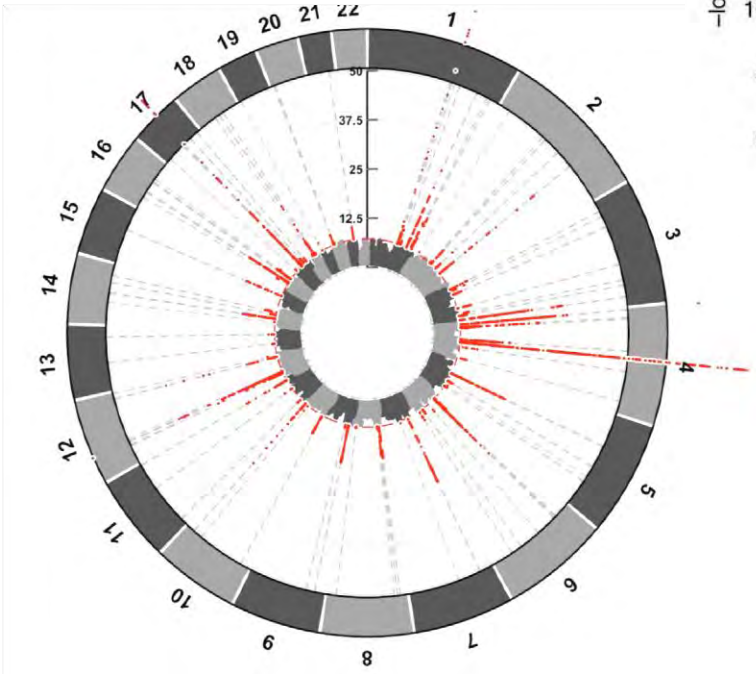
GWAS



2014 24 genes

2017 72 genes

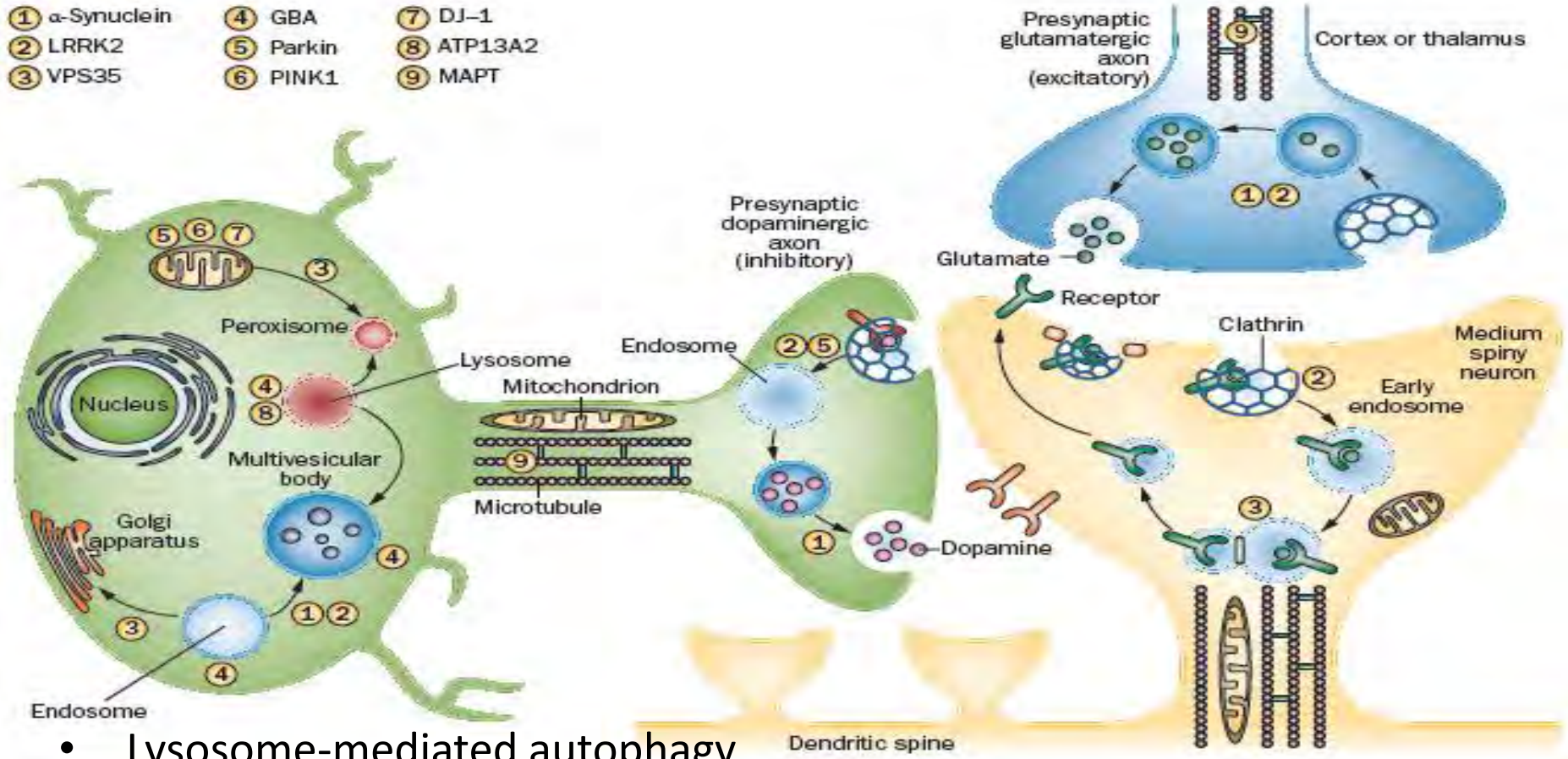




2018 92 genes

- Nalls et al. Nature Genetics 2014;46:989-93
- Chang D, Nalls et al. Nature Genetics 2017;49:1511-6
- Nalls et al. bioRxiv.2018; http://dx.doi.org/10.1101/388165do

Cellular Pathways



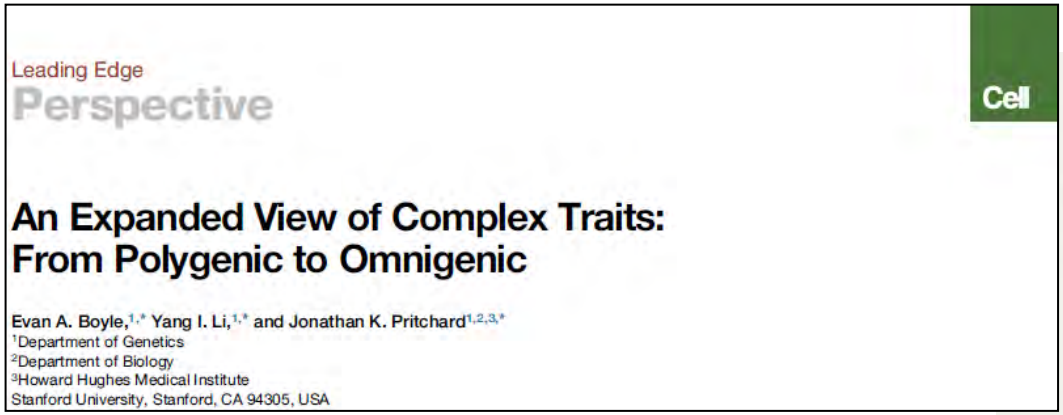
- Lysosome-mediated autophagy
- Mitochondrial and stress response
- Synaptic transmission (exo- endo- cytosis), endosomal receptor sorting & recycling
- Microtubule dynamics
- Ubiquitine-proteasome

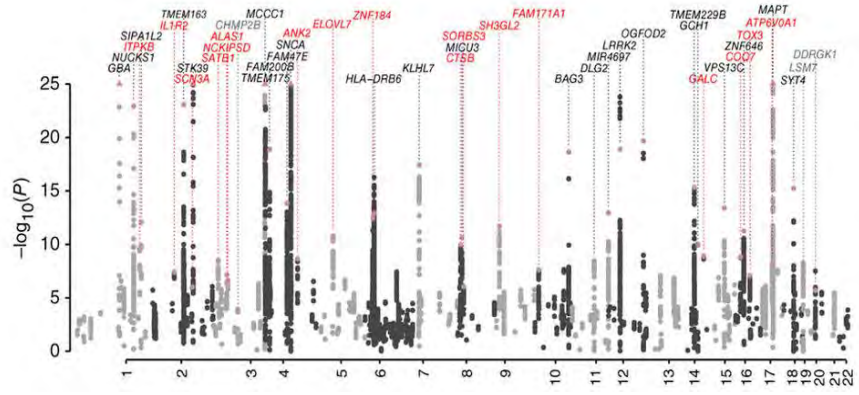
Trinh Nat Rev Neurol 2013

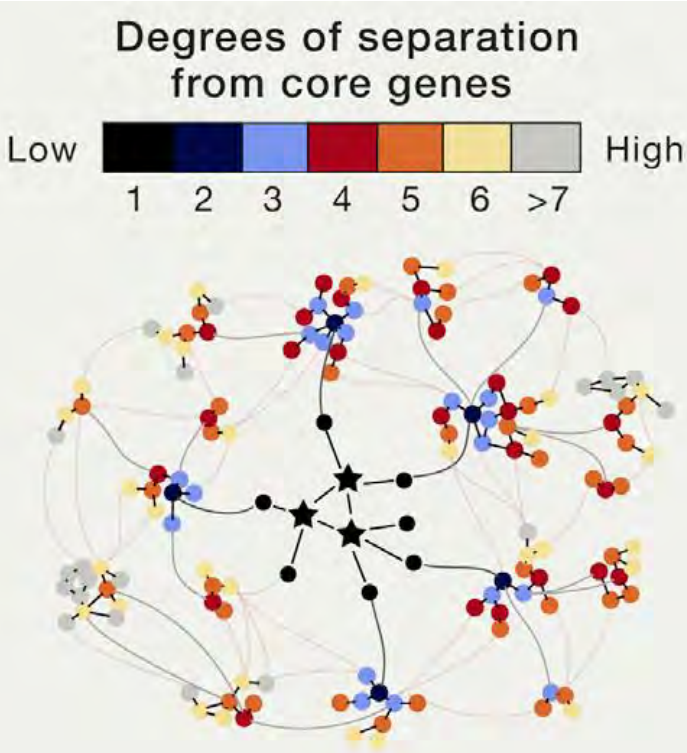
The "**omnigenic**" model

The principals:

- For any given disease phenotype, only a limited number of genes have direct effects on disease risk (core genes).
- Due to the property of networks, most expressed genes are close (only a few steps) to the nearest core gene and thus have effects on disease.
- Since core genes constitute only a tiny fraction of all genes, most heritability comes from genes with indirect effects.







Khan Foundation

Biogen

ISRAEL SCIENCE FOUNDATION

Tel-Aviv Sourasky Medical Center

ALS Association
Fighting Lou Gehrig's Disease

CHAYA CHARITABLE TRUST

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Fondation Adelis