OVERVIEW OF GENETICS IN DIVERSE PD POPULATIONS: UPDATE ON THE LARGE-PD STUDY

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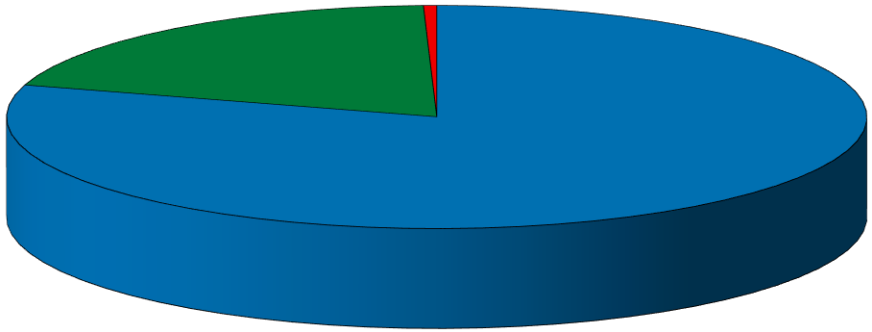
PARKINSON'S DISEASE: INHERITANCE

Sporadic **Familial** **Mendelian <0.1%**



Parkinson's disease/parkinsonism causative genes/loci

PARK1/4: (D, susceptibility), 4q21: *SNCA*
PARK2: (R, susceptibility?), 6q25.2-q27: *PRKN*
PARK6: (R) 1p35-p36: *PINK1*
PARK7: (R) 1p36: *DJ-1*
PARK8: (D, susceptibility) 12q12: *LRRK2*
PARK17: (D) 16q12: *VPS35*
PARK18: (D) 3q27: *EIF4G1*
PARK19: (R) 1p31: *DNAJC6*
PARK20: (R) 21q22: *SYNJ1*
(D) 3q22: *DNAJC13*
(X-linked) Xq28: *RAB39B*

PARK3: (D?, reduced penetrance) 2p13
PARK5: (D?, susceptibility), 4p14: *UCHL1*
PARK9: (R) 1p36 (Kufor-Rakeb syndrome) ATP13A2
PARK10: (susceptibility?) 1p32
PARK11: (D?) 2q36-37 GIGYF2?
PARK12: (X-linked?) Xq
PARK13: (D?) 2p13 HTRA2
PARK14: (R?) 22q13.1 PLA2G6
PARK15: (R?) 22q12-13 FBXO7
FTDP17: (D, susceptibility) 17q21: *MAPT*
Rapid-Onset Dystonia Parkinsonism: ATP1A3
SpinoCerebelar Ataxia: SCA2

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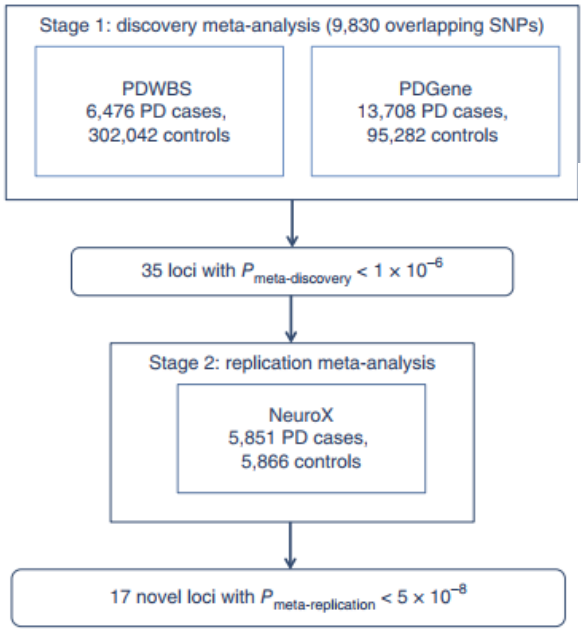
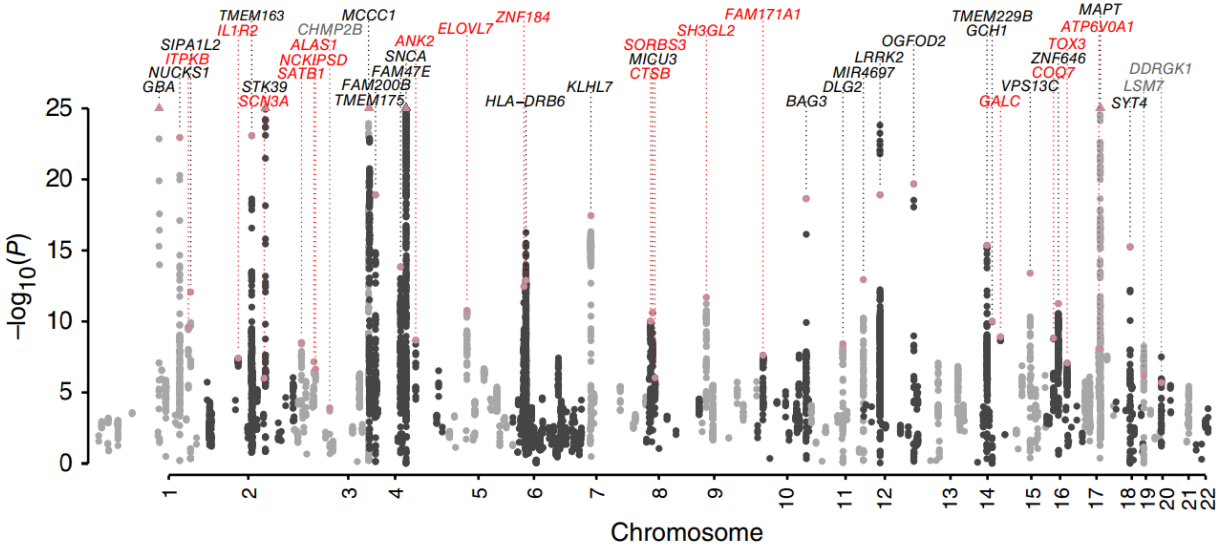
LARGEST META ANALYSIS PUBLISHED



Research participants were restricted to those of mainly (>97%) European ancestry



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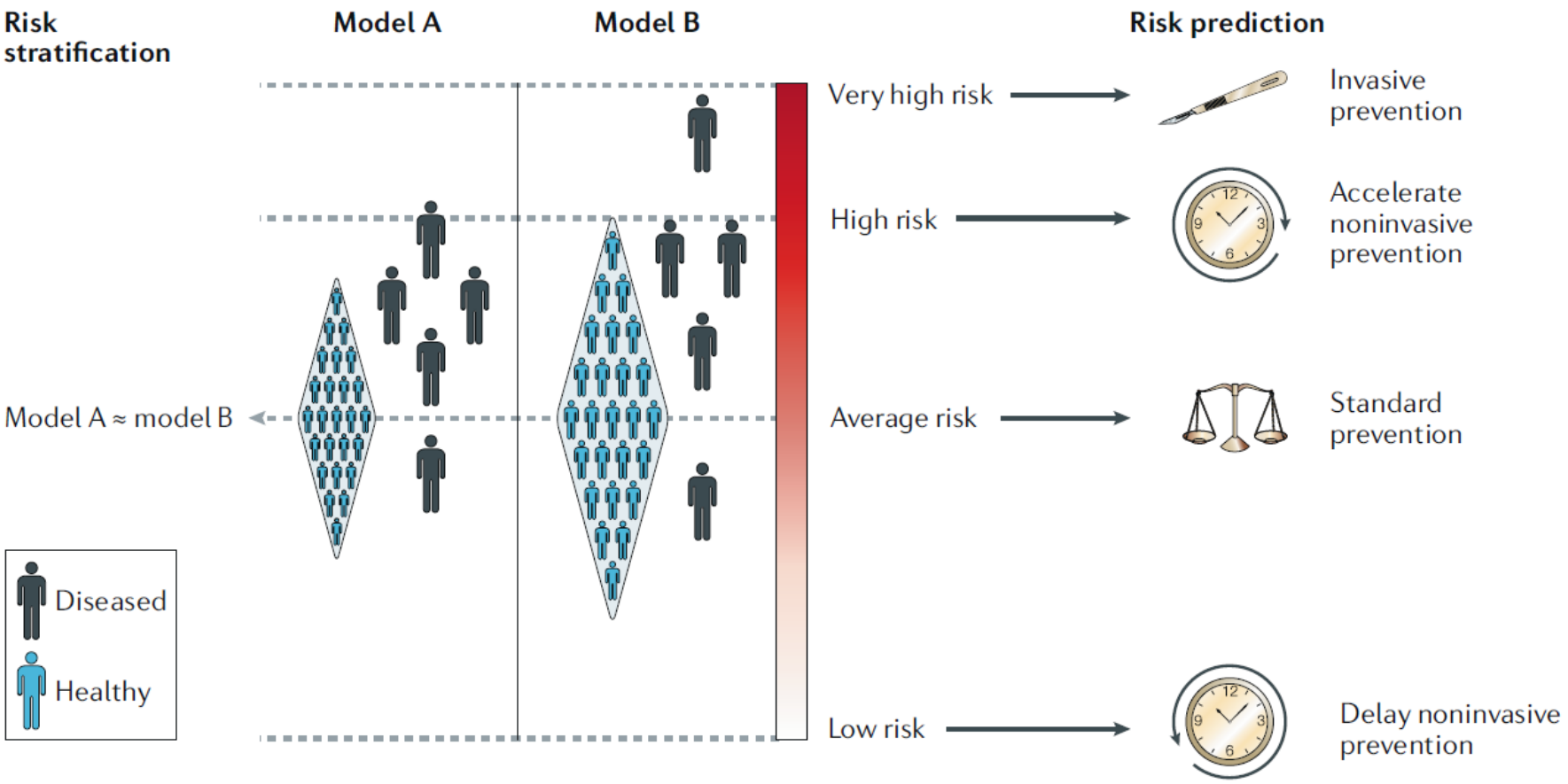
Chang et al. Nature Genetics 2017

POLYGENIC RISK SCORES (PRS)



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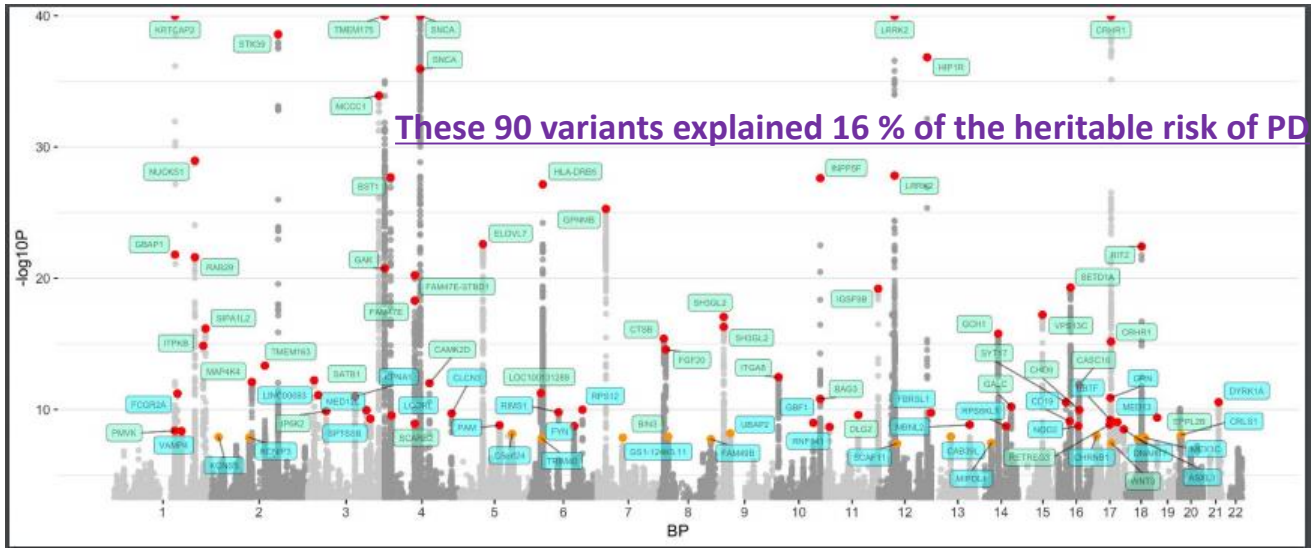
Torkamani et al. 2018 Nature Review Genetics

LARGEST META ANALYSIS

Risk loci discovery

37.7K cases
18.6K proxies
1.4M controls
7.8M SNPs

90 independent risk signals (38 novel). 305 candidate genes under LD peaks.

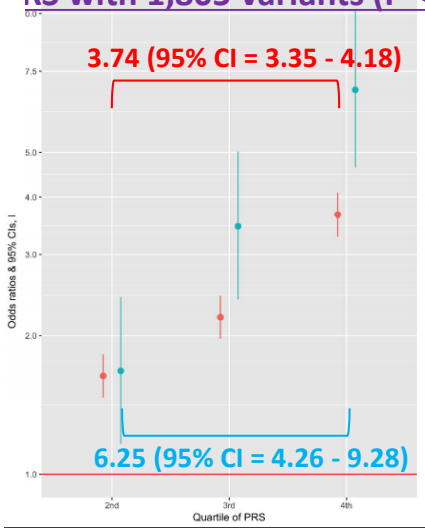


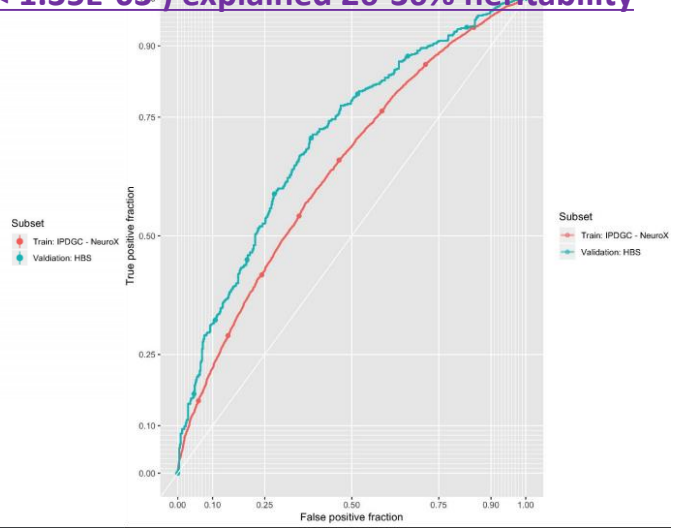
These 90 variants explained 16 % of the heritable risk of PD

NeuroX (5,851 cases and 5,866 controls)

Harvard Biomarker Study (HBS, 527 cases and 472 controls)

RS with 1,805 variants (P < 1.35E-03) explained 26-36% heritability





bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

New Results

Expanding Parkinson's disease genetics: novel risk loci, geno insights and heritable risk

Mike A. Nalls, Cornelis Blauwendraat, Costanza L. Vallerga, Karl Heilbron, Sara Bandres-Ciga, Diana Chang, Manuela Tan, Demis A. Kia, Alastair J. Noyce, Angli Xue, Jose Bras, Emily Young, Rainer von Coelln, Javier Simón-Sánchez, Claudia Schulte, Manu Sharma, Lynne Krohn, Lasse Pihlstrom, Ari Siitonen, Hirotaka Iwaki, Hampton Leonard, Faraz Faghri, J. Raphael Gibbs, Dena G. Hernandez, Sonja W. Scholz, Juan A. Botia, Maria Martinez, Jean-Christophe Corvol, Suzanne Lesage, Joseph Jankovic, Lisa M. Shulman, The 23andMe Research Team, System Genomics of Parkinson's Disease (SGPD) Consortium, Margaret Sutherland, Pentti Tienari, Kari Majamaa, Mathias Toft, Ole A. Andreassen, Tushar Bangale, Alexis Brice, Jian Yang, Ziv Gan-Or, Thomas Gasser, Peter Heutink, Joshua M Shulman, Nicolas Wood, David A. Hinds, John A. Hardy, Huw R Morris, Jacob Gratten, Peter M. Visscher, Robert R. Graham, Andrew B. Singleton, for the International Parkinson's Disease Genomics Consortium

doi: https://doi.org/10.1101/388165

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GWAS IN NON-EUROPEANS

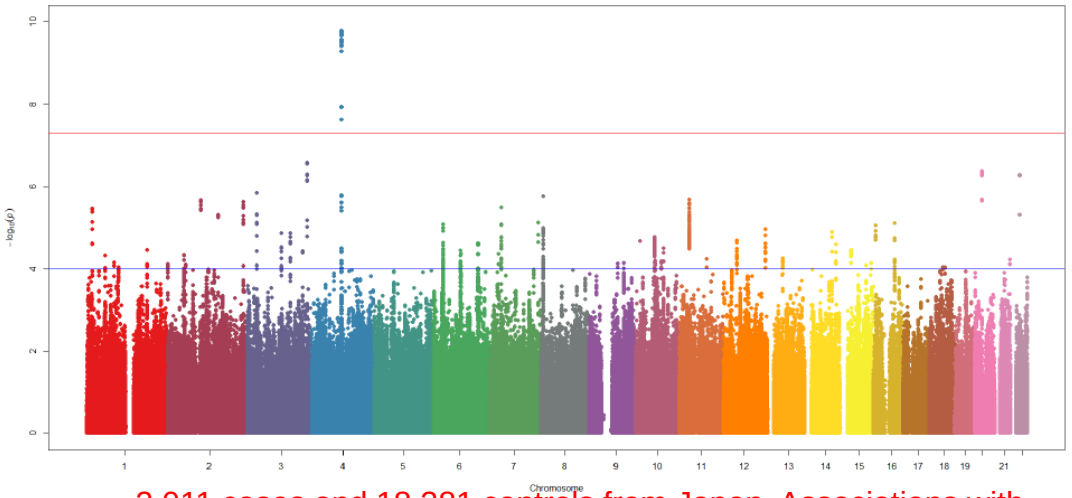
Human Molecular Genetics, 2017, Vol. 26, No. 1 226–232
doi: 10.1093/hmg/ddw379
Advance Access Publication Date: 22 December 2016
Association Studies Article

ASSOCIATION STUDIES ARTICLE

Genome-wide association study of Parkinson's disease in East Asians

Jia Nee Foo[1,2], Louis C. Tan[3], Ishak D. Irwan[2], Wing-Lok Au[3], Hui Qi Low[2], Kumar-M. Prakash[3], Azlina Ahmad-Annuar[4], Jinxin Bei[5], Anne YY Chan[6], Chiung Mei Chen[7], Yi-Chun Chen[7], Sun Ju Chung[8], Hao Deng[9], Shen-Yang Lim[10], Vincent Mok[6], Hao Pang[11], Zhong Pei[12], Rong Peng[13], Hui-Fang Shang[13], Kyuyoung Song[14], Ai Huey Tan[10], Yih-Ru Wu[7], Tin Aung[15,16], Ching-Yu Cheng[15,16,17], Fook Tim Chew[18], Soo-Hong Chew[19], Siow-Ann Chong[20], Richard P. Ebstein[21], Jimmy Lee[17,20], Seang-Mei Saw[15,16,17,22], Adeline Seow[22], Mythily Subramaniam[20], E-Shyong Tai[23], Eranga N. Vithana[15,16,17], Tien-Yin Wong[15,16,17], Khai Koon Heng[2], Wee-Yang Meah[2], Chiea Chuen Khor[2,15,24], Hong Liu[25], Furen Zhang[25], Jianjun Liu[2,†,*] and Eng-King Tan[3,17,†,*]

779 PD cases, 13,227 controls from Singapore, Hong Kong, Malaysia, Korea, mainland China and Taiwan. Strong associations at SNCA, LRRK2 and MCCC1



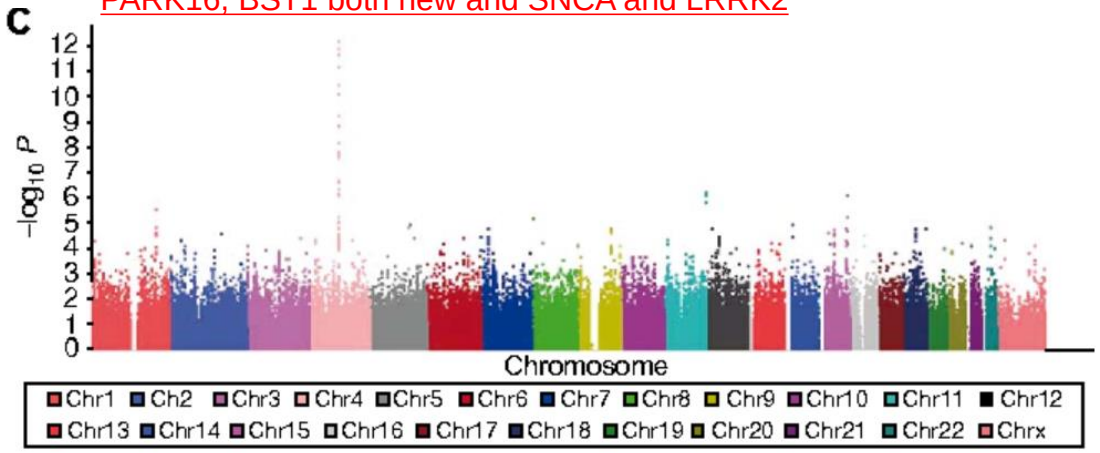
nature genetics

Letter | Published: 15 November 2009

Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

Wataru Satake, Yuko Nakabayashi, Ikuko Mizuta, Yushi Hirota, Chiyomi Ito, Michiaki Kubo, Takahisa Kawaguchi, Tatsuhiko Tsunoda, Masahiko Watanabe, Atsushi Takeda, Hiroyuki Tomiyama, Kenji Nakashima, Kazuko Hasegawa, Fumiya Obata, Takeo Yoshikawa, Hideshi Kawakami, Saburo Sakoda, Mitsutoshi Yamamoto, Nobutaka Hattori, Miho Murata, Yusuke Nakamura & Tatsushi Toda

2,011 cases and 18,381 controls from Japan. Associations with PARK16, BST1 both new and SNCA and LRRK2



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GENETICS OF PD IN LATIN AMERICA

Low frequency of common *LRRK2* mutations in Mexican patients with Parkinson's disease

PD= 319

Petra Yescas[a,1], Marisol López[b,1], Nancy Monroy[a], Marie-Catherine Boll[c], Mayela Rodríguez-Violante[d], Ulises Rodríguez[c], Adriana Ochoa[a], María Elisa Alonso[a,*]

Genetic Mutations in Early-Onset Parkinson's Disease Mexican Patients: Molecular Testing Implications

PD= 127, Control=120

Nancy Monroy-Jaramillo,[1,2] Jorge Luis Guerrero-Camacho,[1] Mayela Rodríguez-Violante,[3] Marie-Catherine Boll-Woehrlen,[4] Petra Yescas-Gómez,[1] María Elisa Alonso-Vilatela,[1] and Marisol López-López[5]*

Low prevalence of most frequent pathogenic variants of six PARK genes in sporadic Parkinson's disease

Silvia García, Luz Berenice López-Hernández, Juan Antonio Suarez-Cuenca, Marlene Solano-Rojas, Martha P. Gallegos-Arreola, Olga Gama-Moreno, Paulina Valdez-Anguiano, Patricia Canto, Luis Dávila-Maldonado, Carlos F. Cuevas-García, Ramón Mauricio Coral-Vázquez

PD= 173, Control= 208

Autosomal dominant Parkinson's disease: Incidence of mutations in *LRRK2, SNCA, VPS35* and *GBA* genes in Brazil

PD= 141

Gabriella de M. Abreu[a,1], Débora Cristina T. Valença[a,1], Mário Campos Júnior[b], Camilla P. da Silva[a], João S. Pereira[c], Marco A. Araujo Leite[d], Ana Lucia Rosso[e], Denise H. Nicaretta[f], Luiz Felipe R. Vasconcellos[g,h], Delson José da Silva[i,j], Marcus V. Della Coletta[k], Jussara M. dos Santos[a], Andressa P. Gonçalves[a], Cíntia B. Santos-Rebouças[a], Márcia M.G. Pimentel[a,*]

Exon dosage variations in Brazilian patients with Parkinson's disease: analysis of SNCA, PARKIN, PINK1 and DJ-1 genes.

PD= 102

Moura KC[1], Junior MC, de Rosso AL, Nicaretta DH, Pereira JS, José Silva D, Santos-Rebouças CB, Pimentel MM.

The rs3857059 variant of the SNCA gene is associated with Parkinson's disease in Mexican Mestizos.

García S[1], Chavira-Hernández G[1], Gallegos-Arreola MP[2], Dávila-Maldonado L[3], García Martínez E[1], Montes Almanza LA[1], Palma-Flores C[1], Mondragón-Terán P[1], Alcaraz Estrada SL[1], López-Hernández LB[1].

PD= 106, Control=135

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A study of *LRRK2* mutations and Parkinson's disease in Brazil

PD= 154

Márcia Mattos Gonçalves Pimentel[a,*], Karla Cristina Vasconcelos Moura[a], Cláudia Bueno Abdalla[a], João Santos Pereira[b], Ana Lúcia Zuma de Rosso[c], Denise Hack Nicaretta[b,d], Mário Campos Junior[a], Richard Morais de Almeida[a], Jussara Mendonça dos Santos[a], Izabel Cristina Constantino Bastos[e], Maria Filomena Xavier Mendes[e], Henryk Maultasch[c], Flavio Henrique de Rezende Costa[c], Antônio Luiz dos Santos Werneck[c], Cíntia Barros Santos-Rebouças[a]

Genetic and Environmental Findings in Early-onset Parkinson's Disease Brazilian Patients

PD= 72, Control= 81

Patricia de Carvalho Aguiar, MD, PhD,[1,2*] Patricia Silva Lessa, PhD,[1,3] Clecio Godeiro Junior, MD,[1,2] Orlando Barsottini, MD, PhD,[1,2] Andre Carvalho Felício, MD,[1,2] Vanderci Borges, MD,[2] Sonia Maria de Azevedo Silva, MD, PhD,[2] Roberta Arb Saba, MD,[2] Henrique Ballalai Ferraz, MD, PhD,[2] Carlos A. Moreira-Filho, PhD,[1,4] and Luiz Augusto F. Andrade, MD, PhD[1]

Familial Parkinsonism and early onset Parkinson's disease in a Brazilian Movement Disorders clinic: Phenotypic characterization and frequency of *SNCA, PRKN, PINK1* and *LRRK2* mutations

PD= 575

Sarah Teixeira Camargos, MD[1], Leonardo Oliveira Dornas, MD[1], Parastoo Momeni, PhD[3], Andrew Lees, MD, PhD[4], John Hardy, PhD[4,5], Andrew Singleton, PhD[2], and Francisco Cardoso, MD, PhD[1]

PINK1 Mutations in a Brazilian Cohort of Early-Onset Parkinson's Disease Patients

PD= 60

Clecio Godeiro-Junior, MD,[1,2*] Patricia M. de Carvalho-Aguiar, MD, PhD,[1,2] Andre C. Felício, MD,[1,2] Orlando G.P. Barsottini, MD, PhD,[1,2] Sonia M.A. Silva, MD, PhD,[1] Vanderci Borges, MD, PhD,[1] Luiz Augusto F. Andrade, MD, PhD,[2] and Henrique Ballalai Ferraz, MD, PhD[1]

Lrrk2 mutations in South America:

A study of Chilean Parkinson's disease

PD= 166, Control=153

Carolina Perez-Pastene[1], Stephanie A. Cobb[2], Fernando Díaz-Grez[1], Mary M. Hulihan[2], Marcelo Miranda[3,4], Pablo Venegas[3], Osvaldo Trujillo Godoy[3], Jennifer M. Kachergus[2], Owen A. Ross[2], Luis Layson[5], Matthew J. Farrer[2], and Juan Segura-Aguilar[1,*]

DIVERSITY IN GENETICS

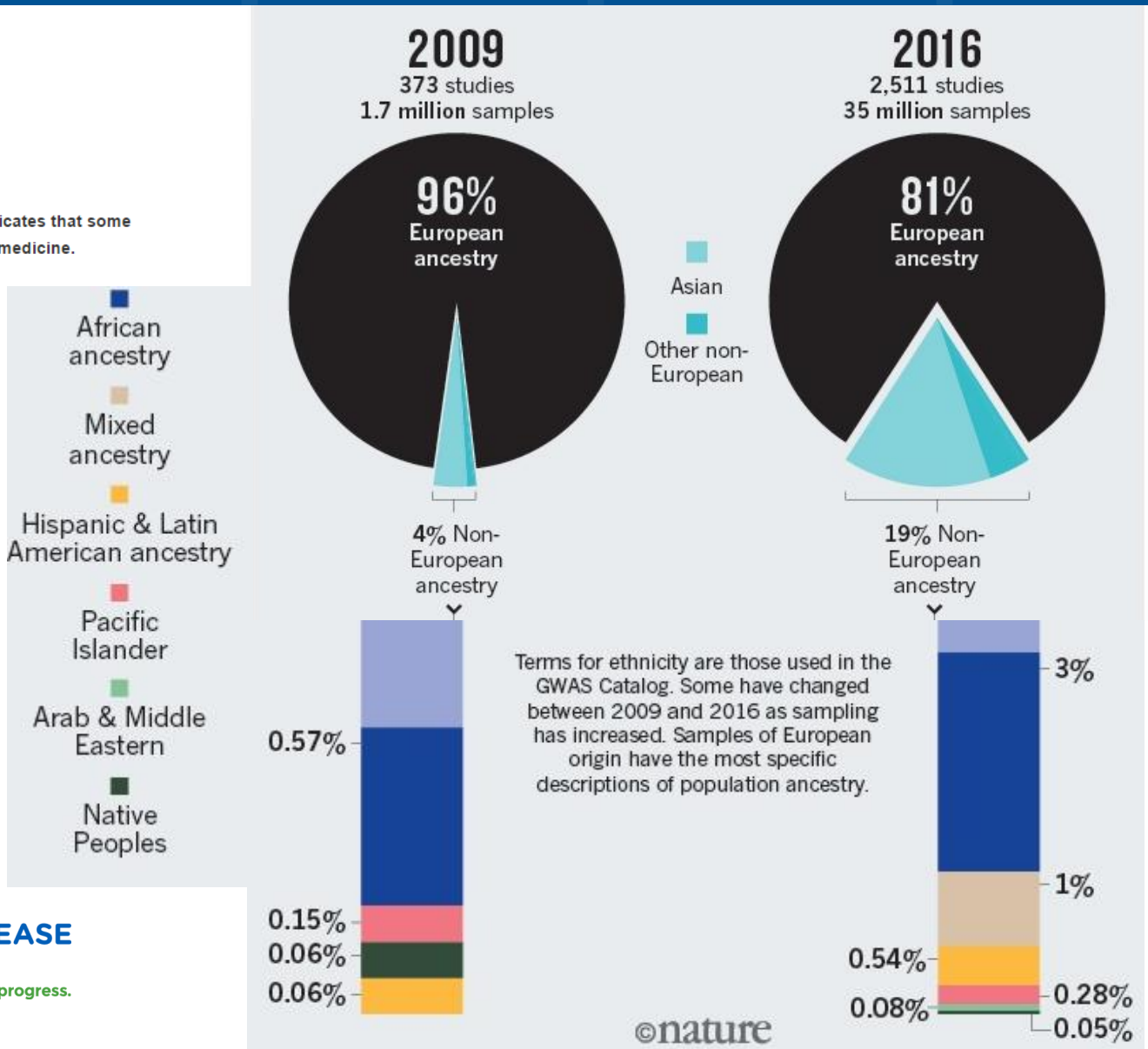
NATURE | COMMENT

Genomics is failing on diversity

Alice B. Popejoy & Stephanie M. Fullerton

12 October 2016

An analysis by Alice B. Popejoy and Stephanie M. Fullerton indicates that some populations are still being left behind on the road to precision medicine.



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PRS ACROSS POPULATIONS

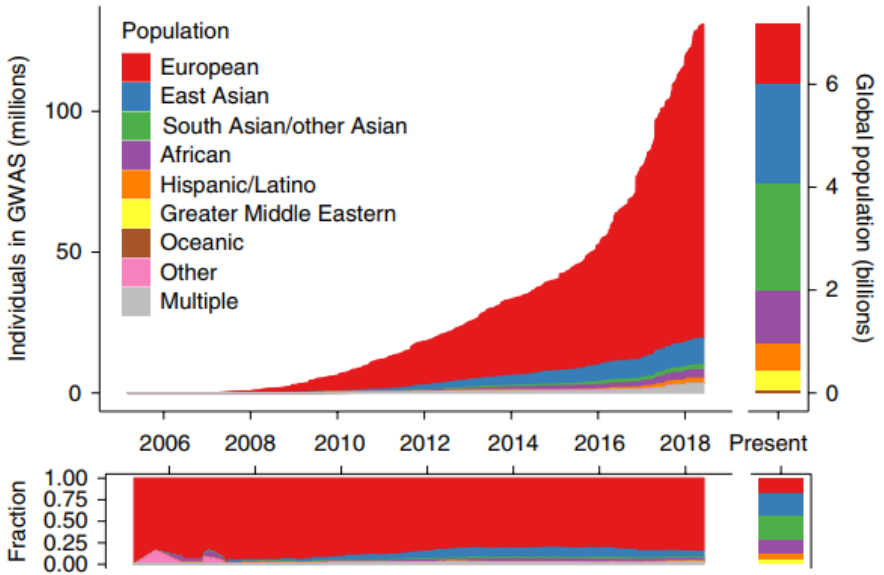

Fig. 1 | Ancestry of GWAS participants over time, as compared with the global population. Cumulative data, as reported by the GWAS catalog[76]. Individuals whose ancestry is 'not reported' are not shown.

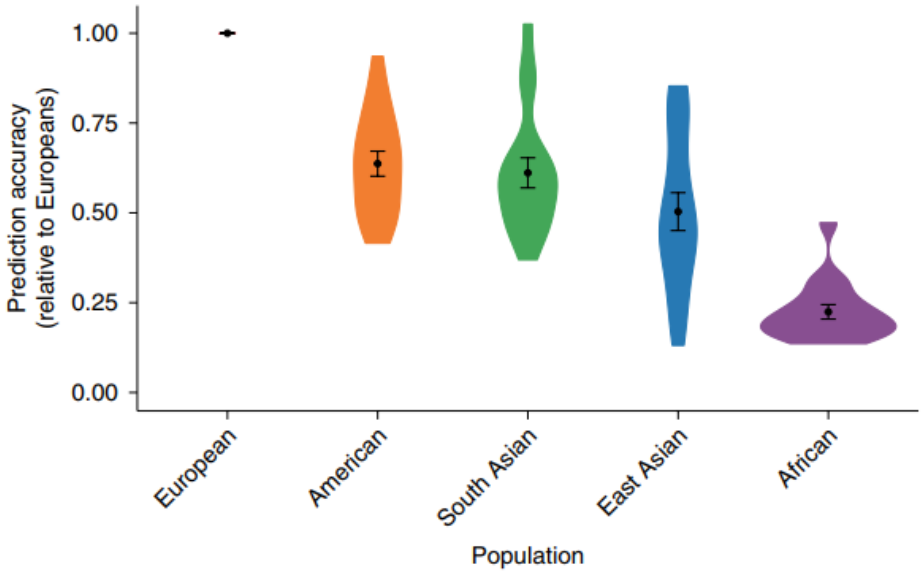

Fig. 3 | Prediction accuracy relative to European-ancestry individuals across 17 quantitative traits and 5 continental populations in the UKBB. All

PERSPECTIVE
https://doi.org/10.1038/s41588-019-0379-x
nature genetics

Clinical use of current polygenic risk scores may exacerbate health disparities

Alicia R. Martin[1,2,3*], Masahiro Kanai[1,2,3,4,5], Yoichiro Kamatani[5,6], Yukinori Okada[5,7,8], Benjamin M. Neale[1,2,3] and Mark J. Daly[1,2,3,9]

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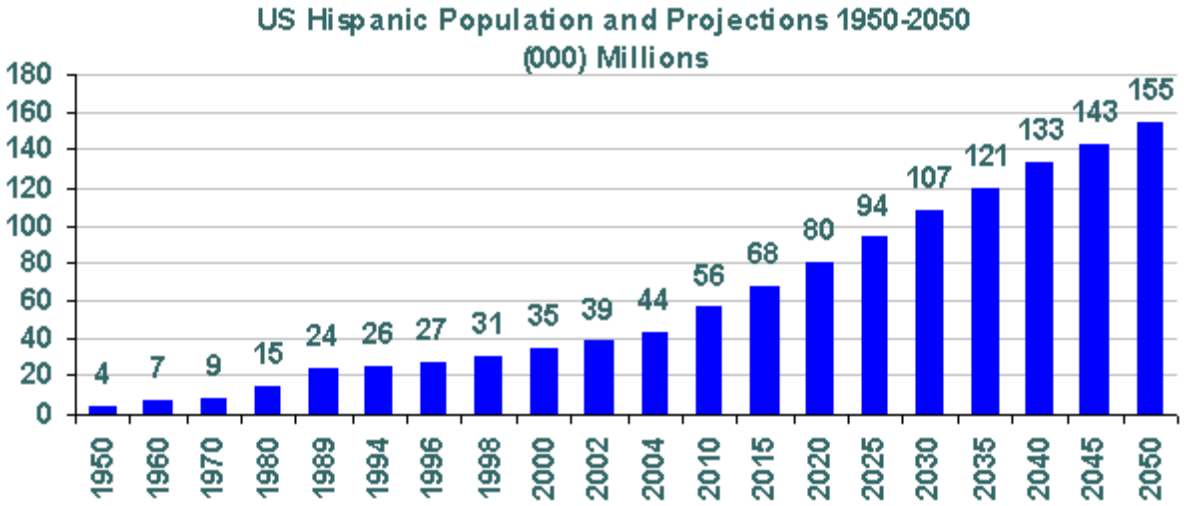
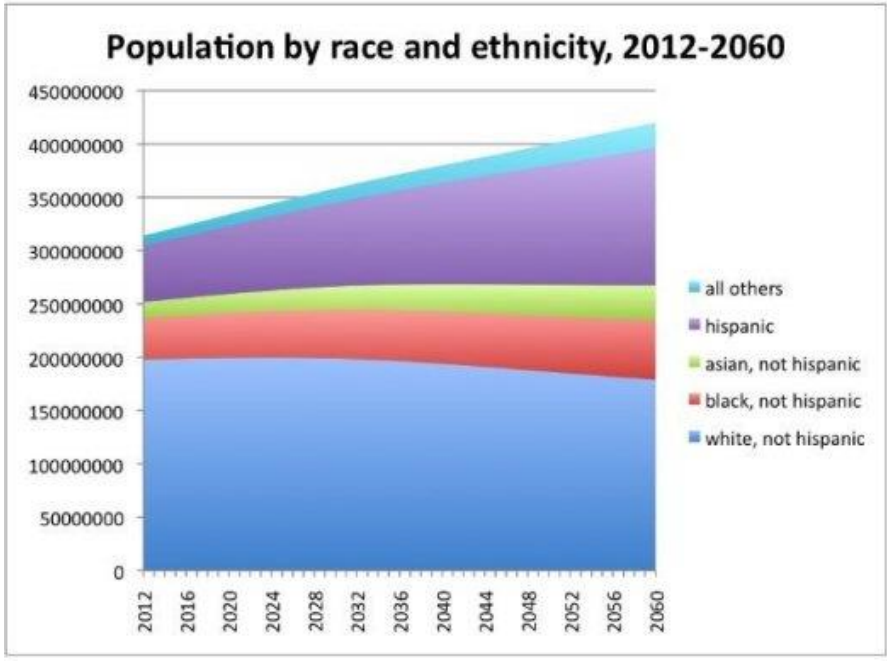
LATINOS IN THE US



Source: Synovate, U.S. Census Bureau



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LARGE-PD

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LARGE-PD IN 2006

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LARGE-PD

LARGE-PD
Latin American Research consortium on the GEnetics of Parkinson's Disease

New sites:

- 8 new sites in Brazil (CBPD consortium)
- Honduras
- Costa Rica
- Puerto Rico
- Mexico

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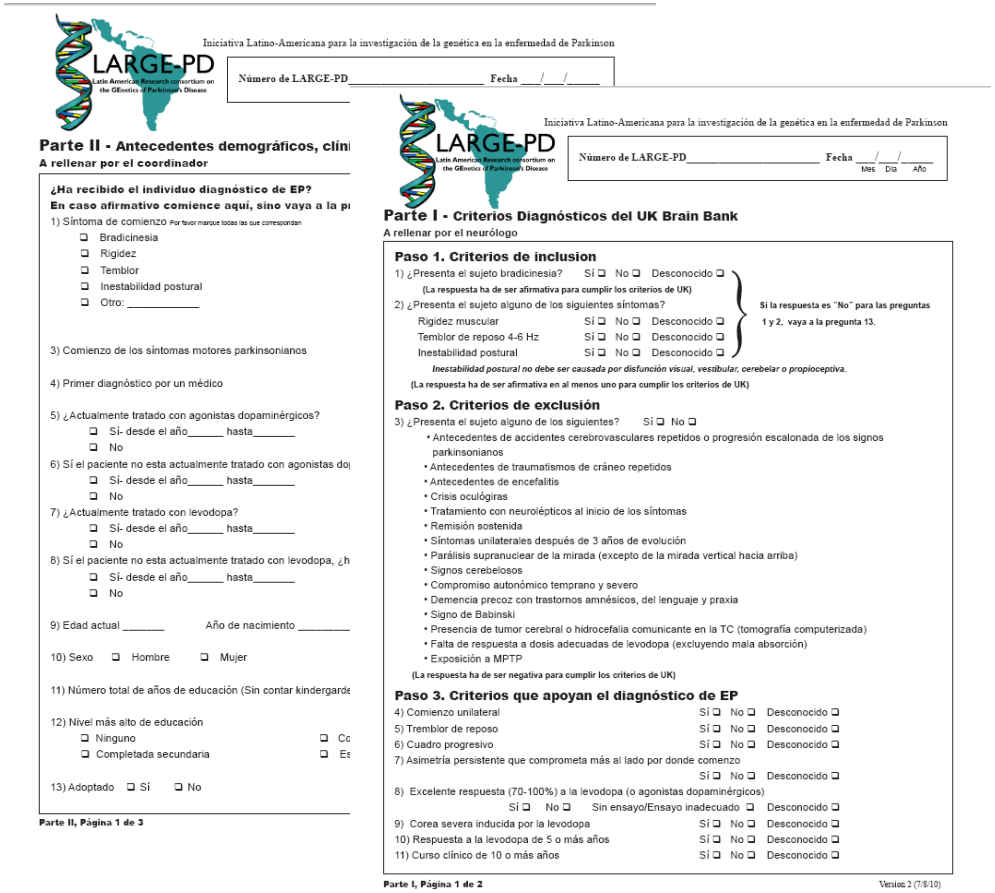
LARGE-PD RECRUITMENT & DATA COLLECTION



Iniciativa Latino-Americana para la investigación de la genética en la enfermedad de Parkinson

LARGE-PD

Número de LARGE-PD_____ Fecha ___/___/_____

Parte II - Antecedentes demográficos, clíni

A rellenar por el coordinador

¿Ha recibido el individuo diagnóstico de EP?

En caso afirmativo comience aquí, sino vaya a la p

1) Síntoma de comienzo Por favor marque todas las que correspondan

- ❑ Bradicinesia
- ❑ Rigidez
- ❑ Temblor
- ❑ Inestabilidad postural
- ❑ Otro: _____

3) Comienzo de los síntomas motores parkinsonianos

4) Primer diagnóstico por un médico

5) ¿Actualmente tratado con agonistas dopaminérgicos?

- ❑ Sí- desde el año_____ hasta_____
- ❑ No

6) Sí el paciente no esta actualmente tratado con agonistas do

- ❑ Sí- desde el año_____ hasta_____
- ❑ No

7) ¿Actualmente tratado con levodopa?

- ❑ Sí- desde el año_____ hasta_____
- ❑ No

8) Sí el paciente no esta actualmente tratado con levodopa, ¿h

- ❑ Sí- desde el año_____ hasta_____
- ❑ No

9) Edad actual _____ Año de nacimiento _____

10) Sexo ❑ Hombre ❑ Mujer

11) Número total de años de educación (Sin contar kindergarde

12) Nivel más alto de educación

- ❑ Ninguno ❑ Co
- ❑ Completada secundaria ❑ Es

13) Adoptado ❑ Sí ❑ No

Parte II, Página 1 de 3

Iniciativa Latino-Americana para la investigación de la genética en la enfermedad de Parkinson

LARGE-PD

Número de LARGE-PD_____ Fecha ___/___/_____ Mes Día Año

Parte I - Criterios Diagnósticos del UK Brain Bank

A rellenar por el neurólogo

Paso 1. Criterios de inclusion

1) ¿Presenta el sujeto bradicinesia? Sí ❑ No ❑ Desconocido ❑

(La respuesta ha de ser afirmativa para cumplir los criterios de UK)

2) ¿Presenta el sujeto alguno de los siguientes síntomas?

Si la respuesta es "No" para las preguntas 1 y 2, vaya a la pregunta 13.

- Rigidez muscular Sí ❑ No ❑ Desconocido ❑
- Temblor de reposo 4-6 Hz Sí ❑ No ❑ Desconocido ❑
- Inestabilidad postural Sí ❑ No ❑ Desconocido ❑

Inestabilidad postural no debe ser causada por disfunción visual, vestibular, cerebelar o propioceptiva.

(La respuesta ha de ser afirmativa en al menos uno para cumplir los criterios de UK)

Paso 2. Criterios de exclusión

3) ¿Presenta el sujeto alguno de los siguientes? Sí ❑ No ❑

- Antecedentes de accidentes cerebrovasculares repetidos o progresión escalonada de los signos parkinsonianos
- Antecedentes de traumatismos de cráneo repetidos
- Antecedentes de encefalitis
- Crisis oculógiras
- Tratamiento con neurolépticos al inicio de los síntomas
- Remisión sostenida
- Síntomas unilaterales después de 3 años de evolución
- Parálisis supranuclear de la mirada (excepto de la mirada vertical hacia arriba)
- Signos cerebelosos
- Compromiso autonómico temprano y severo
- Demencia precoz con trastornos amnésicos, del lenguaje y praxia
- Signo de Babinski
- Presencia de tumor cerebral o hidrocefalia comunicante en la TC (tomografía computerizada)
- Falta de respuesta a dosis adecuadas de levodopa (excluyendo mala absorción)
- Exposición a MPTP

(La respuesta ha de ser negativa para cumplir los criterios de UK)

Paso 3. Criterios que apoyan el diagnóstico de EP

4) Comienzo unilateral Sí ❑ No ❑ Desconocido ❑

5) Temblor de reposo Sí ❑ No ❑ Desconocido ❑

6) Cuadro progresivo Sí ❑ No ❑ Desconocido ❑

7) Asimetría persistente que comprometa más al lado por donde comenzo Sí ❑ No ❑ Desconocido ❑

8) Excelente respuesta (70-100%) a la levodopa (o agonistas dopaminérgicos) Sí ❑ No ❑ Sin ensayo/Ensayo inadecuado ❑ Desconocido ❑

9) Corea severa inducida por la levodopa Sí ❑ No ❑ Desconocido ❑

10) Respuesta a la levodopa de 5 o más años Sí ❑ No ❑ Desconocido ❑

11) Curso clínico de 10 o más años Sí ❑ No ❑ Desconocido ❑

Parte I, Página 1 de 2 Version 2 (7/8/10)

Country	No. of samples recruited
Peru	788
Peru	49
Brazil	430
Brazil	429
Chile	13
Colombia	1,233
Colombia	33
Colombia	23
Argentina	192
Uruguay	559
Honduras	23
Ecuador	85
Total	3,857

Questionnaire

- 11 Pages (aprox 20 min)
- Self administered or research coordinator
- 3 languages (English, Spanish and Portuguese)
- Environmental exposure questionnaire (Tobbaco, Caffeine, NSAIDs,….)
- Cognitive function (Montreal Cognitive Assessment, MoCA)

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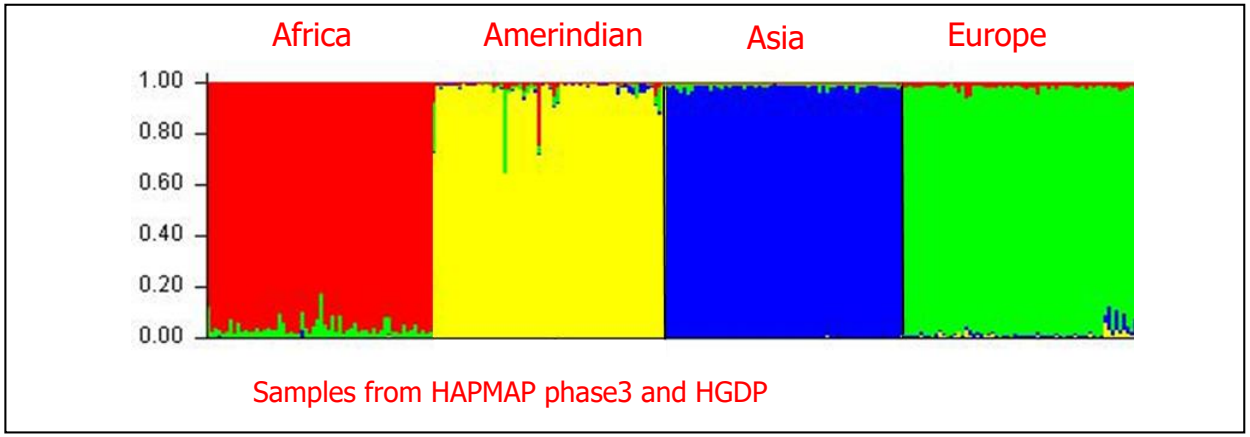
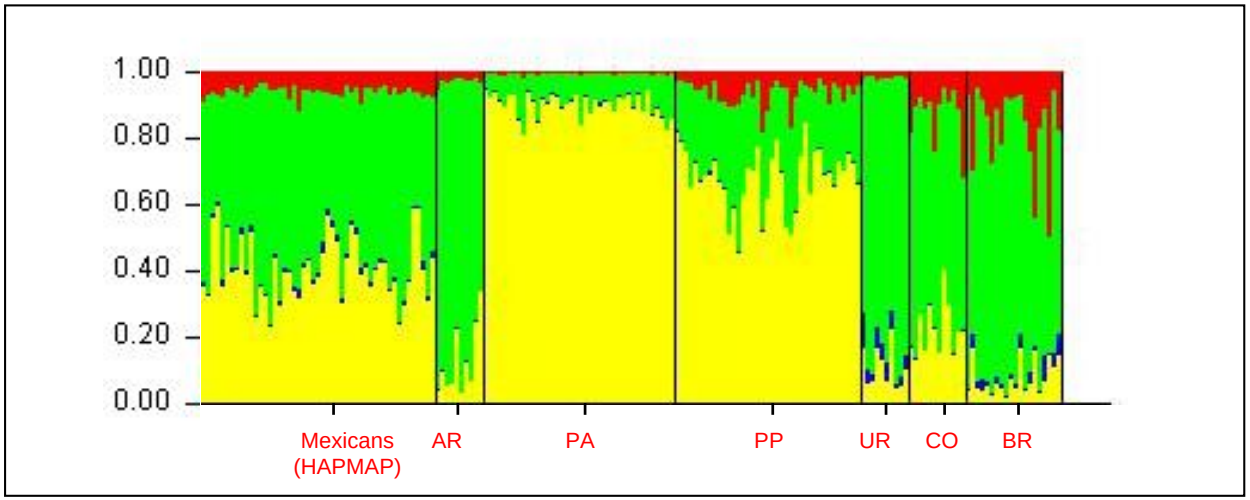
ANCESTRY INFORMATIVE MARKERS (AIMS) GLOBAL ANCESTRY

RS id	Chromosc	Position (Build 36.3)
rs7541084	1	51762179
rs1834619	2	17764966
rs9308872	2	104101223
rs1348587	2	154440039
rs17627058	2	177478841
rs9840466	3	72175958
rs842223	3	196968747
rs1010574	5	10847152
rs149138	5	55562970
rs10434525	5	59592218
rs10079352	5	117522539
rs1366220	5	153477973
rs3997520	6	44659465
rs10763013	10	55283129
rs2716454	11	24710115
rs590616	11	100353685
rs932055**	12	22591655
rs739787**	12	111465954
rs1924373	13	49843707
rs10483393	14	31530235
rs3211166	14	68772911
rs2676765	15	54636697
rs17675813	16	64367041
rs4924980	17	19145456
rs9960403	18	13427993
rs6094461*	20	44823556
rs433632	21	42893492
rs131026	22	47561914
rs10008281	4	100361325
rs9568431	13	49953648





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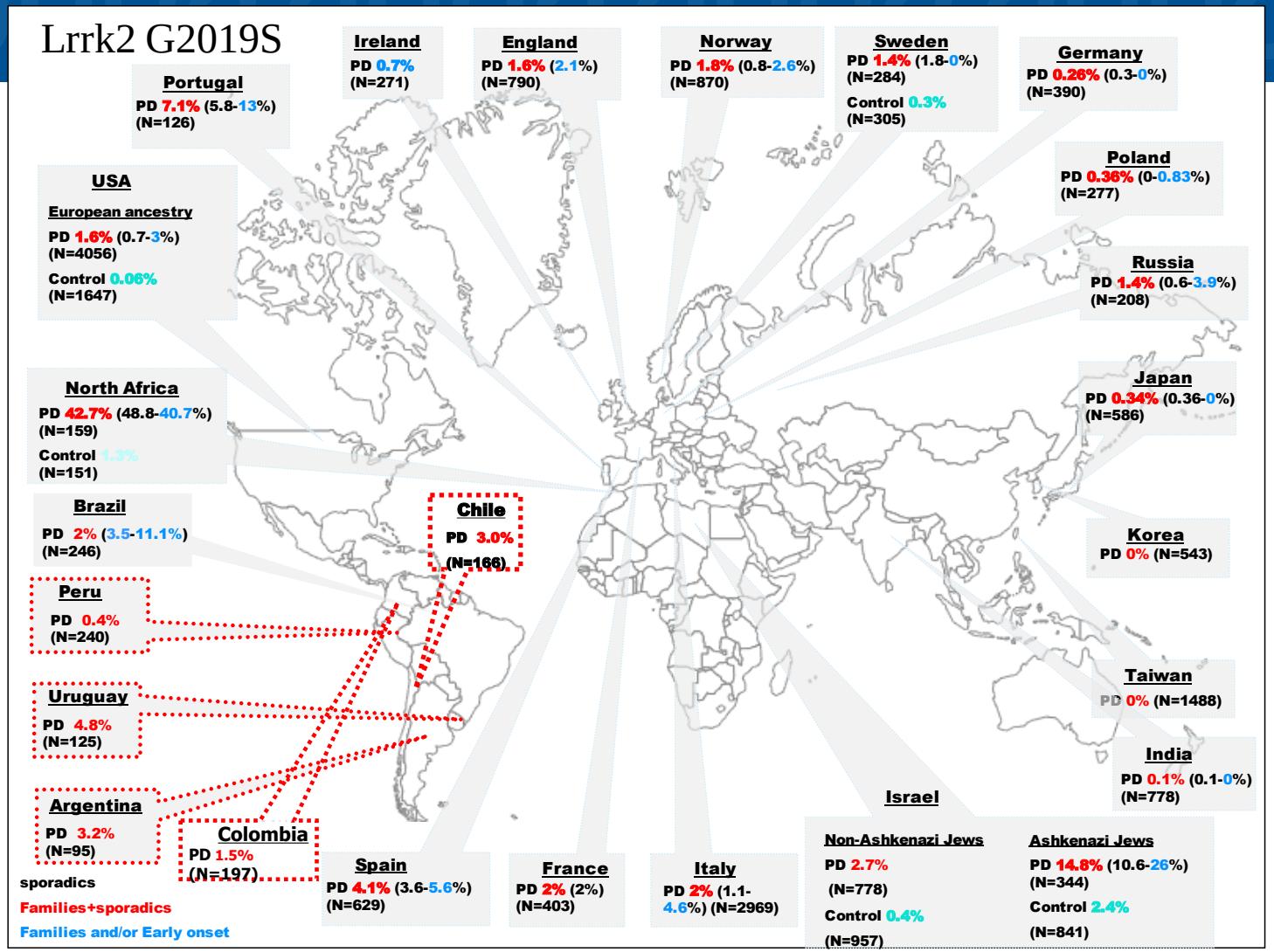
Josh Akey & Timothy O'Connor

LRRK2



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LRRK2

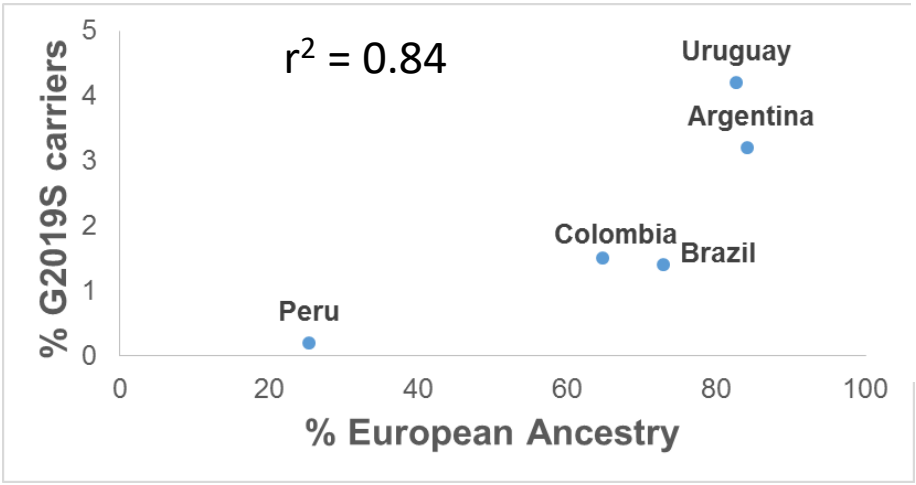
npj | Parkinson's Disease

www.nature.com/npjparkd

ARTICLE OPEN

Variable frequency of *LRRK2* variants in the Latin American research consortium on the genetics of Parkinson's disease (LARGE-PD), a case of ancestry

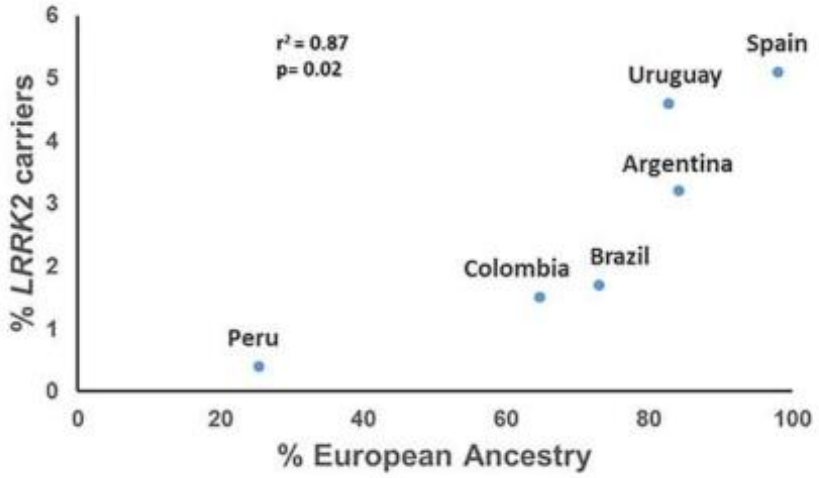
Mario Cornejo-Olivas[1,2], Luis Torres[3,4], Mario R. Velit-Salazar[1,5], Miguel Inca-Martinez[1], Pilar Mazzetti[1,4], Carlos Cosentino[3,4], Federico Micheli[6], Claudia Perandones[6], Elena Dieguez[7], Victor Raggio[8], Vitor Tumas[9], Vanderci Borges[10], Henrique B. Ferraz[10], Carlos R. M. Rieder[11], Artur Shumacher-Schuh[11], Carlos Velez-Pardo[12], Marlene Jimenez-Del-Rio[12], Francisco Lopera[12], Jorge Chang-Castello[13], Brennie Andreë-Munoz[14], Sarah Waldherr[15,16], Dora Yearout[15,16], Cyrus P. Zabetian[15,16] and Ignacio F. Mata[15,16]



Mov Disord. 2017 Sep;32(9):1330-1331. doi: 10.1002/mds.27081. Epub 2017 Jun 28.

LARGE-PD: Examining the genetics of Parkinson's disease in Latin America.

Zabetian CP[1,2], Mata IF[1,2]; Latin American Research Consortium on the Genetics of PD (LARGE-PD).



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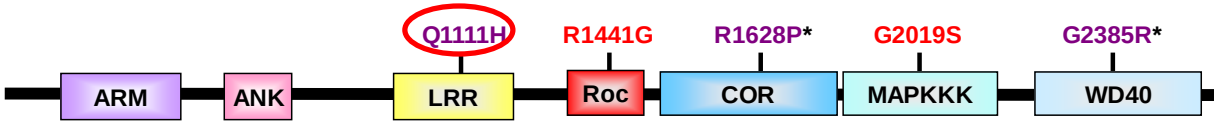
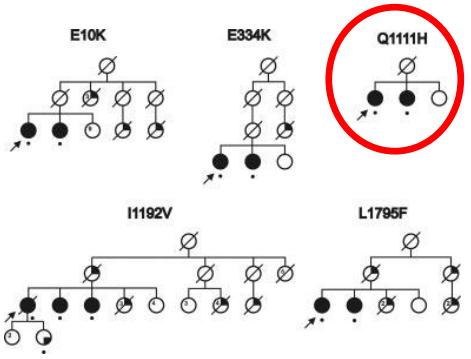
LRRK2

*** Only in Asia**

Pathogenic

Risk factors





Nichols et al. Neurology 2007

Q1111H	GG	GT	TT	T
Perú Cases "mestizos"(n=420)	350 (83.3%)	62 (14.8%)	8 (1.9%)	9.3%
Perú Controls "mestizos" (n=146)	127 (87%)	17 (11.6%)	2 *(1.4%)	7.2%
Perú Controls Amerindians (n=49)	34 (69.4%)	12 (24.5%)	3 (6.1%)	18.4%
Chile Cases (n=358)	326 (91%)	31 (8.7%)	1 (0.3%)	4.6%
Chile Controls (n=162)	151 (93%)	11 (7%)	0	3.4%
Uruguay controls (n=149)	147 (98%)	3 (2%)	0	1%
Argentina Controls (n=95)	93 (97.9%)	2 (2.1%)	0	1%
Spain Controls (n=59)	59 (100%)	0	0	0%

Owen Ross, Mayo Clinic

* 1 with Family History

Parkinsonism and Related Disorders xxx (2011) 1–3

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Lrrk2 p.Q1111H substitution and Parkinson's disease in Latin America☆

Ignacio F. Mata[a,b,*], Greggory J. Wilhoite[c], Dora Yearout[a,b], Justin A. Bacon[c], Mario Cornejo-Olivas[d], Pilar Mazzetti[d], Victoria Marca[d], Olimpio Ortega[d], Oscar Acosta[e], Carlos Cosentino[f], Luis Torres[f], Angel C. Medina[g], Carolina Perez-Pastene[h], Fernando Díaz-Grez[h], Carles Vilariño-Güell[c,i], Pablo Venegas[j], Marcelo Miranda[j,k], Osvaldo Trujillo-Godoy[l], Luis Layson[l], Rodrigo Avello[m], Elena Dieguez[n], Victor Raggio[o], Federico Micheli[p], Claudia Perandones[p], Victoria Alvarez[q], Juan Segura-Aguilar[d], Matthew J. Farrer[c,i], Cyrus P. Zabetian[a,b], Owen A. Ross[c]

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LRRK2

Table 2. Allele and genotype frequencies of *LRRK2* p.Q1111H (rs78365431)

Site	Affection status	Samples No.	Genotype GG No. (%)	Genotype GT No. (%)	Genotype TT No. (%)	G allele No. (%)	T allele No. (%)	Odds ratio (95% CI)	p-value
Argentina	Cases	179	175 (97.8)	4 (2.2)	0	354 (98.9)	4 (1.1)	NA	NA
	Controls	NA	NA	NA	NA	NA	NA		
Brazil	Cases	412	408 (99.0)	4 (1)	0	820 (99.5)	4 (0.5)	0.93 (0.24-3.51)	0.919
	Controls	283	281 (99.3)	1 (0.35)	1 (0.35)	563 (99.5)	3 (0.5)		
Colombia	Cases	197	188 (95.4)	9 (4.6)	0	385 (97.7)	9 (2.3)	1.7 (0.56-5.21)	0.342
	Controls	184	179 (97.3)	5 (2.7)	0	363 (98.6)	5 (1.4)		
Ecuador	Cases	85	80 (94.1)	5 (5.9)	0	165 (97.1)	5 (2.9)	NA	NA
	Controls	NA	NA	NA	NA	NA	NA		
Peru	Cases	536	444 (82.8)	82 (15.3)	10 (1.9)	970 (90.5)	102 (9.5)	1.03 (0.72-1.46)	0.884
	Controls	248	204 (82.3)	42 (16.9)	2 (0.8)	450 (90.7)	46 (9.3)		
Uruguay	Cases	280	276 (98.6)	4 (1.4)	0	548 (99.3)	4 (0.7)	0.67 (0.25-1.88)	0.447
	Controls	272	265 (97.4)	7 (2.6)	0	537 (98.7)	7 (1.3)		
Combined	Cases	1689	1571 (93.0)	108 (6.4)	10 (0.6)	3250 (96.2)	128 (3.8)	1.02 (0.75-1.40)	0.873
	Controls	987	929 (94.1)	55 (5.6)	3 (0.3)	1913 (96.9)	61 (3.1)		

Estimated odds ratios (ORs) with confidence intervals (CIs) and p-values result from logistic regression models adjusted for age, sex, and site (for the combined sample only).

Parkinsonism and Related Disorders 17 (2011) 629–631

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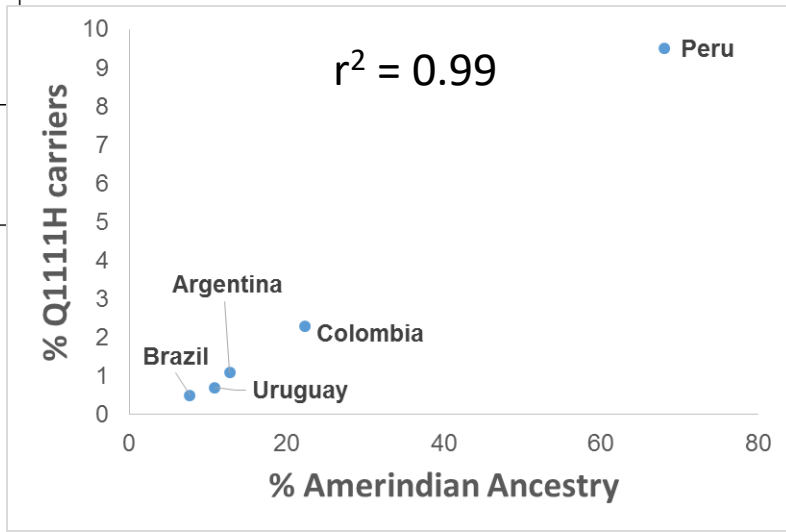
Short communication

Lrrk2 p.Q1111H substitution and Parkinson's disease in Latin America

Ignacio F. Mata[a,b,*], Greggory J. Wilhoite[c], Dora Yearout[a,b], Justin A. Bacon[c], Mario Cornejo-Olivas[d], Pilar Mazzetti[d], Victoria Marca[d], Olimpio Ortega[d], Oscar Acosta[e], Carlos Cosentino[f], Luis Torres[f], Angel C. Medina[g], Carolina Perez-Pastene[h], Fernando Díaz-Grez[h], Carles Vilariño-Güell[c,i], Pablo Venegas[j], Marcelo Miranda[j,k], Osvaldo Trujillo-Godoy[j], Luis Layson[l], Rodrigo Avello[m], Elena Dieguez[n], Victor Raggio[o], Federico Micheli[p], Claudia Perandones[p], Victoria Alvarez[q], Juan Segura-Aguilar[d], Matthew J. Farrer[c,i], Cyrus P. Zabetian[a,b], Owen A. Ross[c]



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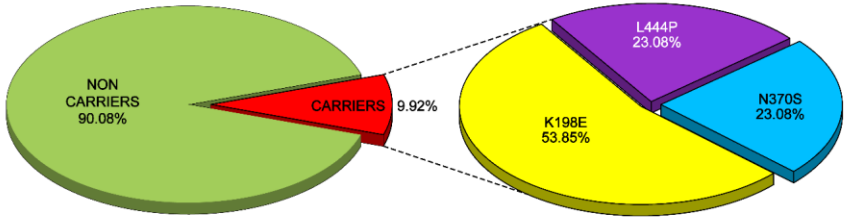
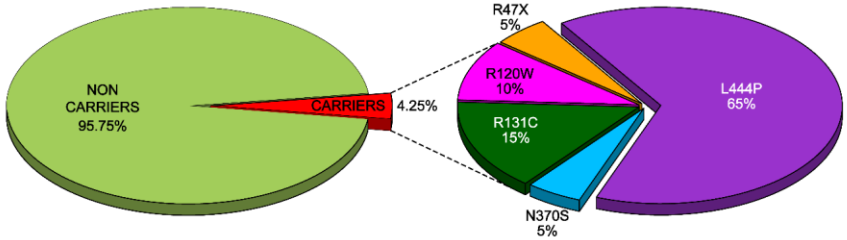
GBA

Colombian *GBA* mutations (n = 13)



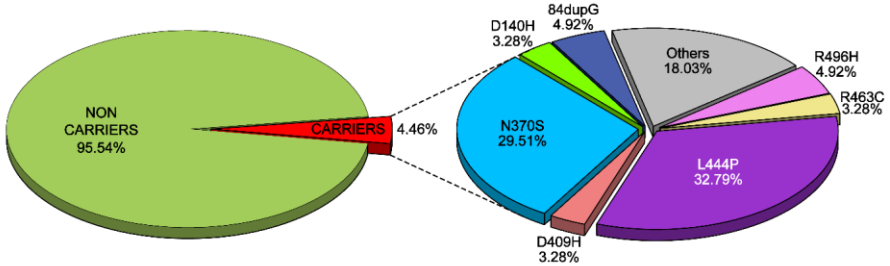
Colombian mutation distribution

Peruvian *GBA* mutations (n=20)



Peruvian mutation distribution

USA *GBA* mutations (n=61)



USA mutation distribution

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Parkinsonism and Related Disorders

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

Short communication

The distribution and risk effect of *GBA* variants in a large cohort of PD patients from Colombia and Peru

Carlos Velez-Pardo[a,*,1], Oswaldo Lorenzo-Betancor[b,c,1], Marlene Jimenez-Del-Rio[a,**], Sonia Moreno[a], Francisco Lopera[a], Mario Cornejo-Olivas[d,f], Luis Torres[e,g], Miguel Inca-Martinez[d], Pilar Mazzetti[d,g], Carlos Cosentino[e,g], Dora Yearout[b,c], Sarah M. Waldherr[b,c], Cyrus P. Zabetian[b,c], Ignacio F. Mata[b,c,h,***]

	Colombia			*Peru*			*Combined*		
	PD	CTRL	OR (95% CI) *p*	PD	CTRL	OR (95% CI) *p*	PD	CTRL	OR (95% CI) *p*
N[a]	131	164		471	155		602	319	
N males (%)	63 (49.2)	82 (50)		258 (54.8)	49 (31.8)		321 (53.6)	131 (41.2)	
AAE, y	64.6 ± 13.4	53.8 ± 14.1		62.1 ± 12.2	54 ± 12.8		62.6 ± 12.5	62.1 ± 12.2	
AAO, y	49.3 ± 16.4	N/A		57.1 ± 13.2	N/A		55.4 ± 14.3	N/A	
Pathogenic Carriers[b] (%)	13 (9.9)	3 (1.8)	5.9 (1.5-23.7) 0.012	20 (4.2)	2 (1.3)	4.1 (0.9-18.6) 0.063	33 (5.5)	5 (1.6)	4.3 (1.6-11.5) 0.004
Pathogenic Carriers + E326K (%)	15 (11.4)	4 (2.4)	6.2 (1.8-21.2) 0.003	23 (4.9)	2 (1.3)	4.5 (1.0-19.9) 0.048	38 (6.3)	6 (1.9)	4.2 (1.7-10.4) 0.002

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Parkinson's Foundation

NEW PROJECTS

Stanley Fahn Junior Faculty Awards | $900,000

High Throughput *in Vivo* Screens for Targeted Parkinson's Disease Gene Therapies
James Dahlman, Ph.D., Georgia Institute of Technology

Parkinson's Genetic Risk Factors in Latino Populations
Ignacio Fernandez Mata, Ph.D., University of Washington

Direct Pathway Striatal Activity in Dyskinesia
Alexandra Nelson, M.D., Ph.D., University of California, San Francisco

June 2016- May 2019

$300,000

Parkinson's Foundation

SPECIFIC AIMS

Aim 1: Identify PD-susceptibility variants in Latinos.
We will genotype almost 2 million variants across the entire genome in 1,500 LARGE-PD participants using the newly designed MEGA chip.
Aim1a: Admixture mapping approach
Aim1b: Conventional GWAs and GWAs combination using a newly developed cross-population empirical Bayes (XPEB) approach.

Aim 2: Sequence known PD causal genes in Latino families.
Aim2a: We will select 20 individuals with a strong family history of PD and sequence all known PD-causal genes using a next-generation sequencing (NGS) panel to identify the variant causing PD in those families.
Aim2b: We will enroll and obtain DNA from additional family members (affected and non-affected) for those families that were identified as not carrying a causal variant in Aim 2a.

This proposal will provide the first large-scale PD genetic study conducted in a Latino population. Completing these aims will improve our understanding of the role of known PD genes in Latinos, as well as identify novel susceptibility variants/genes.

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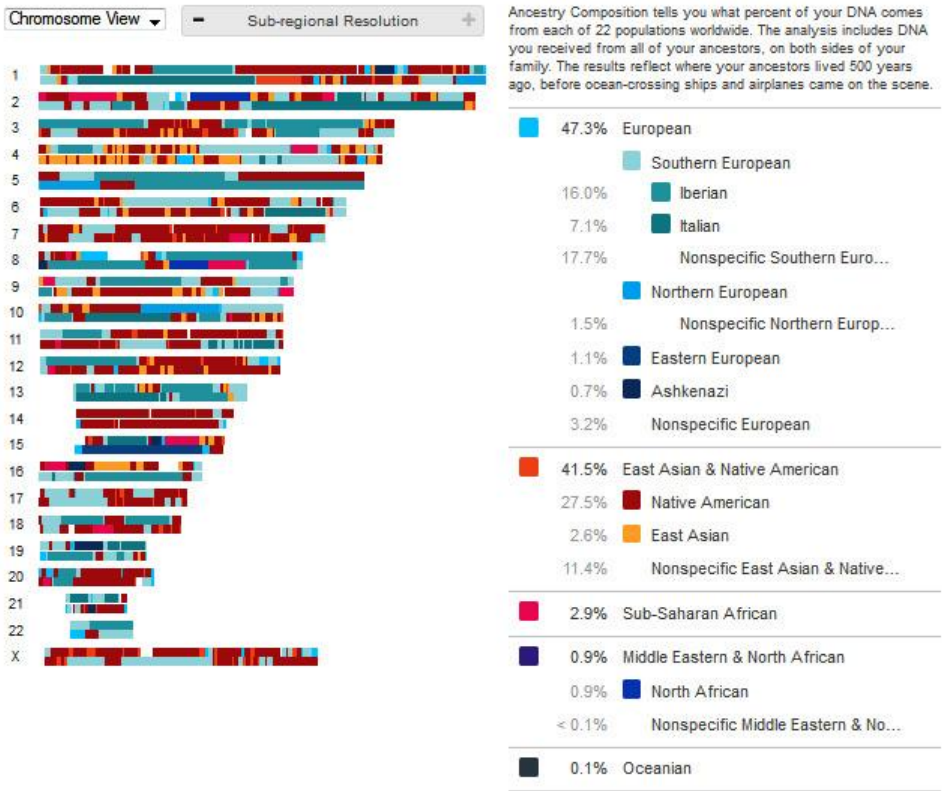
AIM 1: IDENTIFY PD-SUSCEPTIBILITY VARIANTS IN LATINOS

POP	STUDY	African	European	East_Asian	Amerindians
Africa	HapMap3 + HGDP	93.1%	6.6%	0.2%	0.1%
America	HapMap3 + HGDP	1.2%	1.9%	0.6%	96.3%
East_Asia	HapMap3 + HGDP	0.4%	2.3%	96.9%	0.4%
Europe	HapMap3 + HGDP	2.0%	96.3%	0.9%	0.9%
MEX	HapMap3 + HGDP	6.0%	51.8%	1.3%	40.9%
Argentina	LARGE-PD	2.7%	84.1%	0.5%	12.8%
Peru (Puno)	LARGE-PD	0.6%	8.9%	0.4%	90.1%
Peru (Lima)	LARGE-PD	6.1%	25.3%	0.4%	68.1%
Uruguay	LARGE-PD	1.5%	82.7%	4.8%	10.9%
Colombia	LARGE-PD	12.6%	64.7%	0.3%	22.4%
Brazil	LARGE-PD	16.8%	72.9%	2.5%	7.7%

Local Ancestry



A good set of reference panels for each of the ancestral populations is necessary

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AIM 1: IDENTIFY PD-SUSCEPTIBILITY VARIANTS IN LATINOS

1,536 individuals
1,779,819 variants

QC

1,498 individuals
1,294,079 variants

Genotyping rate=0.998493

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Infinium® Multi-Ethnic Global BeadChip

A cost-effective array for understanding complex disease in diverse human populations.

Introduction

The Infinium Multi-Ethnic Global BeadChip harnesses content from Phase 3 of the 1000 Genomes Project (1kGP)[1], Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA), Population Architecture using Genomics and Epidemiology (PAGE), T2D-Genes Consortium, OMIM, ClinVar, ACMG, carrier screening panels, and other resources to create a multipurpose, multiethnic array. With > 1.7 million expertly selected markers, the Infinium Multi-Ethnic Global BeadChip enables identification of genetic associations with common and rare traits, providing insight across diverse populations to epidemiologists, health care researchers, population geneticists, and genomic researchers (Tables 1–5).

Maximized Imputation Accuracy

Consortium partners developed content for the Infinium Multi-Ethnic Global BeadChip using tagging strategies with the power to perform more effective association studies in diverse populations. The novel algorithm selects population-specific and transethnic tag SNPs that maximize imputation accuracy, as imputation has become a standard practice in the interpretation of genotyping data and allows for more accurate statistical inference of genotypes not directly genotyped.

Expert-Selected Content

The Infinium Multi-Ethnic Global BeadChip combines expertly selected markers and content from the most popular Illumina commercial arrays with the most current genomic information. Researchers can detect both common and rare variants across the most commonly studied 5 superpopulations and impute variants in a vast number of subpopulations.

The Infinium Multi-Ethnic Global BeadChip contains the following content:

- Infinium HumanCore-24 BeadChip content with highly informative genome-wide tag SNPs
- African Diaspora Consortium Power Chip content identified through sequencing of 692 individuals by CAAPA
- Genome-wide coverage for diverse populations selected by PAGE

Table 1: Multi-Ethnic Global BeadChip Product Information

Feature	Description	
Total No. of Markers	1,779,819	
Capacity for Custom Bead Types	245,000	
No. Samples per BeadChip	8	
DNA Input Requirement	200 ng	
Assay Chemistry	Infinium LCG	
Instrument Support	iScan® or HiScan® System	
Sample Throughput[a]	~ 1067 samples/week	
Scan Time per Sample	iScan System 11.3 min	HiScan System 6.5 min
Data Performance	**Value[b]**	**Product Specification**
Call Rate	99.87%	> 99% avg.
Reproducibility	99.99%	> 99.9%
Log R Deviation	0.10	< 0.30
Spacing	**Mean**	**Median** **90th %[c]**
Spacing (kb)	1.68	0.78 4.22

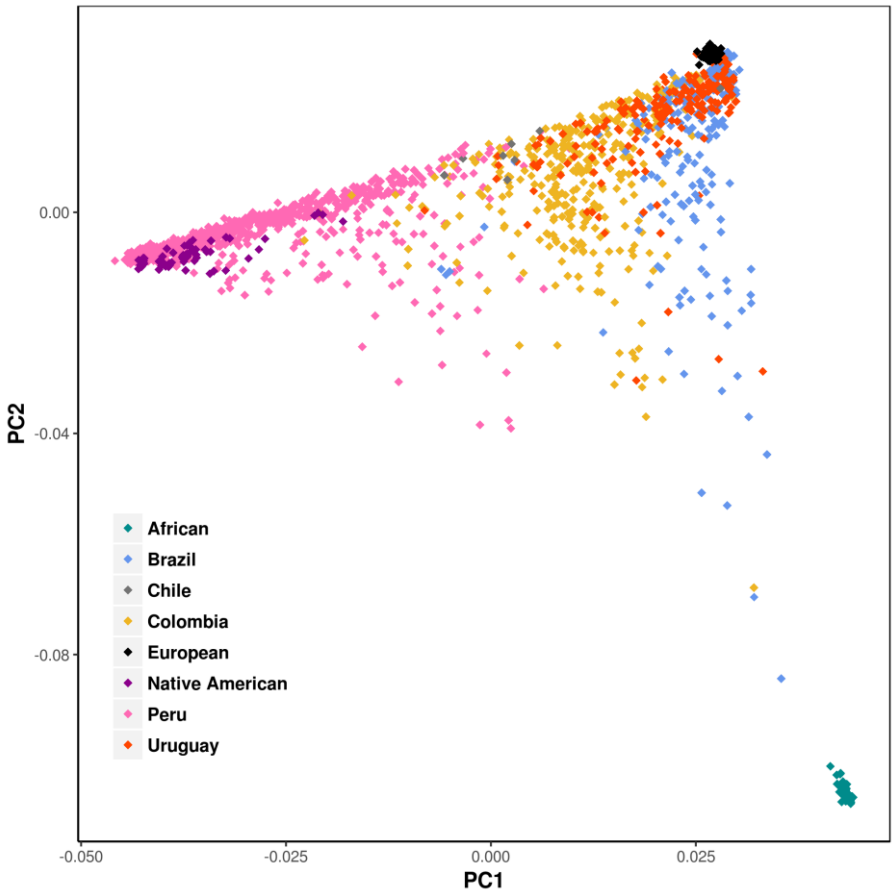
a. Estimated sample throughput based on use of 1 HiScan System, 1 AutoLoader 2.x, 1 Tecan robot, and a 5-day work week.
b. Values are derived from genotyping 708 HapMap reference samples.
c. Values are expected for typical projects using standard Illumina protocols. Tumor samples and samples prepared by methods other than standard Illumina protocols are excluded.

Table 2: Imputation Accuracy for 5 Populations from 1kGP at Different MAF Thresholds

	Minor Allele Frequency (MAF) Threshold		
Population[a]	0.5–1%	1–5%	≥ 5%
AFR	78.1%	89.5%	95.8%
AMR	82.7%	90.2%	96.9%
EAS	57.4%	82.4%	96.1%
EUR	70.3%	87.9%	97.2%
SAS	61.6%	84.8%	96.4%

a. AFR: African; AMR: Ad-mixed American; EAS: East Asian; EUR: European; SAS: South Asian.[1]

AIM 1: IDENTIFY PD-SUSCEPTIBILITY VARIANTS IN LATINOS



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NEXT-GENERATION SEQUENCING OF PARKINSON'S GENES IN UNDERSTUDIED LATIN AMERICAN POPULATIONS

Sept 2017- Aug 2018

$50,000

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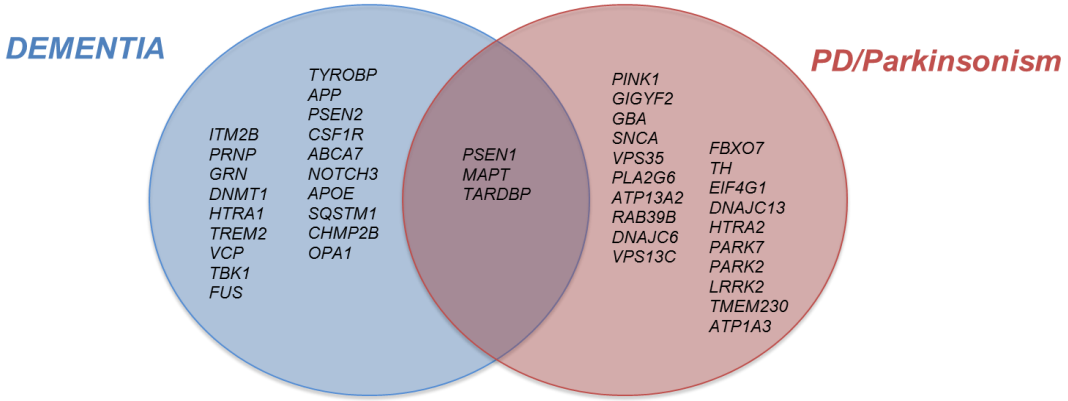
Figure. Genes included in the NGS panel



Goal: 300 individuals with family history

To date: We have done 164 PD patients with family history
(~25% have mutations in known PD genes)

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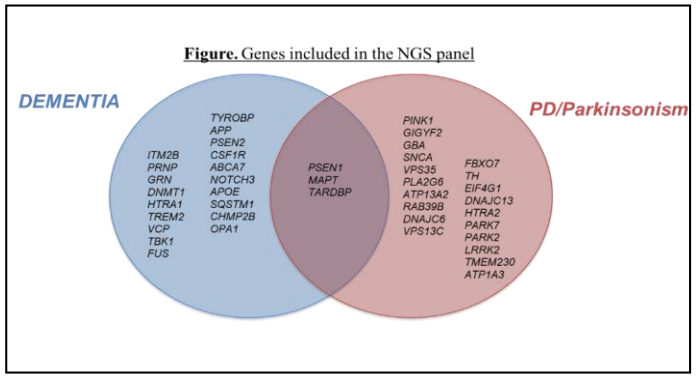
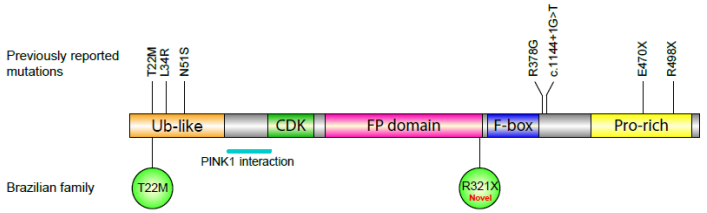
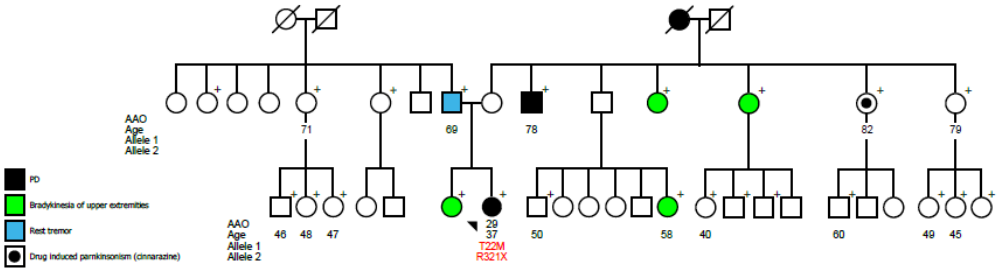
NEXT-GENERATION SEQUENCING OF PARKINSON'S GENES IN UNDERSTUDIED LATIN AMERICAN POPULATIONS

Family proband	SEX	AAO	AGE	# PD samples	PD genes sequencing panel
Lima					
PPP0132	F	44	46	2	None
PPP0148	F	61	64	NA	None
PPP0156	M	40	48	2	None
PPP0704	F	29	49	3	*PARK2* p.Q165E heterozygote (novel)*
PPP0709	F	24	36	3	***PINK1* p.L532delinsLQ homozygote**
PPP0714	F	62	73	2	*PARK7* p.A56T heterozygote. ***African MAF = 0.01506*** *VPS35* p.K382R heterozygote. ***African MAF = 0.01641***
PPP0715	M	37	40	2	None
PPP0732	M	19	29	4	None
PPP0757	F	51	71	2	None
Ribeirão Preto					
RPP0870	M	66	71	4	None
RPP2761[$]	M	22	29	4	None
RPP3275	M	30	36	3	*LRRK2* p.T1410M heterozygote. ***African MAF = 0.02085***
RPP3728	M	30	42	3	*PARK7* c.252+2insA heterozygote*
RPP4534	M	54	62	5	None
RPP5573[$]	F	32	41	3	None
RPP9213	F	29	34	3	***FBXO7* p.T22M + p.R321X (novel)**
Buenos Aires					
ARP0115	F	68	75	5	**ATP13A2 p.V89I homozygote**
ARP0159[$]	F	50	67	4	None
ARP0100[$]	F	78	82	3	*LRRK2* p.R1514Q heterozygote (not pathogenic)
ARP0143	M	61	63	4	None







Sept 2017- August 2018

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INCIDENCE OF PD IN LATINAMERICA

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Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity

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TABLE 3. Age-specific and age-adjusted annual incidence rate* of Parkinson's disease by gender and race/ethnicity, Kaiser Permanente, 1994–1995

Race/ethnicity and age (years)	Female					Male					Male: female ratio	Total		
	Cases (no.)	Person-years	Age-specific rate	Age-adjusted rate†	95% CI‡	Cases (no.)	Person-years	Age-specific rate	Age-adjusted rate†	95% CI		Age-specific rate	Age- and gender-adjusted rate§	95% CI
Non-Hispanic White														
30–39	2	248,177	0.81			0	246,535	0.00				0.40		
40–49	4	274,203	1.46			8	266,945	3.00			2.1	2.22		
50–59	15	210,674	7.12			21	194,732	10.78			1.5	8.88		
60–69	46	154,803	29.72			75	141,661	52.94			1.8	40.81		
70–79	88	108,293	81.26			131	91,473	143.21			1.8	109.63		
≥80	28	42,647	65.66			56	27,940	200.43			3.1	119.00		
Total	183	1,038,797		9.9	7.4, 12.3	291	969,286		19.5	16.5, 22.5	2.0		13.6	11.5, 15.7
Black														
30–39	0	38,881	0.00			0	28,271	0.00				0.00		
40–49	0	39,778	0.00			1	28,720	3.48				1.46		
50–59	2	23,321	8.58			3	22,707	13.21			1.5	10.86		
60–69	3	13,845	21.67			3	14,406	20.82			1.0	21.24		
70–79	5	8,217	60.85			5	6,366	78.54			1.3	68.57		
≥80	2	2,747	72.81			4	1,830	218.58			3.0	131.09		
Total	12	126,789		8.1	3.9, 12.3	16	102,300		14.0	8.7, 19.2	1.7		10.2	6.4, 14.0
Asian														
30–39	0	55,424	0.00			0	45,404	0.00				0.00		
40–49	1	59,291	1.69			3	45,534	6.59			3.9	3.82		
50–59	6	31,381	19.12			1	29,091	3.44			0.2	11.58		
60–69	3	22,199	13.51			4	17,434	22.94			1.7	17.66		
70–79	5	7,381	67.74			9	8,162	110.27			1.6	90.07		
≥80	2	1,322	151.29			1	1,852	54.00			0.4	94.52		
Total	17	176,998		11.1	6.2, 16.0	18	147,477		10.8	6.3, 15.4	1.0		11.3	7.2, 15.3
Hispanic/Latino														
30–39	0	64,808	0.00			1	57,539	1.74				0.82		
40–49	2	47,257	4.23			1	40,355	2.48			0.6	3.42		
50–59	2	23,482	8.52			5	21,837	22.90			2.7	15.45		
60–69	8	15,665	51.07			12	15,287	78.50			1.5	64.62		
70–79	4	5,772	69.30			10	5,297	188.79			2.7	126.48		
≥80	1	1,147	87.18			1	897	111.48			1.3	97.85		
Total	17	158,131		11.9	6.8, 17.1	30	141,212		23.0	16.8, 29.2	1.9		16.6	12.0, 21.3

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INCIDENCE OF PD IN LATIN AMERICA

Elison Sarapura, MD

Nominated From: University of Washington

Research Site: Peru

Research Area: Neurology

Primary Mentor: Ignacio Mata

RESEARCH PROJECT

Environmental and genetic factors of Parkinson's disease in a rural village in Peru: a population based study

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity or tremor together with a variety of non-motor symptoms.(1) Etiology of PD is multifactorial, and the majority of PD cases comprise susceptibility genetic variants that are influenced by environmental factors that determine its clinical heterogeneity. (2) Mutations in eight causal genes; SNCA, PARK2, PINK1, DJ-1, LRRK2, VPS35, DNAJCJ13 and RAB39B; and over 30 susceptibility genes and loci are widely associated with the etiology of PD. The exposure to toxic environmental agents such as pesticides, solvents and heavy metals, have been traditionally associated with PD. However, there is limited evidence in systematic studies, due probably to the heterogeneity of the studies. (3) There are very few studies about the association between

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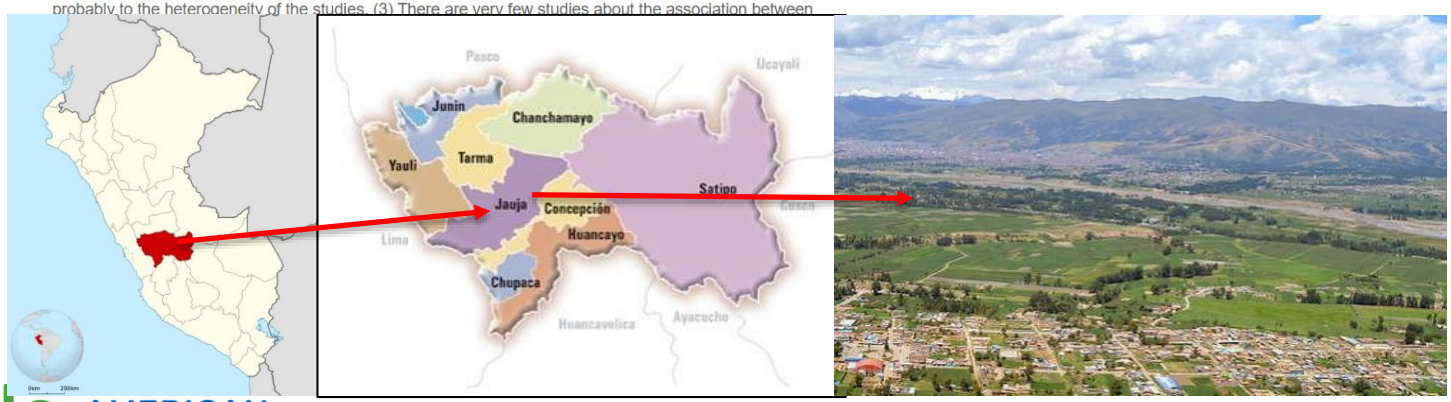

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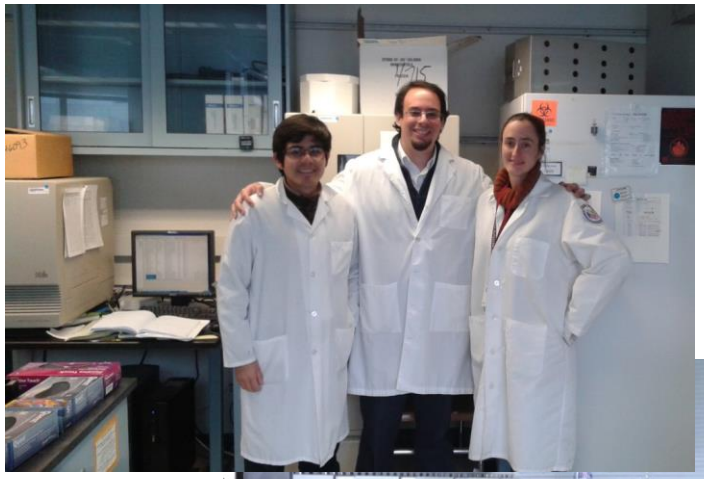
MENTORING AND TRAINING FELLOWS



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MENTORING AND TRAINING SCIENTIST IN THEIR OWN COUNTRIES

Genetic epidemiology in neurodegenerative disorders International workshop

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SUPPORT THE COMMUNITIES

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Cell, Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

The Huntington's Disease Collaborative Research Group*

Introduction

Huntington's disease (HD) is a progressive neurodegener-

1/10 (vs 1/10,000)

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World Report

Left by the lakeside

Two decades ago, researchers flocked to a small fishing community on the shores of Venezuela's Lake Maracaibo to study the villagers' susceptibility to early-onset Huntington's disease. The scientists are now gone but, says Mike Ceaser, the residents of Lake Maracaibo are no better off.

Huntington's disease: the new gene therapy that sufferers cannot afford

Efforts to treat Huntington's disease involve costly drugs way beyond the reach of the poor communities in South America who take part in research studies

▲ Ferdinand, 42, lost his job last year. His father having died early, neither Ferdinand or his wife knew the disease was in the family. Photograph: Nick Garcia for the Observer

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