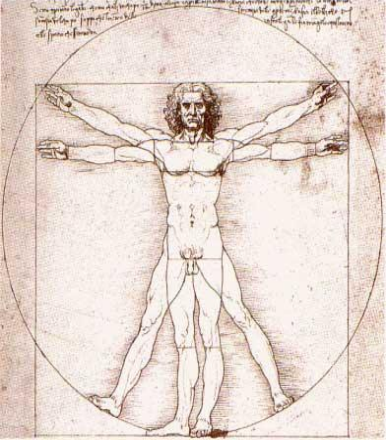
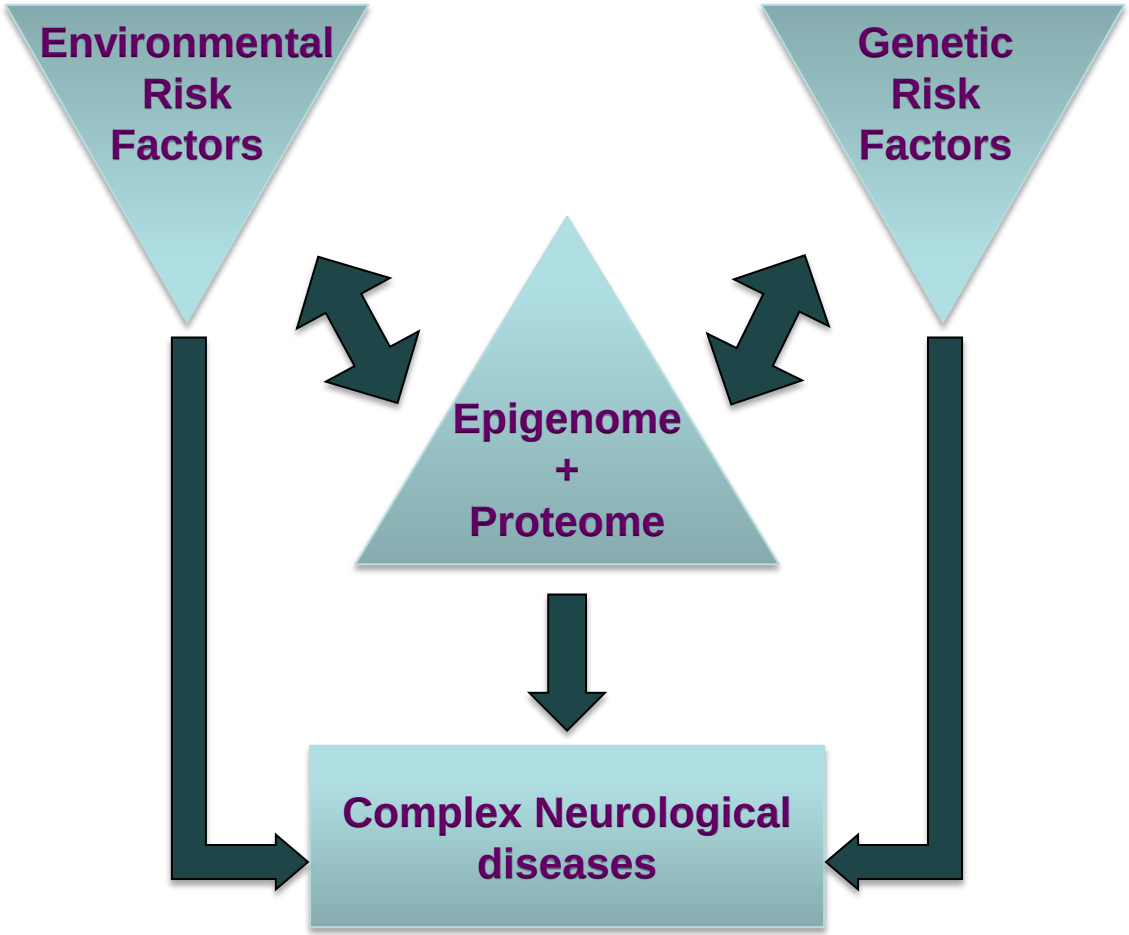
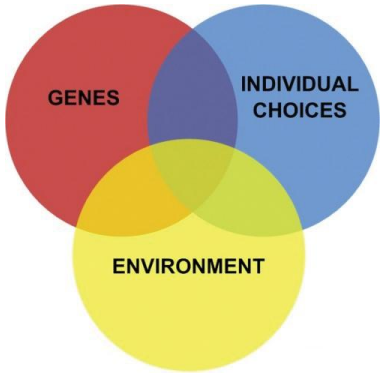
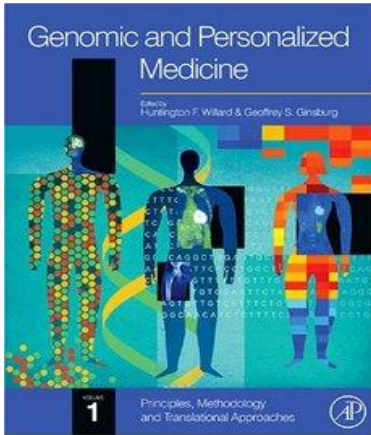
Antoni Matilla Dueñas
Director Unidad Básica, Traslacional y Neurogenética Molecular en Neurociencias y Coordinador Red Iberoamericana RIBERMOV
Editor Genética Revista “The Cerebellum”
Instituto de Investigación Germans Trias y Pujol (IGTP)
Universitat Autònoma de Barcelona
Badalona (Barcelona)



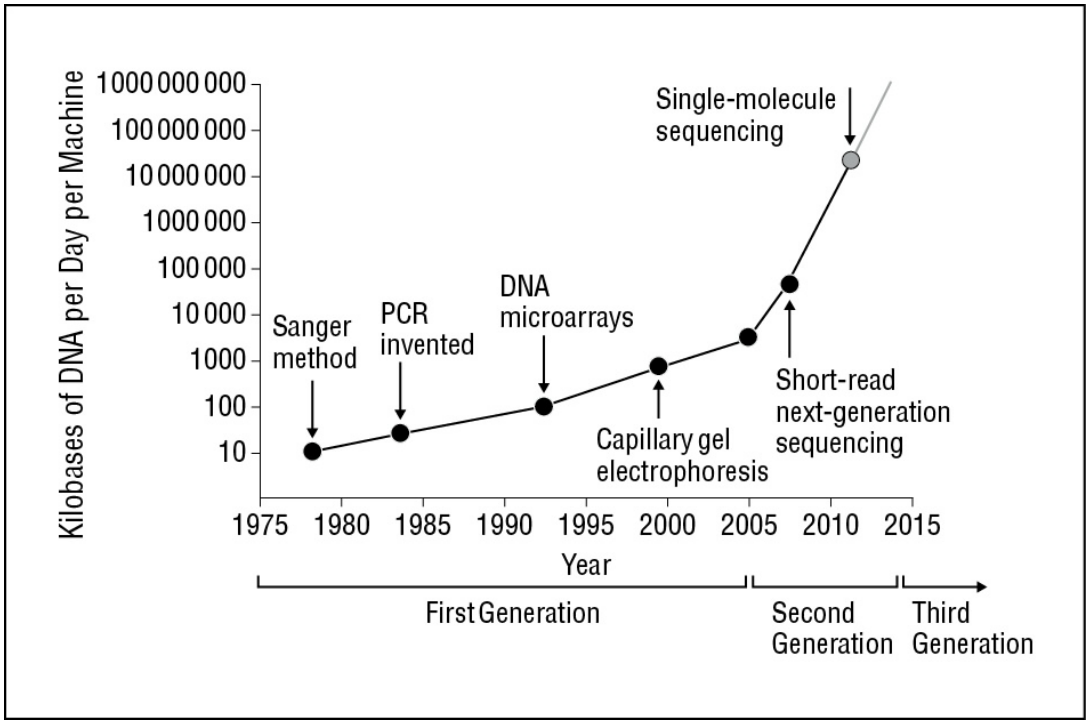

DYS 390 24
DYS 391 11
DYS 392 13
DYS 393 13
DYS 426 12
DYS 438 12
DYS 439 12


Environmental Risk Factors
Genetic Risk Factors
Epigenome + Proteome
Complex Neurological diseases


GENES
INDIVIDUAL CHOICES
ENVIRONMENT


Genomic and Personalized Medicine
Huntington F. Willard & Geoffrey S. Ginsburg
1
Principles, Methodology and Translational Approaches

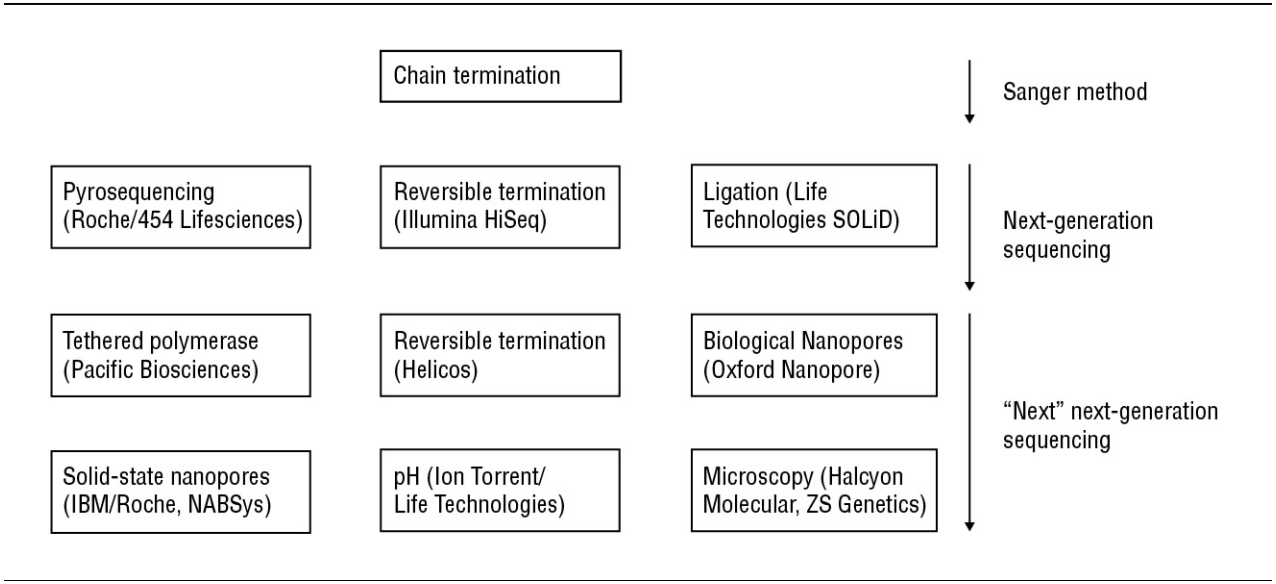
Genetic Analysis in Neurology: The Next 10 Years.



Genetic Analysis in Neurology: The Next 10 Years.
Pittman, Alan; Hardy, John

JAMA Neurology. 70(6):696-702, June 2013.
DOI: 10.1001/jamaneurol.2013.2068

Genetic Analysis in Neurology: The Next 10 Years.



Genetic Analysis in Neurology: The Next 10 Years.
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DOI: 10.1001/jamaneurol.2013.2068

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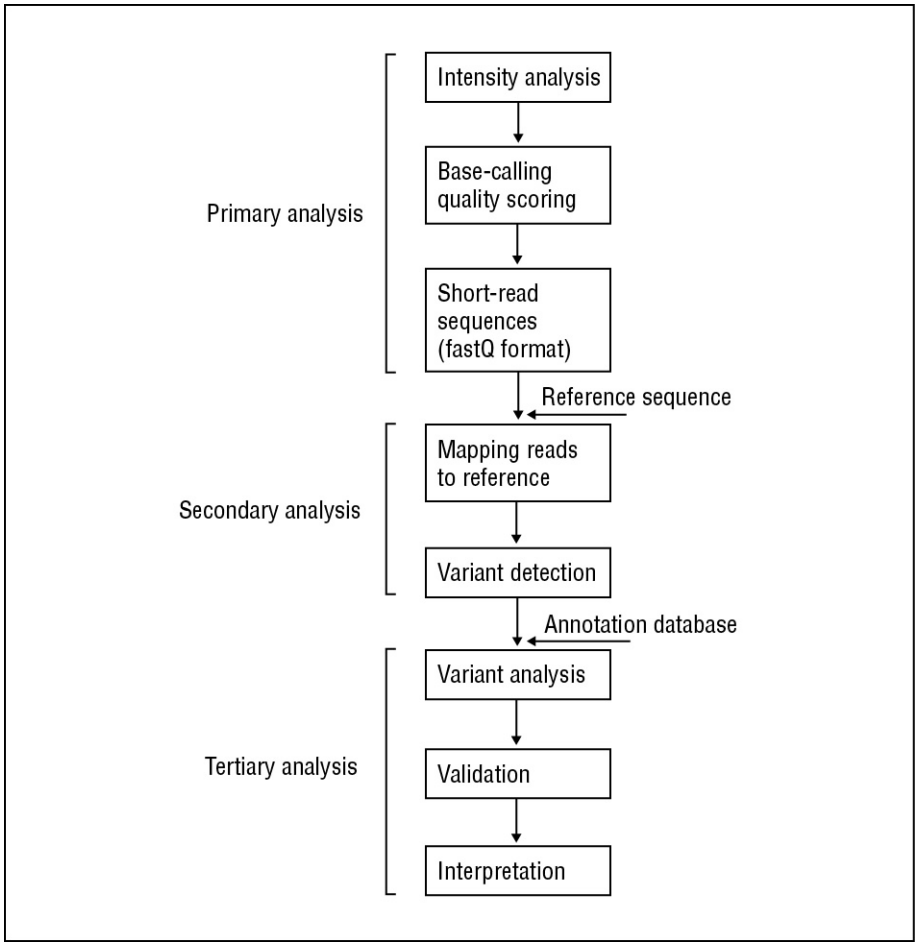
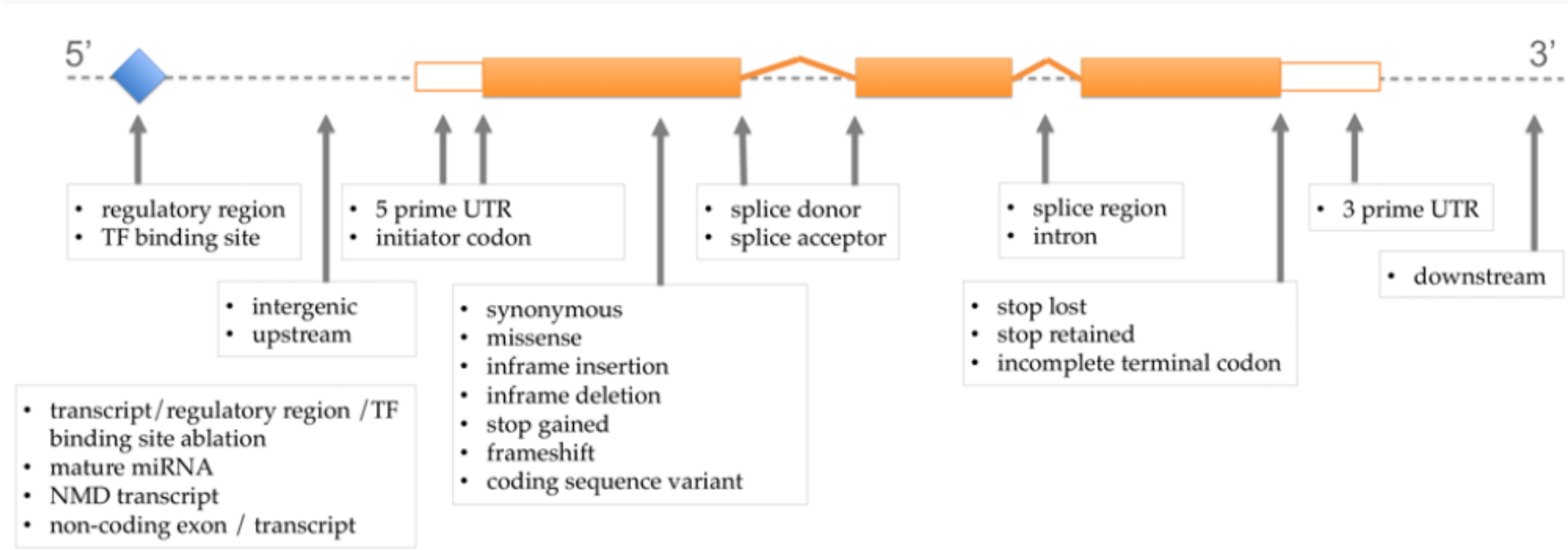


Genetic Analysis in Neurology: The Next 10 Years.
Pittman, Alan; Hardy, John

JAMA Neurology. 70(6):696-702, June 2013.
DOI: 10.1001/jamaneurol.2013.2068



Variant classification according to their consequence or position on transcripts. The set of consequence terms, defined by the Sequence Ontology (http://www.sequenceontology.org/)

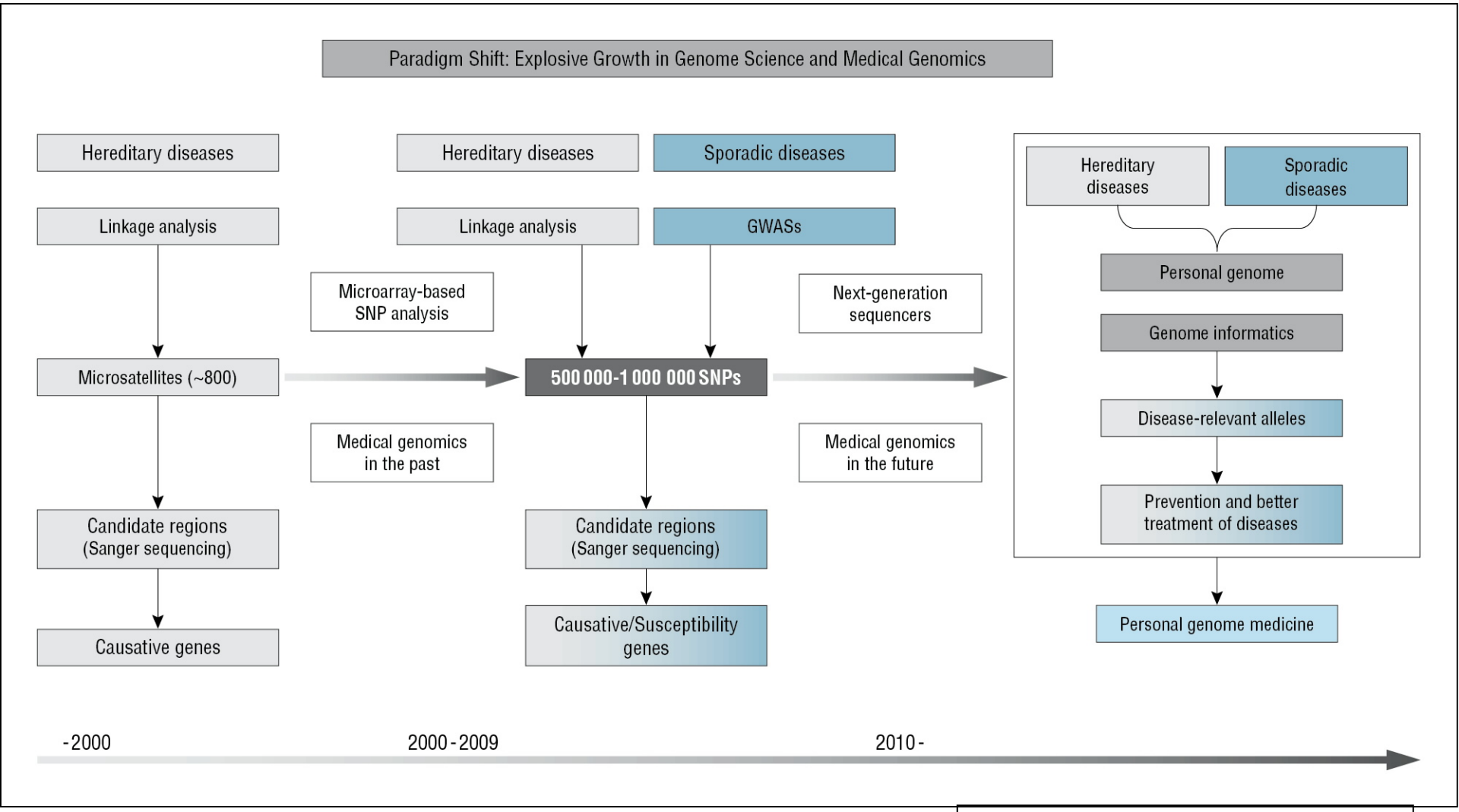
Read alignment statistics are summarized in **Table 2.**

Sample	Total reads	Mapped reads	Percentage of mapped reads	Reads after low quality reads removal	Percentage of reads after low quality reads removal	Reads after duplicate removal	Percentage of reads after duplicate removal
EX71e2013000034	191567802	189651946	99.00	188073624	98.18	132380366	88.78

Table 2. Alignment quality metrics. Sample – sample name; Total reads – total number of generated reads; % mapped reads - percentage of mapped reads; % reads after duplicate removal – percentage of reads that remain after removing read duplicates.

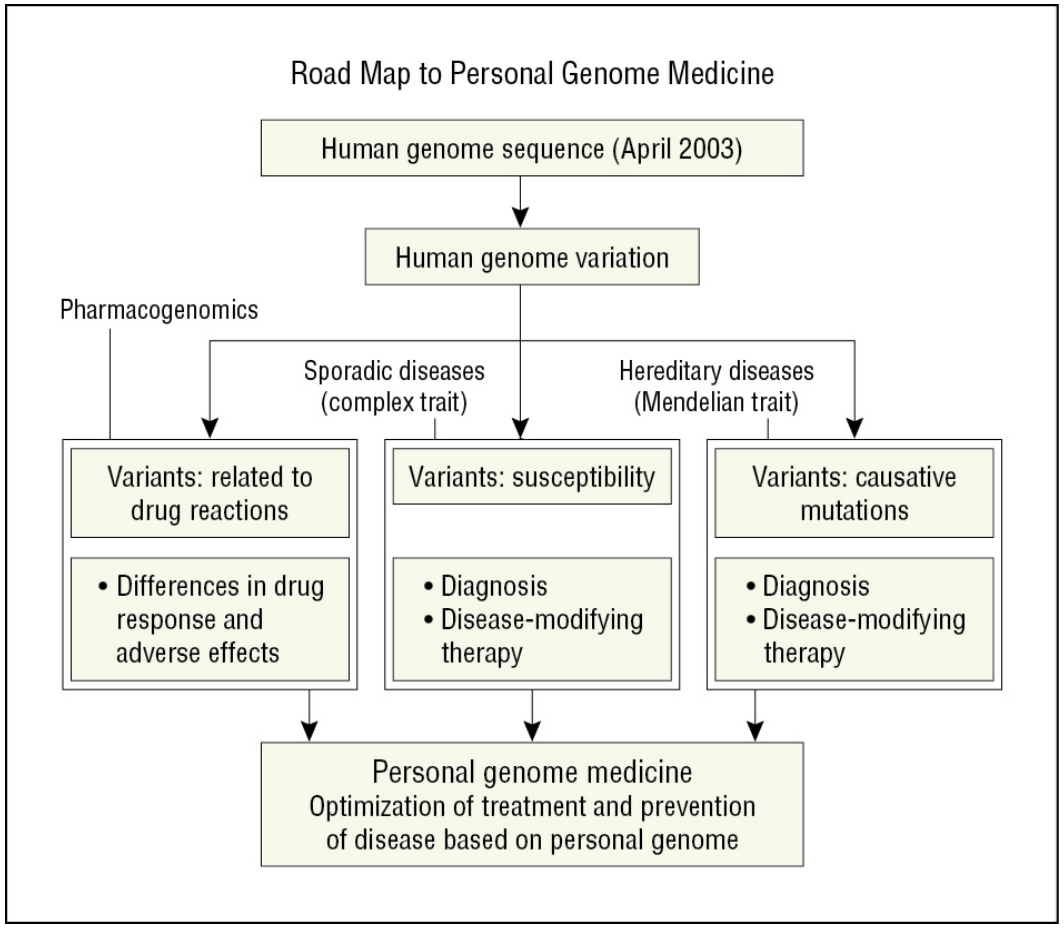
Experiment	Samples	Number of candidate genes	
		Dominant model	Recessive model
Experiment_1	EX71-S1469-1	1814	1396

Table 4. Candidate genes for each experiment and inheritance mode



The Neurogenomics View of Neurological Diseases.
Tsuji, Shoji; MD, PhD

JAMA Neurology. 70(6):689-694, June 2013.
DOI: 10.1001/jamaneurol.2013.734



The Neurogenomics View of Neurological Diseases.
Tsuji, Shoji; MD, PhD

JAMA Neurology. 70(6):689-694, June 2013.
DOI: 10.1001/jamaneurol.2013.734

Genes & Disease

OMIM, 27 Septiembre 2013

OMIM Entry Statistics:

Number of Entries in OMIM (Updated 27 September 2013) :

Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
* Gene description	13,624	664	48	35	14,371
+ Gene and phenotype, combined	112	4	0	2	118
# Phenotype description, molecular basis known	3,597	278	4	28	3,907
% Phenotype description or locus, molecular basis unknown	1,596	132	5	0	1,733
Other, mainly phenotypes with suspected mendelian basis	1,755	119	2	0	1,876
Totals	20,684	1,197	59	65	22,005

Table 1. Mendelian Genes for Parkinson Disease

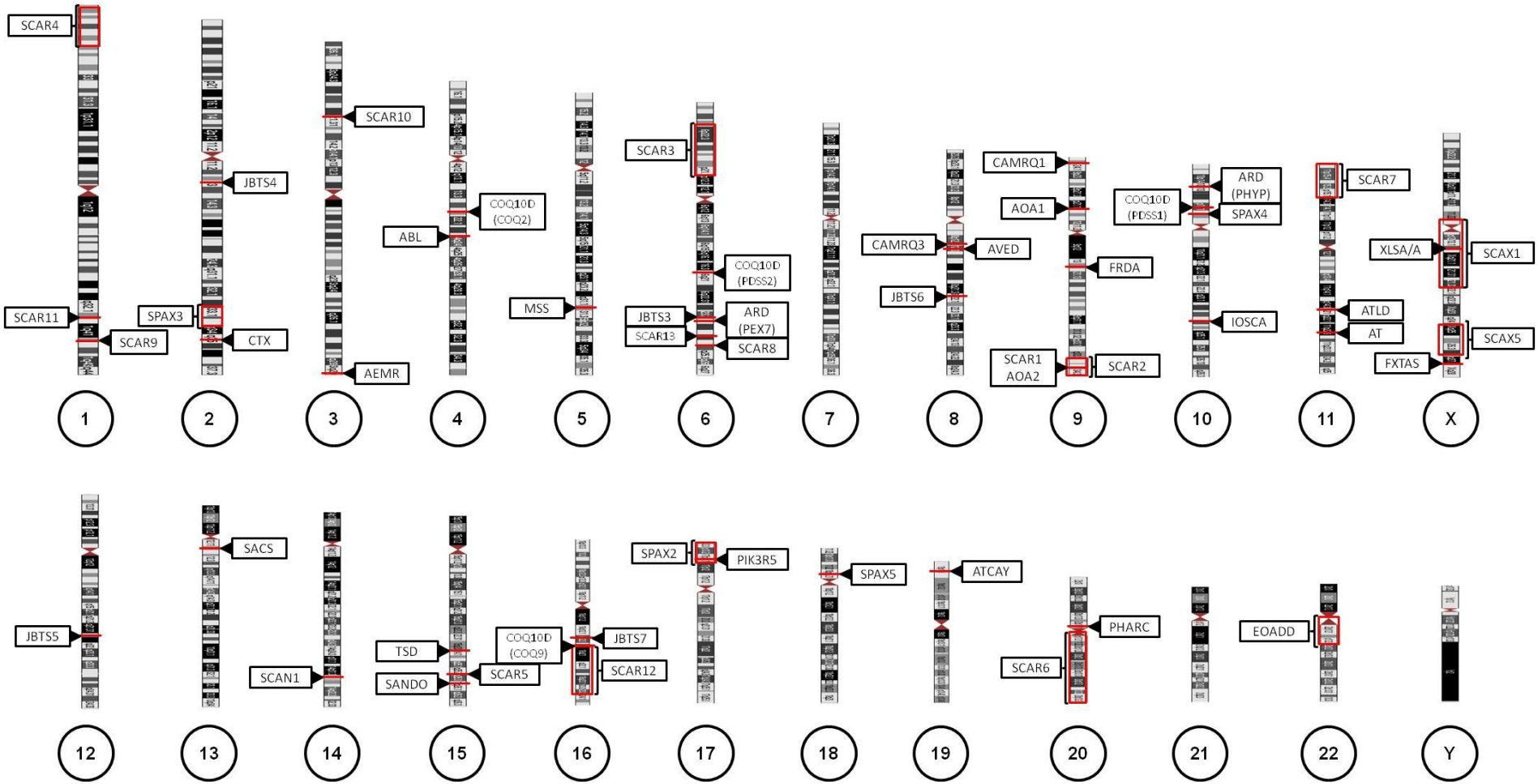
Gene	Location	Protein	Inheritance	Source
LRRRK	12q12	Leucine-rich repeat kinase 2	Dominant	Zimprich et al,[12] Paisán-Ruíz et al[13]
PARK2	6q26	Parkin	Recessive	Kitada et al[14]
PARK7	1p36.23	Protein DJ-1-like	Recessive	Bonifati et al[15]
PINK1	1p36.12	PTEN induced putative kinase 1	Recessive	Valente et al[16]
SNCA	4q22.1	Synuclein, alpha	Dominant	Polymeropoulos et al,[17] Singleton et al[18]
VPS35	16q12	Vacuolar protein sorting 35 homologue	Dominant	Zimprich et al,[19] Vilariño-Güell et al[20]
EIF4G1	3q27.1	Eukaryotic translation initiation factor 4 gamma, 1	Dominant	Chartier-Harlin et al[21]

Table 2. Common Risk Loci for Parkinson Disease

Gene/Locus	Location	Protein	Marker	Odds Ratio (95% CI)
ACMSD/TMEM163	2q21.3	Unknown	rs6710823	1.40 (1.20-1.63)
BST1	4p15.32	Bone marrow stromal cell antigen 1	rs11724635	1.40 (1.20-1.63)
CCDC62/HIP1R	12q24.31	Unknown	rs12817488	1.17 (1.09-1.25)
FAM47E/STBD1	4q21.1	Unknown	rs6812193	1.12 (1.09-1.25)
GAK/DGKQ	4p16.3	Unknown	rs1564282	1.29 (1.20-1.38)
GBA	1q22	Glucosidase, beta, acid	N370S	3.51 (2.55-4.83)
GPNMB	7p15.3	Glucoprotein (transmembrane) nmb	rs156429	1.12 (1.08-1.16)
GWA_8p22/F GF20	8p22	Unknown	rs591323	1.12 (1.08-1.17)
HLA II	6p21.32	Major histocompatibility complex, class II	HLA locus	1.33 (1.19-1.48)
LRRK2	12q12	Leucine-rich repeat kinase 2	rs1491942	1.17 (1.13-1.22)
MAPT	17q21.31	Microtubule-associated protein tau	17q21.31	1.29 (1.25-1.33)
MCCC1/LAMP3	3q27.1	Unknown	3q27.1	1.18 (1.13-1.24)
PARK16	1q32.1	Unknown	1q32.1	1.26 (1.18-1.34)
SETD1A/STX1B	16p11.2	Unknown	16p11.2	1.14 (1.09-1.19)
SNCA	4q22.1	Synuclein, alpha	4q22.1	1.30 (1.26-1.35)
SREBF1/RAI1y	17q11.2	Unknown	17p11.2	1.18 (1.11-1.25)
STK39	2q24.3	Serine threonine kinase 39	2q24.3	1.28 (1.19-1.38)
SYT11/RAB25	1q22	Unknown	1q22	1.67 (1.41-1.98)

Las ataxias espinocerebelosas

Las ataxias espinocerebelosas son genéticamente heterogéneas



Las ataxias espinocerebelosas

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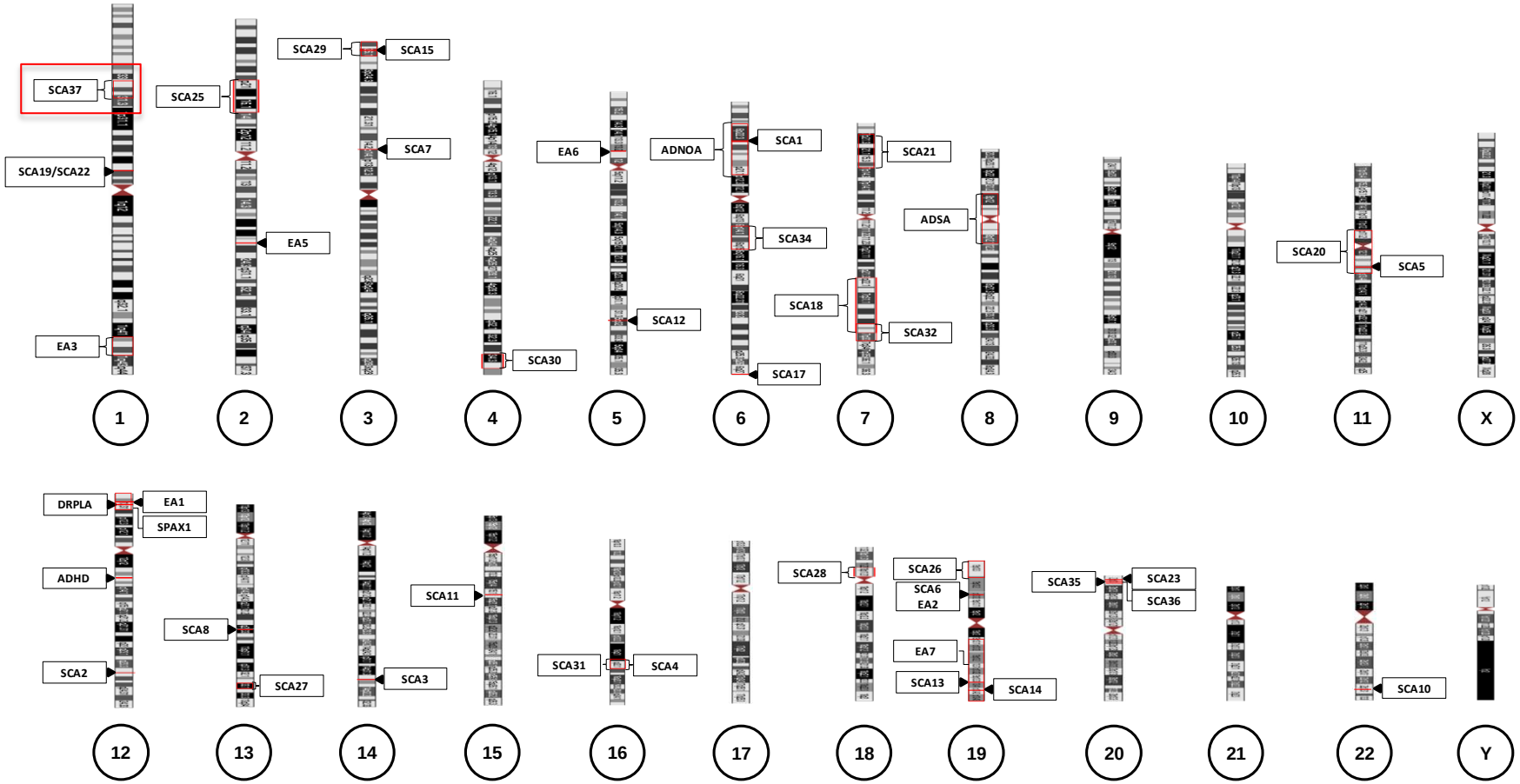


A Matilla-Dueñas. The ever expanding spinocerebellar ataxias. Editorial. Cerebellum 11 (4), 821-827 (2012)

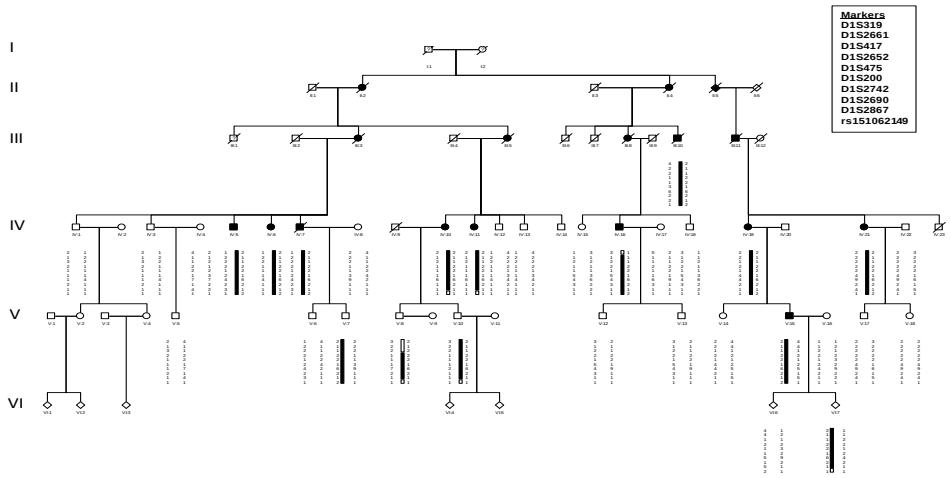
JAMA Neurology

ORIGINAL CONTRIBUTION

ONLINE FIRST

New Subtype of Spinocerebellar Ataxia With Altered Vertical Eye Movements Mapping to Chromosome 1p32

Carmen Serrano-Munuera, MD; Marc Corral-Juan, BSc; Giovanni Stevanin, PhD; Hector San Nicolás, BSc; Carles Roig, MD, PhD; Jordi Corral, BSc; Berta Campos, PhD; Laura de Jorge, BSc; Carlos Morcillo-Suárez, PhD; Arcadi Navarro, PhD; Sylvie Forlani, MD, PhD; Alexandra Durr, MD, PhD; Jaime Kulisevsky, MD, PhD; Alexis Brice, MD, PhD; Ivelisse Sánchez, PhD; Victor Volpini, MD, PhD; Antoni Matilla-Dueñas, PhD



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Science News ... from

New Subtype of Ataxia Identified

Apr. 29, 2013 — Researchers from the Germans Trias i Pujol Health Sciences Research Institute Foundation (IGTP), the Bellvitge Biomedical Research Institute (IDIBELL), and the Sant Joan de Déu de Martorell Hospital, has identified a new subtype of ataxia, a rare disease without treatment that causes atrophy in the cerebellum and affects around 1.5 million people in the world.

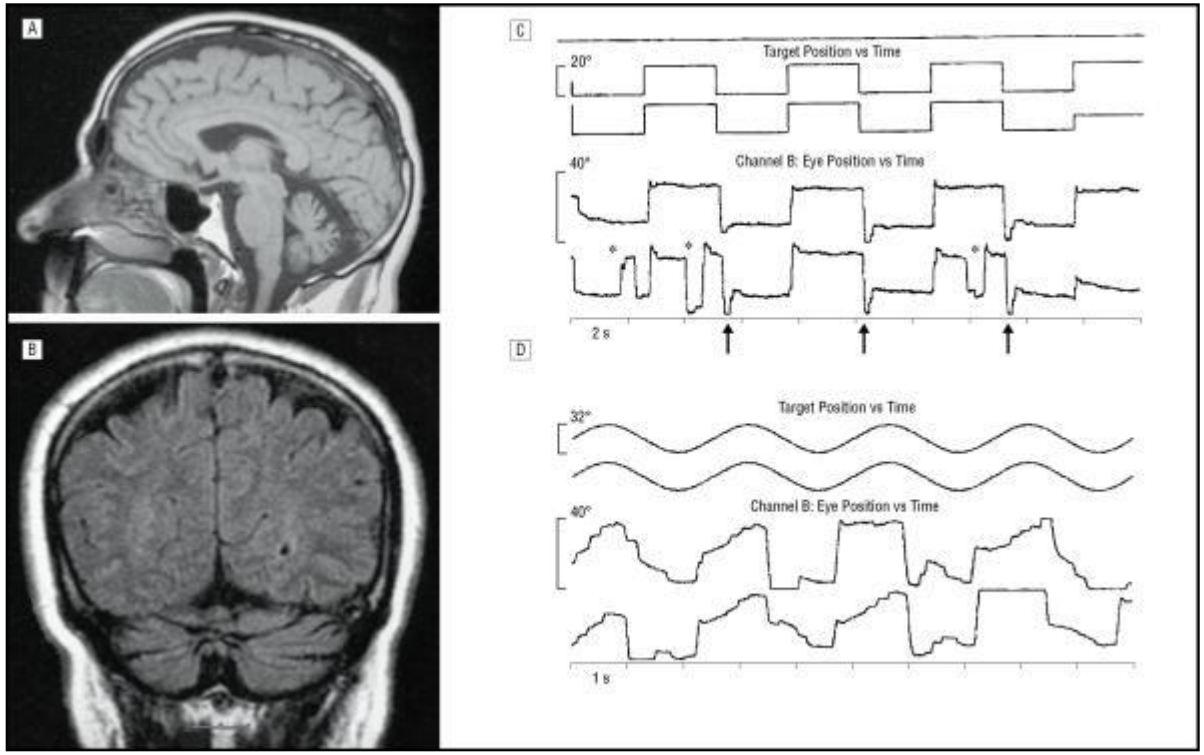


Figure 2. A and B, Sagittal and coronal T1-weighted magnetic resonance imaging scans of the brain of patient IV:5. The eye movements during vertical fixed saccades (C) (20[degrees] amplitude; top line, upward saccades; bottom line, downward saccades [arrows]) and smooth pursuit (D) (0.4 Hz; 16[degrees] amplitude; and peak velocity, 40[degrees]/s) are shown for patient IV:6. The asterisks indicate saccadic intrusions.

New Subtype of Spinocerebellar Ataxia With Altered Vertical Eye Movements Mapping to Chromosome 1p32.

Serrano-Munuera, Carmen; Corral-Juan, Marc; Stevanin, Giovanni; San Nicolas, Hector; Roig, Carles; MD, PhD; Corral, Jordi; Campos, Berta; de Jorge, Laura; Morcillo-Suarez, Carlos; Navarro, Arcadi; Forlani, Sylvie; MD, PhD; Durr, Alexandra; MD, PhD; Kulisevsky, Jaime; MD, PhD; Brice, Alexis; MD, PhD; Sanchez, Ivelisse; Volpini, Victor; MD, PhD; Matilla-Duenas, Antoni

JAMA Neurology. 70(6):764-771, June 2013.
DOI: 10.1001/jamaneurol.2013.2311

sistemas genómicos

Ataxias Sindrómicas y No Sindrómicas

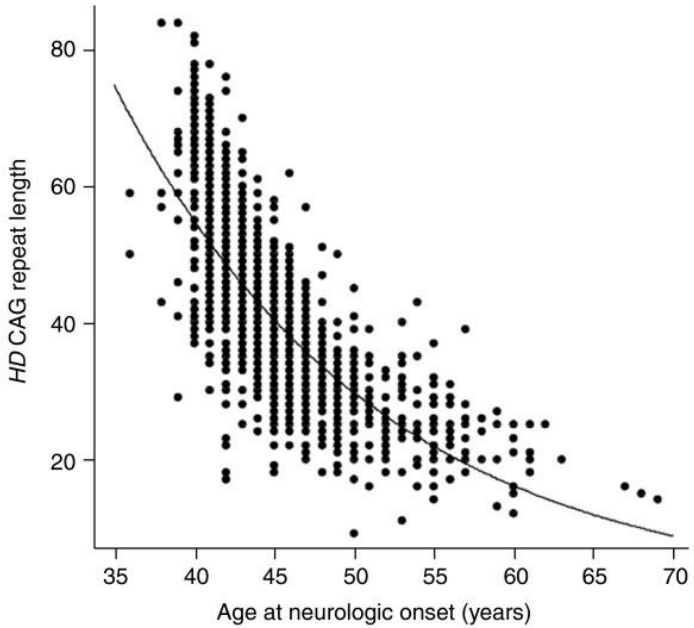
Ataxias no sindrómicas	Secuenciación masiva panel de **30 genes**: ADCK3, AFG3L2, ANO10, APTX, BEAN, CACNA1A, CACNB4, FGF14, FXN, IFRD1, ITPR1, KCNA1, KCNC3, MTP, MTPAP, PDYN, PIK3R5, PLEKHG4, PRKCG, SACS, SETX, SLC1A3, SPTBN2, SYNE1, SYT14, TDP1, TGM6, TTBK2, TTPA, ZNF592
Ataxias Sindrómicas	Secuenciación masiva panel de **55 genes**: ABCB7, ABHD12, ADCK3, ALS2, ANG, ATCAY, ATM, ATR, CA8, CEP290, C10orf2, COQ2, COQ9, CYP27A1, DNAJC19, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, FIG4, FLVCR1, FMR1, FUS, GJC2, GPR56, HSPD1, ITM2B, KCNJ10, KIAA0226, MRE11A, NPHP1, OPA1, PAX6, PC, PDHA1, PDSS1, PDSS2, PEX7, PHYH, PLP, POLG, POLR3A, PRNP, PRPS1, RPGRIP1L, SCN8A, SETX, SIL1, SLC9A6, SOD1, TARDBP, TMEM67, VAPB, VLDLR

sistemas genómicos

Enfermedad de Parkinson

Parkinson, Enfermedad, tipos 1, 4, 5, 8, 11, 13, 17, 18, autosómica dominante	Secuenciación masiva panel de **7 genes**: EIF4G1, GIGYF2, HTRA2, LRRK2, SNCA, UCHL1, VPS35
Parkinson, enfermedad, tipos 2, 6, 7, 9, 14, 15, autosómica recesiva, de inicio temprano	Secuenciación masiva panel de **6 genes**: ATP13A2, FBXO7, PARK2, PARK7, PINK1, PLA2G6

Parkinson asociado a demencia frontotemporal, Enfermedad de Pick y parálisis supranuclear progresivay Demencia con cuerpos de Lewy	Secuenciación masiva panel de **2 genes**: MAPT, SNCB
Parkinson, Enfermedad sindrómica y no sindrómica	Secuenciación masiva panel de **23 genes**: ADH1C, ATP13A2, ATP1A3, DCTN1, EIF4G1, FBXO7, GBA, GCH1, GIGYF2, HTRA2, LRRK2, MAPT, PARK2, PARK7, PDXK, PINK1, PLA2G6, POLG1, SNCA, SNCAIP, SNCB, UCHL1, VPS35

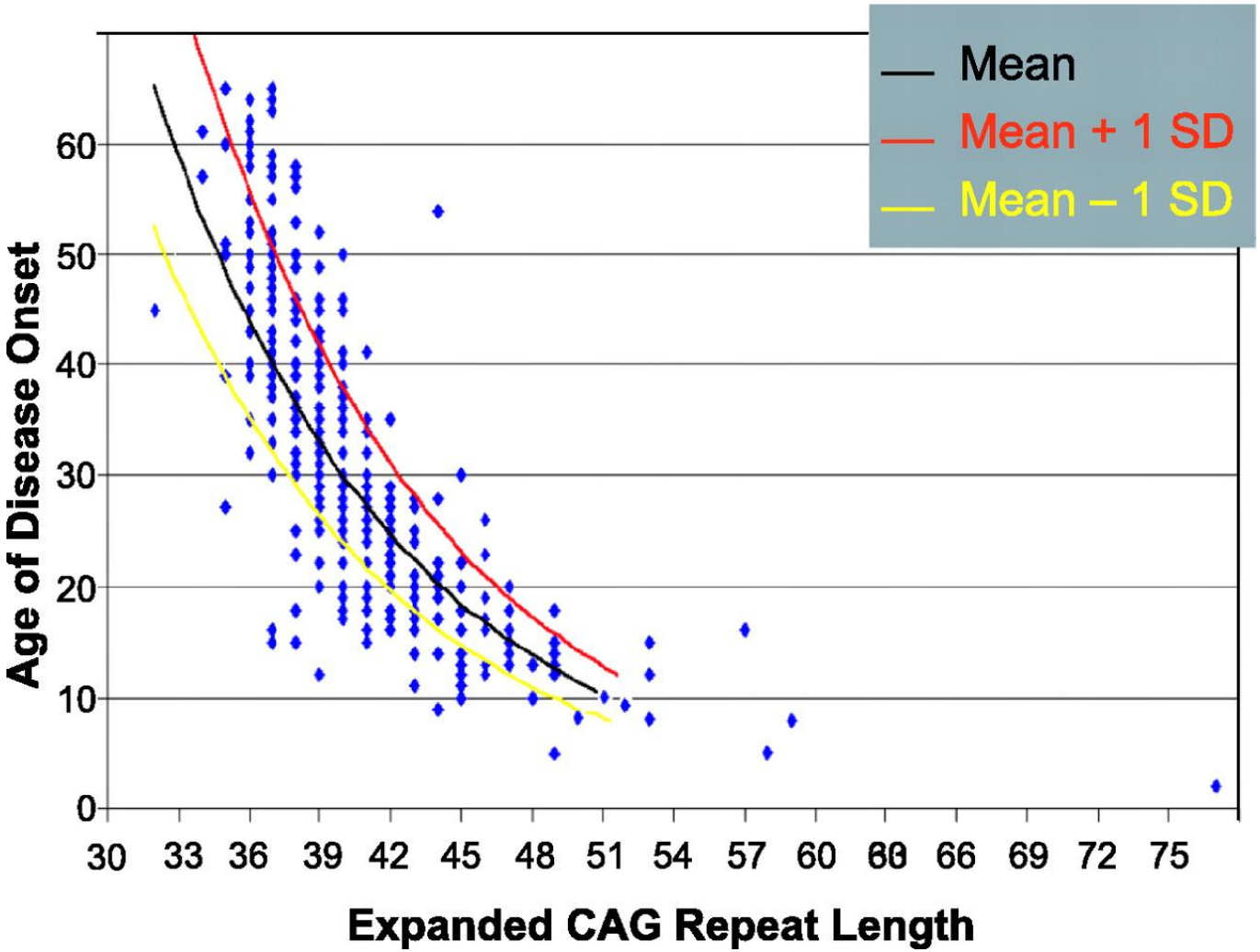


	SCA1*	SCA2	SCA3	HD
AO/expanded	60.6% (p<0.0001)	64% (p= 0.0002)	60.5% (p<0.0001)	63.4% ($p<2x10^{-16}$)
AO/expanded + normal	66.4% (p<0.003)	65% (p=0.1300)	-	63.8% ($p<2x10^{-16}$)*
AO/expanded + normal + gender	78.5% (p<0.0001)	-	61.1% (p<0.0001)	-

AO: Edad de inicio

*Matilla-Dueñas, ..., Volpini. Hum Mol Gen 1993.

Scatterplot of SCA2 CAG repeat length and age of onset in Cuban SCA2 patients; red and yellow lines denote one standard deviation boundaries for age of onset.



Pulst S et al. Brain 2005;128:2297-2303

BRAIN A JOURNAL OF NEUROLOGY

Brain. 2005 Oct;128(Pt 10):2297-303. Epub 2005 Jul 6.

Spinocerebellar ataxia type 2: polyQ repeat variation in the CACNA1A calcium channel modifies age of onset.

Pulst SM, Santos N, Wang D, Yang H, Huynh D, Velazquez L, Figueroa KP.

Division of Neurology, Department of Medicine and Rose Moss Laboratory for Parkinson and Related Diseases, Burns and Allen Research Institute, Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90048, USA. Pulst@CSHS.org

Table 3

Analysis of allele and genotype distribution

Gene	Disease	Mann–Whitney significance level	
		For largest allele	For genotype
Ataxin-1	SCA1	$P = 0.0846$	$P = 0.0891$
Ataxin-3	SCA3	$P = 0.2309$	$P = 0.2043$
CACNA1A	SCA6	$P = 0.0050$	$P = 0.0029$
Ataxin-7	SCA7	$P = 0.9420$	$P = 0.9543$
TBP	SCA17	$P = 0.6567$	$P = 0.6478$
Atrophin-1	DRPLA	$P = 0.1136$	$P = 0.1215$
AR	SBMA	$P = 0.6241$	$P = 0.6202$
Huntingtin	HD	$P = 0.8490$	$P = 0.9216$

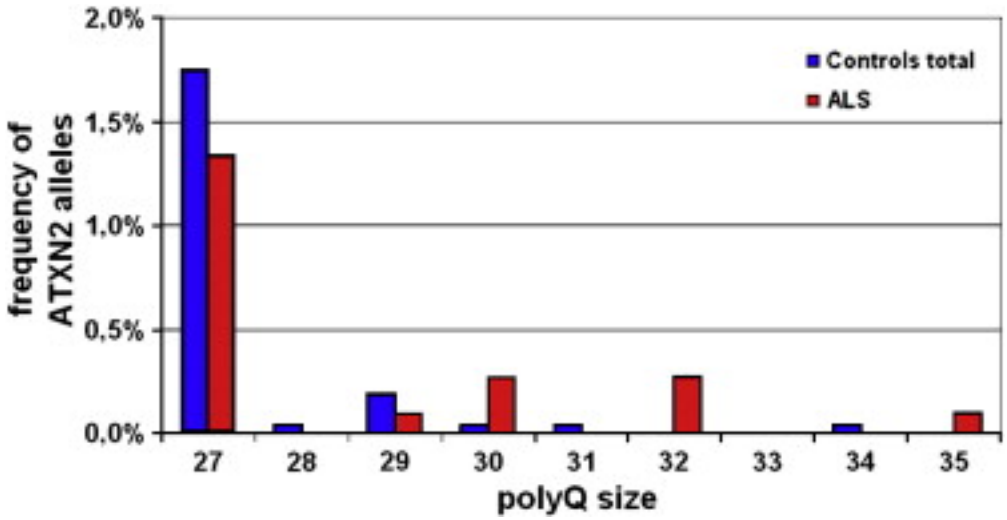
AR, androgen receptor; DRPLA, dentatorubral-pallidoluysian atrophy; SBMA, spinobulbar muscular atrophy. HD, Huntington disease.

Neurobiol Dis. 2012 Jan;45(1):356-61. Epub 2011 Aug 25.

The modulation of Amyotrophic Lateral Sclerosis risk by ataxin-2 intermediate polyglutamine expansions is a specific effect.

Gispert S, Kurz A, Waibel S, Bauer P, Liepelt I, Geisen C, Gitler AD, Becker T, Weber M, Berg D, Andersen PM, Krüger R, Riess O, Ludolph AC, Auburger G.

Experimental Neurology, Goethe University Medical School, Theodor Stern Kai 7, 60590 Frankfurt am Main, Germany.



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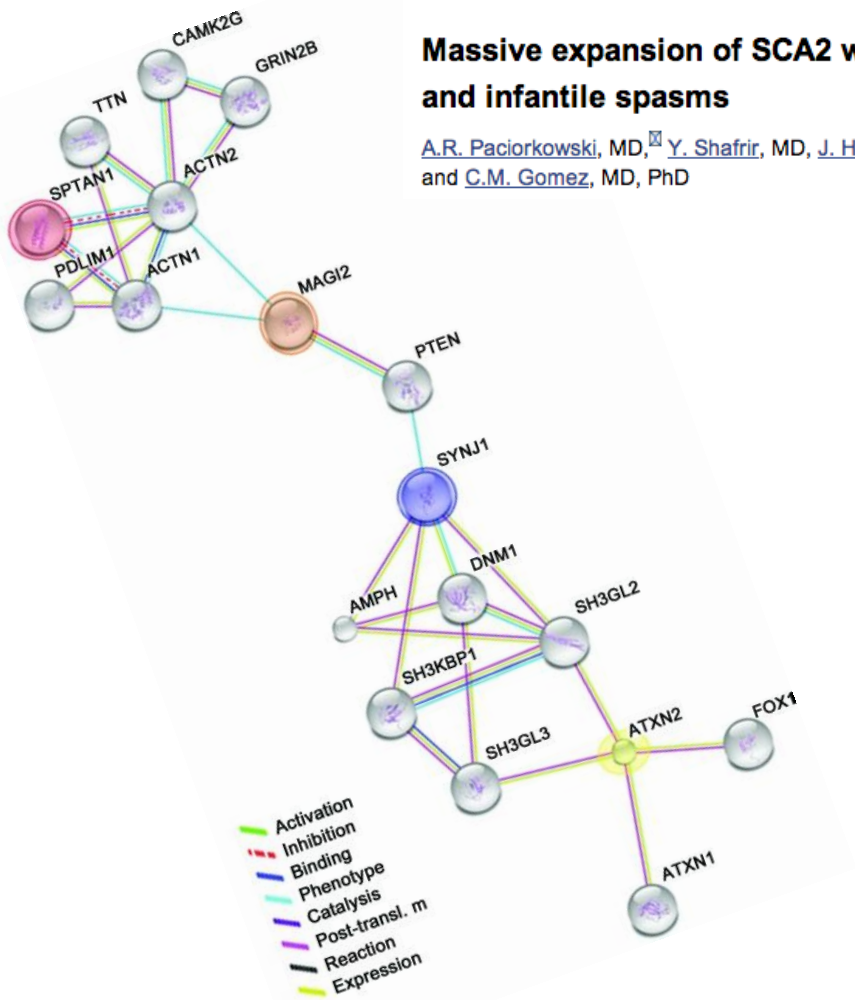
Neurology. 2011 September 13; 77(11): 1055–1060.
doi: 10.1212/WNL.0b013e31822e5627
PMCID: PMC3174070

Massive expansion of SCA2 with autonomic dysfunction, retinitis pigmentosa, and infantile spasms

A.R. Paciorkowski, MD,[✉] Y. Shafrir, MD, J. Hrivnak, MD, M.C. Patterson, MD, M.B. Tennison, MD, H.B. Clark, MD, PhD, and C.M. Gomez, MD, PhD



ORIGINAL CONTRIBUTION

The *APOE* ε2 Allele Increases the Risk of Earlier Age at Onset in Machado-Joseph Disease

Conceição Bettencourt, PhD; Mafalda Raposo, BSc; Nadiya Kazachkova, PhD; Teresa Cymbron, PhD; Cristina Santos, PhD; Teresa Kay, MD; João Vasconcelos, MD; Patrícia Maciel, PhD; Karina C. Donis; Maria Luiza Saraiva-Pereira, PhD; Laura B. Jardim, PhD; Jorge Sequeiros, MD, PhD; Manuela Lima, PhD

Arch Neurol. 2011;68(12):1580-1583

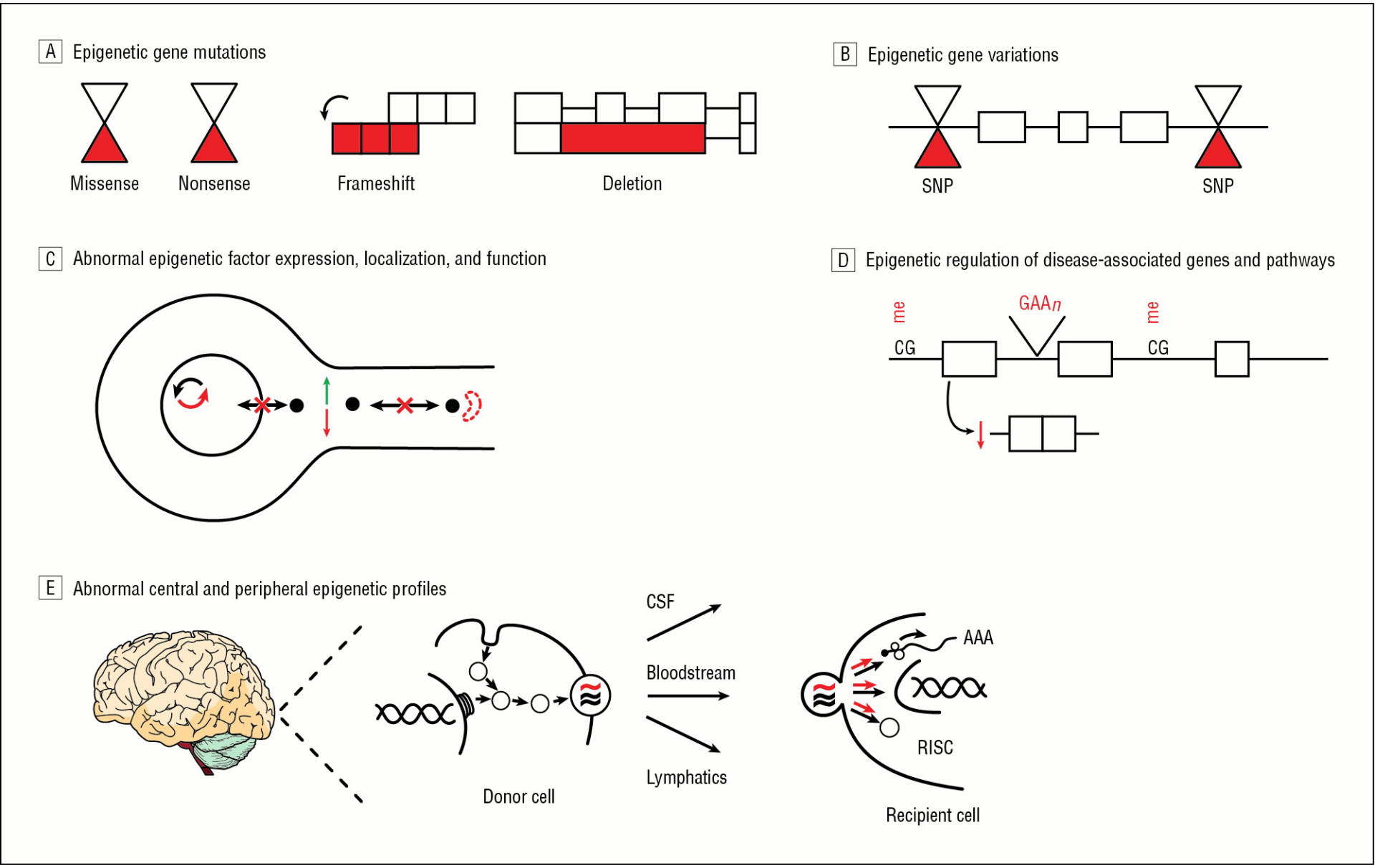
Table 1. Principal Epigenetic Mechanisms and Factors

Epigenetic Mechanism	Epigenetic Factors
DNA (de)methylation and hydroxymethylation	DNA methyltransferase enzymes
	Methyl-CpG-binding domain proteins
	DNA excision repair enzymes
	Cytidine deaminase enzymes
	Gadd45 proteins
	Ten-Eleven Translocation enzymes
Histone and chromatin modifications	Histone-modifying (histone [de]acetylase and [de]methylase) enzymes
	SWI/SNF nucleosome remodeling complexes
	Polycomb group proteins
	Trithorax group proteins
	RE1-silencing transcription factor
	CoREST
Noncoding RNAs	MicroRNAs
	Small nucleolar RNAs
	Endogenous short-interfering RNAs
	PIWI-interacting RNAs
	Long noncoding RNAs
RNA editing	Adenosine deaminases that act on RNA enzymes
	Apolipoprotein B editing catalytic subunit enzymes

Abbreviations: CoREST, corepressor for element-1–silencing transcription factor; RE1, repressor for element-1.

Understanding Neurological Disease Mechanisms in the Era of Epigenetics.
Qureshi, Irfan; Mehler, Mark

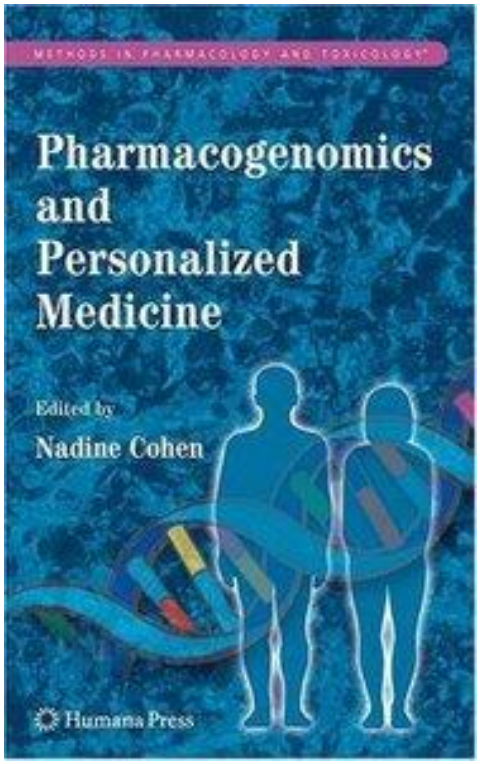
JAMA Neurology. 70(6):703-710, June 2013.
DOI: 10.1001/jamaneurol.2013.1443



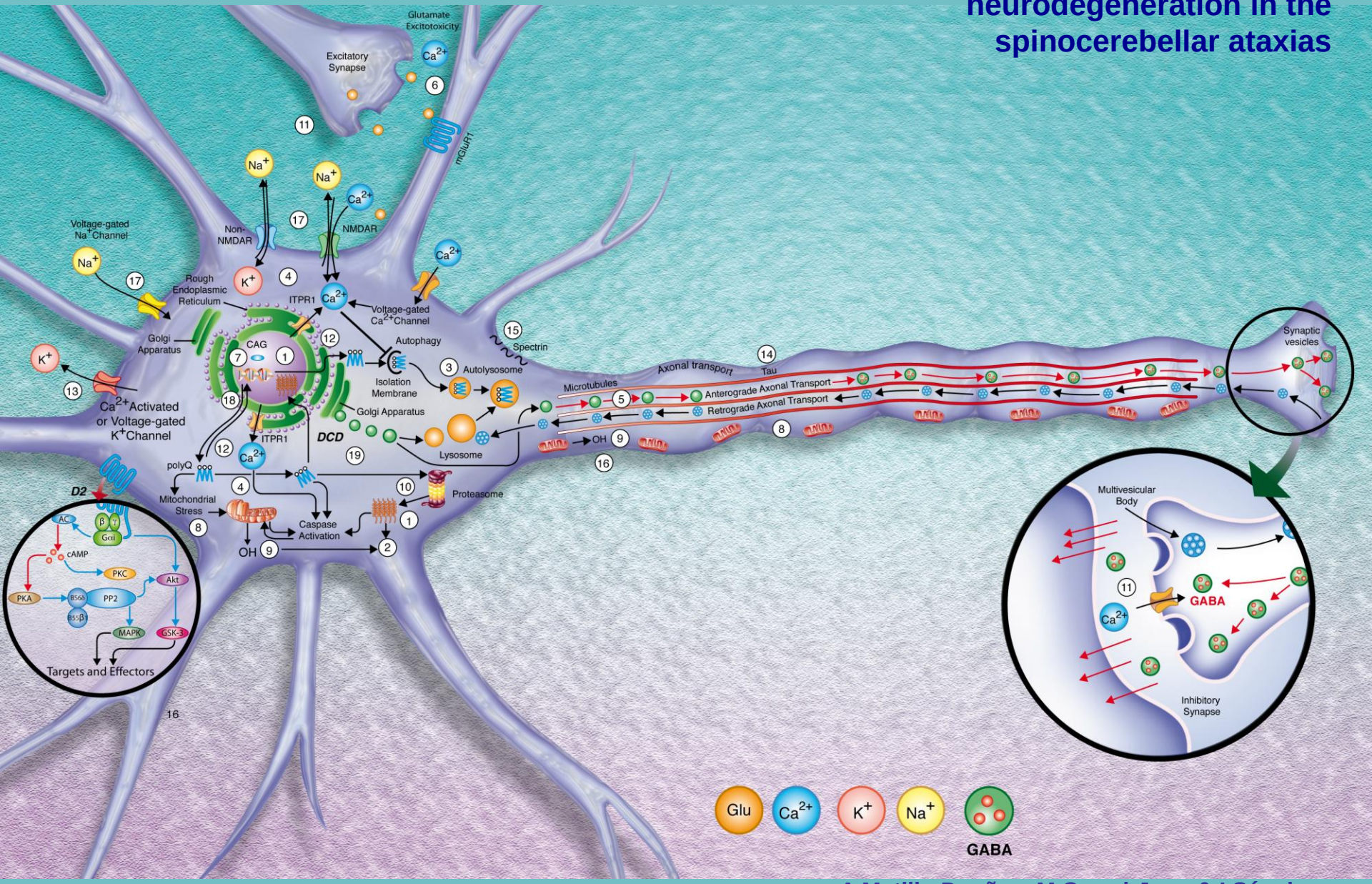
JAMA Neurology. 70(6):703-710, June 2013.
DOI: 10.1001/jamaneurol.2013.1443

Farmacogenética

Fármacos a la carta



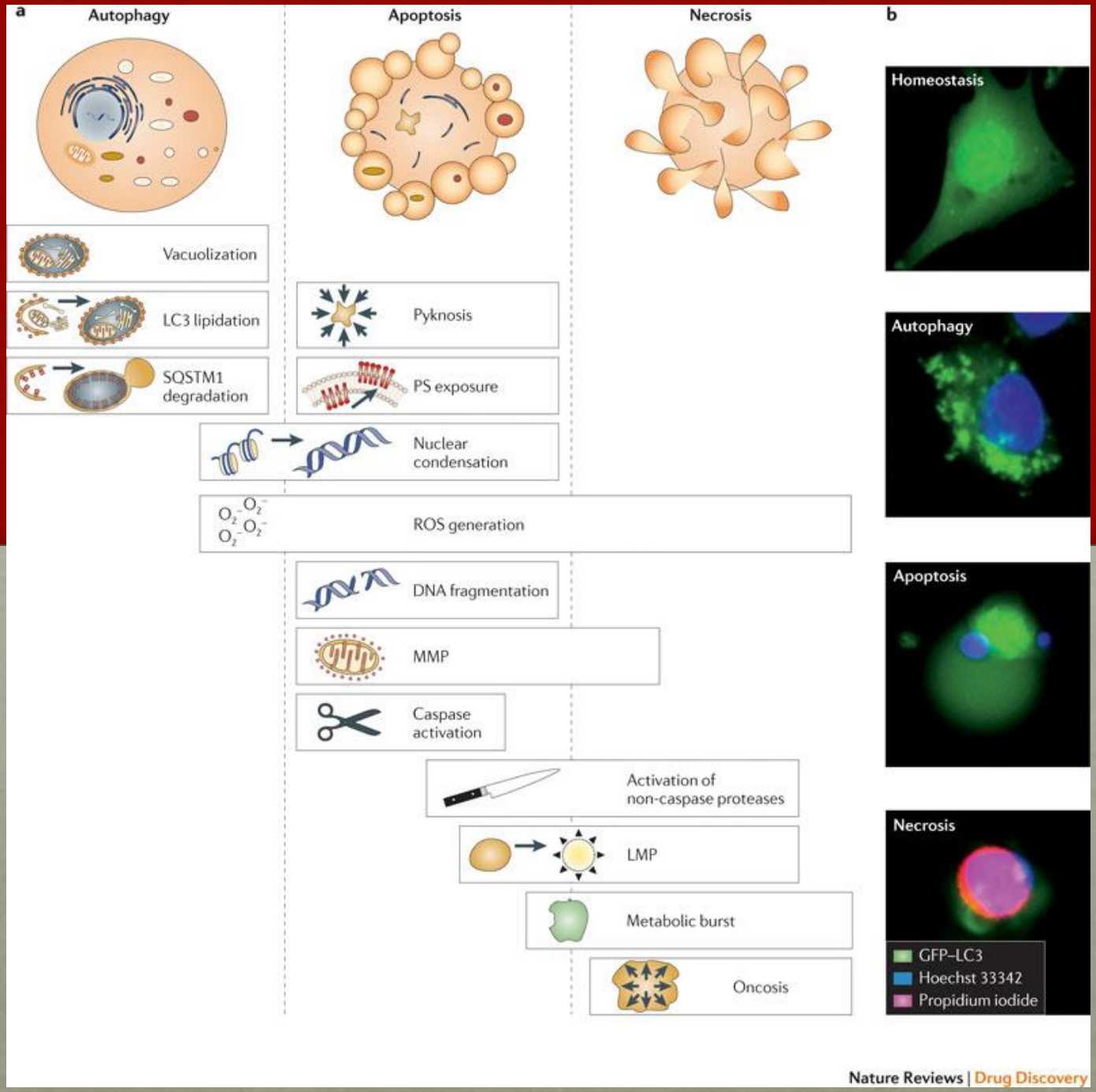
Molecular pathways triggering neurodegeneration in the spinocerebellar ataxias



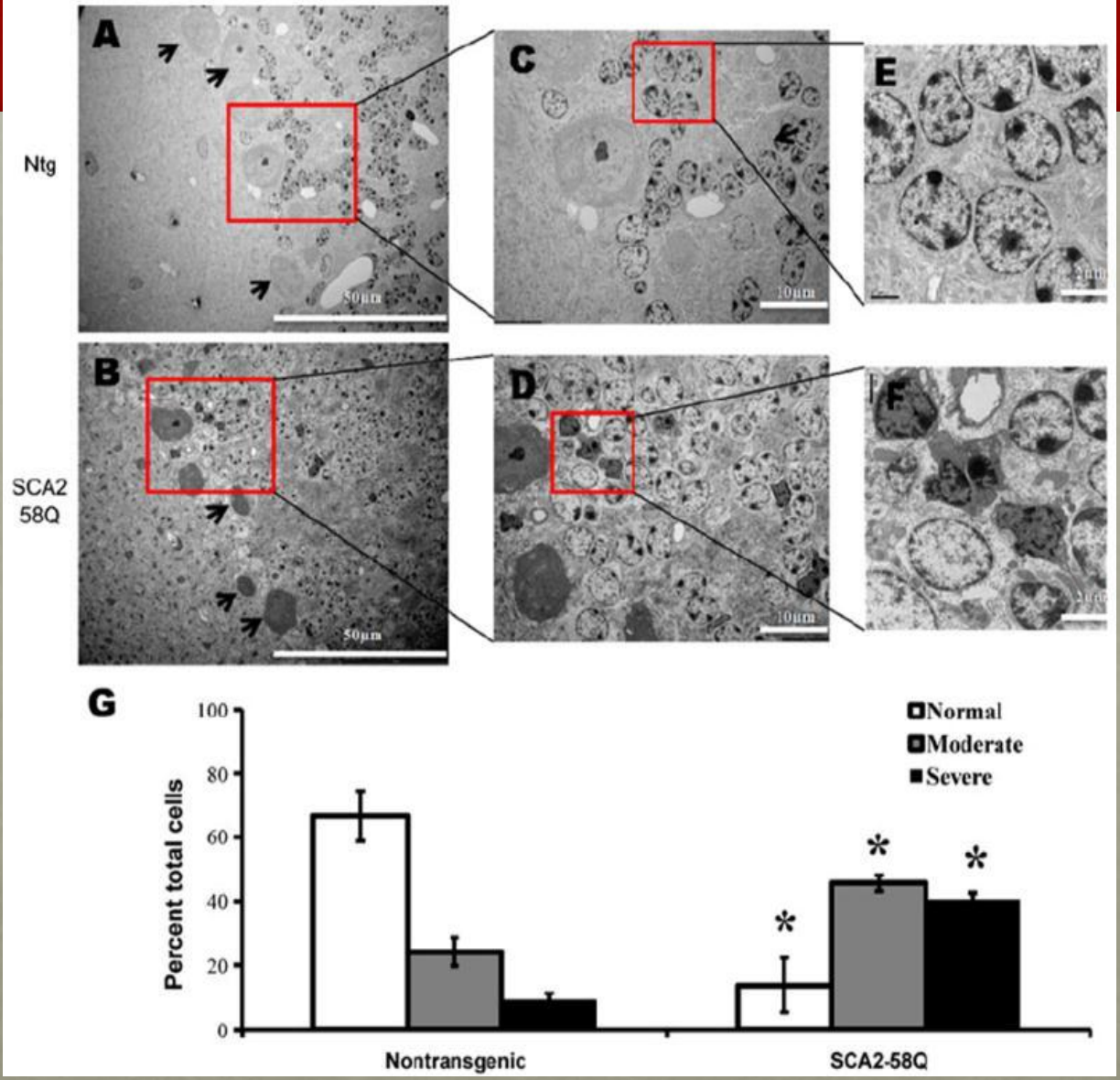
A.Matilla-Dueñas, M.Corral-Juan & I.Sánchez.
Cerebellum 9 (2), 148-166 (2010)

Tipos de muerte celular [programada]: MCP

- **APOPTOSIS (MCP tipo I): Intrínseca (Mitocondria/apoptosoma) y Extrínseca**
- **AUTOFAGIA (MCP tipo II): incluye mitofagia**
- **MUERTE CELULAR CITOPLÁSMICA (MCP tipo III):**
  - **NECROSIS PROGRAMADA**
  - **NECROPTOSIS***
  - **PARAPTOSIS**
  - **PARTHANATOS:** mediada por poly ADP-ribose polimerasa-1 (PARP1) y AIF
- **DEGENERACIÓN NEURONAL OSCURA (DARK CELL DEGENERATION)**
- **ANOIKIS**
- **ENTOSIS**
- **PIROPTOSIS:** respuesta antimicrobiana durante inflamación (caspasa-1)


a
Autophagy
Apoptosis
Necrosis
b
Vacuolization
LC3 lipidation
SQSTM1 degradation
Pyknosis
PS exposure
Nuclear condensation
ROS generation
DNA fragmentation
MMP
Caspase activation
Activation of non-caspase proteases
LMP
Metabolic burst
Oncosis
Homeostasis
Autophagy
Apoptosis
Necrosis
GFP–LC3
Hoechst 33342
Propidium iodide
Nature Reviews | Drug Discovery

PCs in aging SCA2 transgenic mice die by dark cell degeneration)
(10 months old SCA2-58Q)

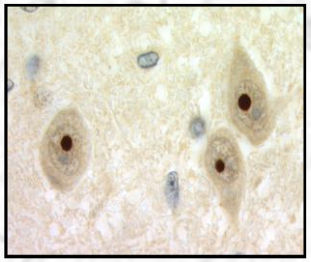


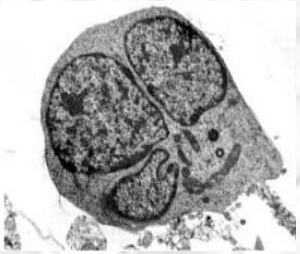
Cerebellum. **2012** September; 11(3): 630–639.
doi: 10.1007/s12311-010-0182-9

Las ataxias espinocerebelosas

Rutas Celulares y Moleculares en Neurodegeneración

1. Activación de muerte neuronal: apoptosis, necroptosis, DCD, etc.
2. Agregación proteica: plegado, insolubilidad
3. Degradación: proteasoma, autofagia
4. Disregulación transcripcional
5. Excitotoxicidad: Glutamato
6. glia de bergmann
7. Homeostasis Calcio
8. Mitocondria
9. Neurotransmisión
10. Transporte axonal
11. Señalización intracelular: Kinasas, Drd2, Pp2a





Las ataxias están causadas por alteraciones de rutas moleculares y proteínas comunes

- 54 interacciones proteicas relacionadas con ataxias hereditarias:
  - recesivas (AF) y dominantes.
  - Factores modificadores
  - Muchas regulatorias (directa o indirectamente) de transcripción.

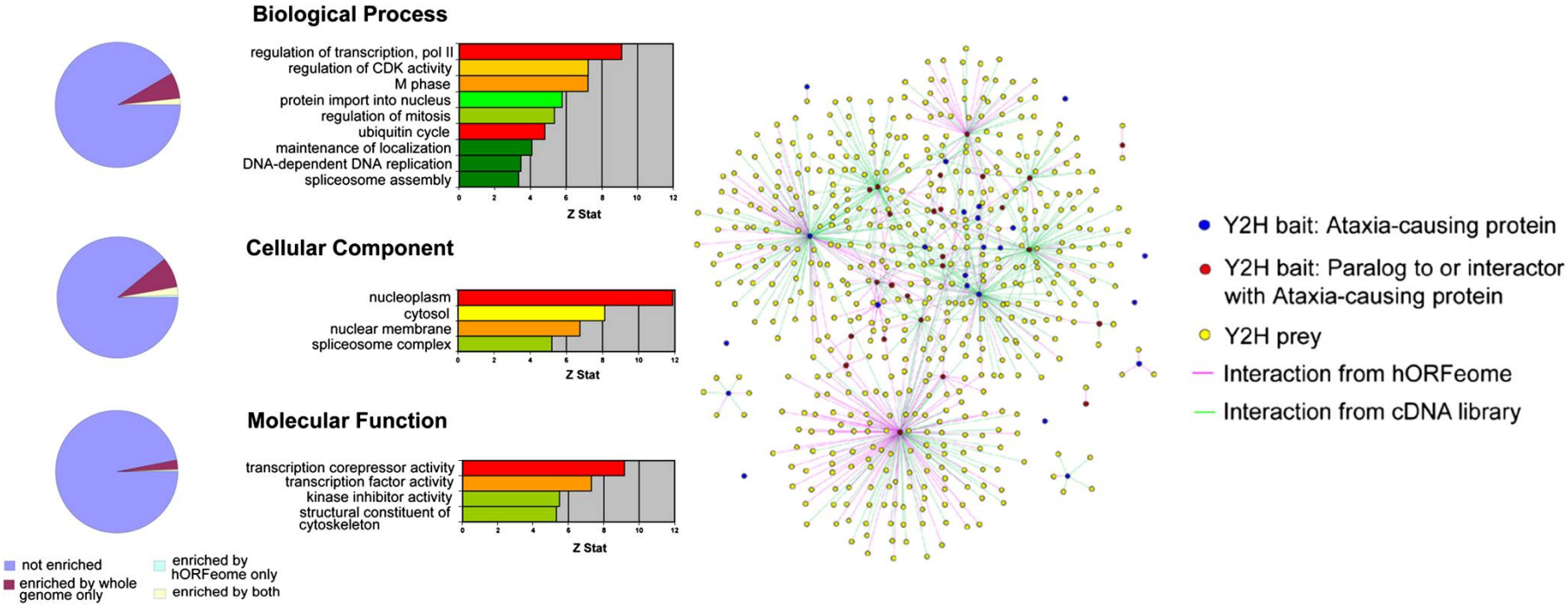
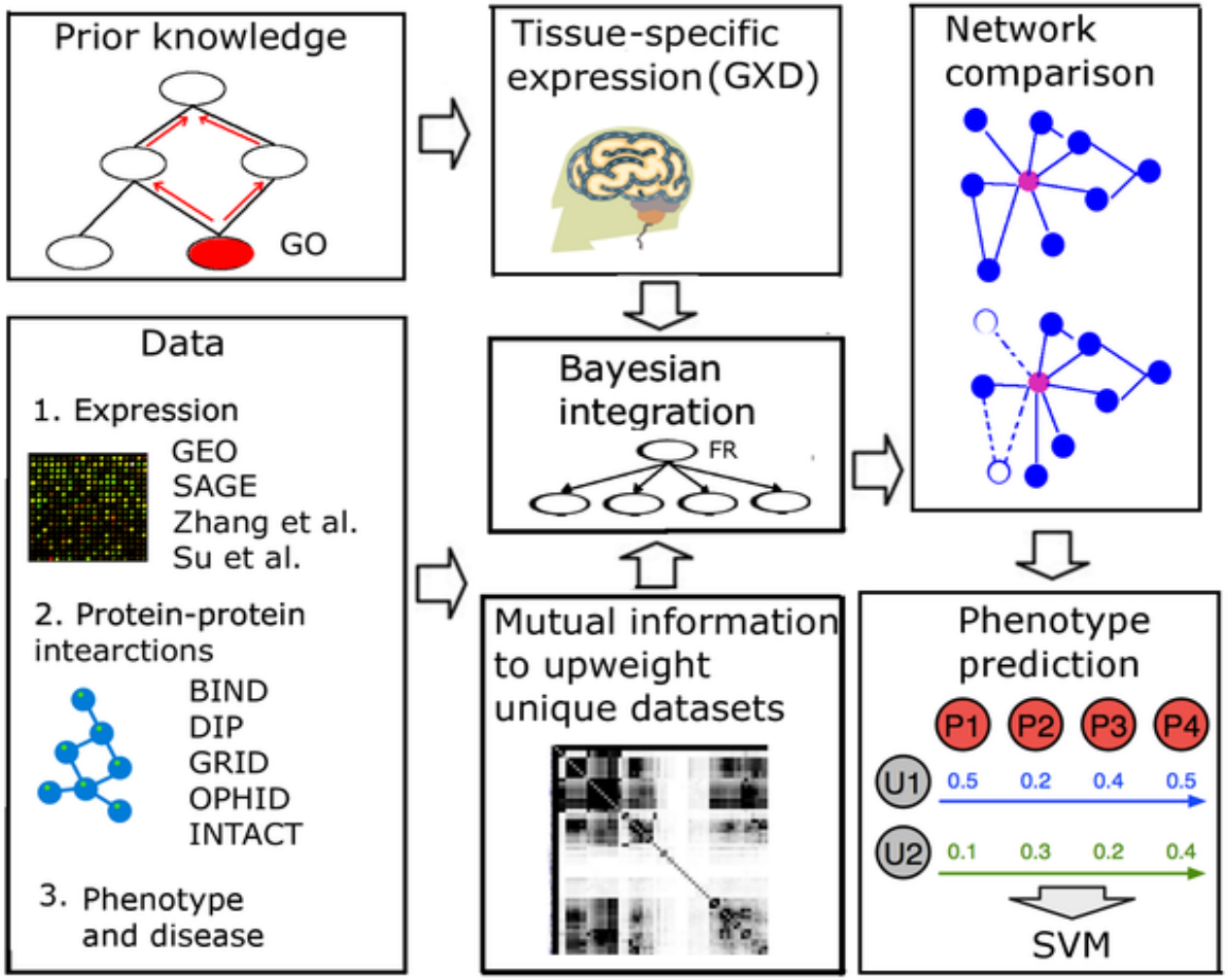
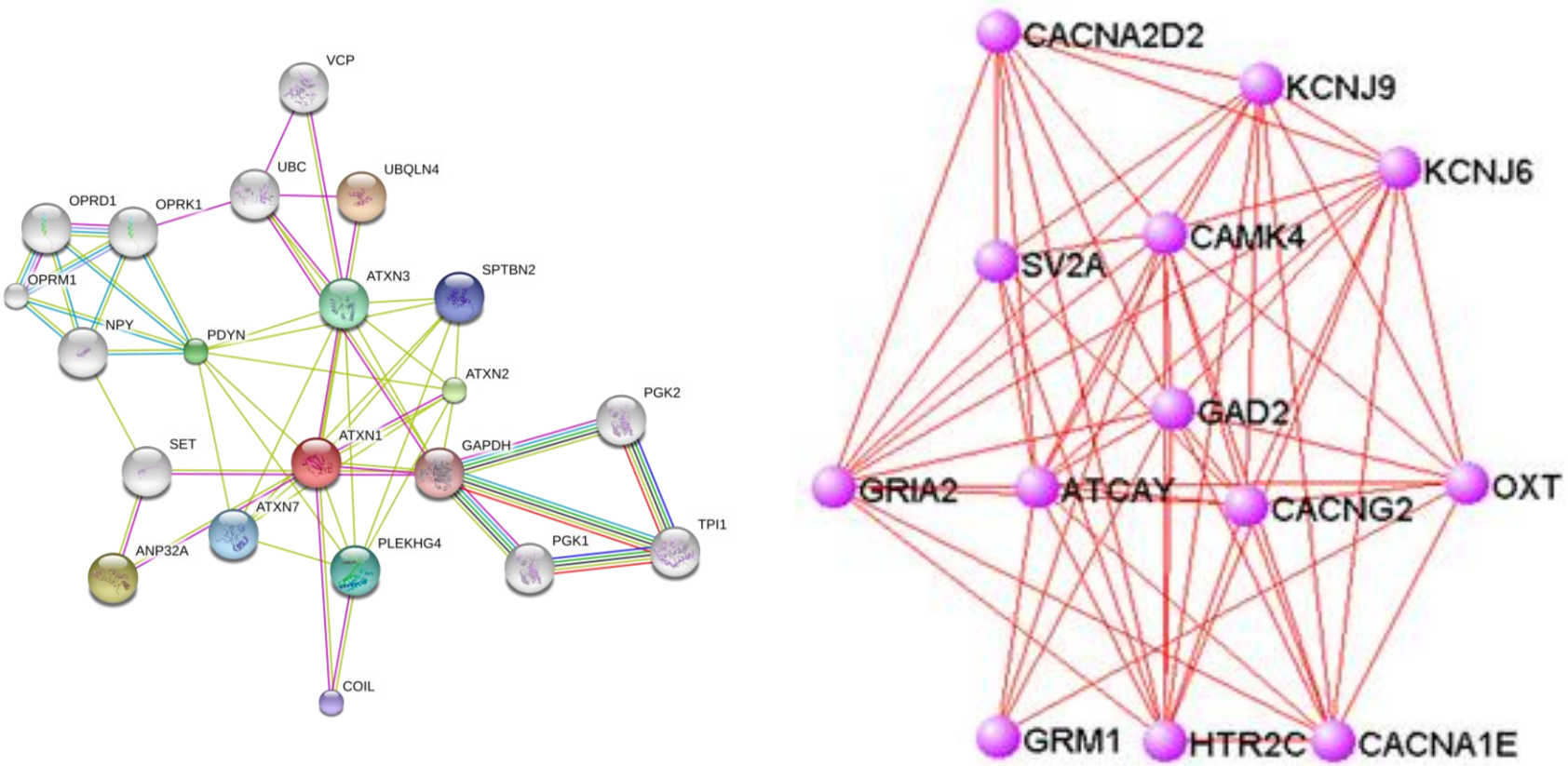


Figure 1. Strategy for constructing tissue-specific networks and predicting phenotype-associated genes.



Guan Y, Gorenshteyn D, Burmeister M, Wong AK, et al. (**2012**) Tissue-Specific Functional Networks for Prioritizing Phenotype and Disease Genes. PLoS Comput Biol 8(9): e1002694. doi:10.1371/journal.pcbi.1002694

Figure 6. Top connected genes to Atcay in the cerebellum-specific network reveals likely ataxia candidates.

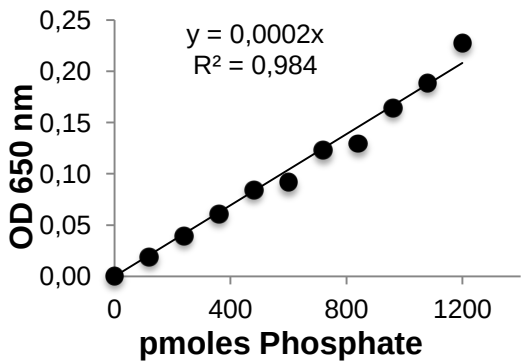


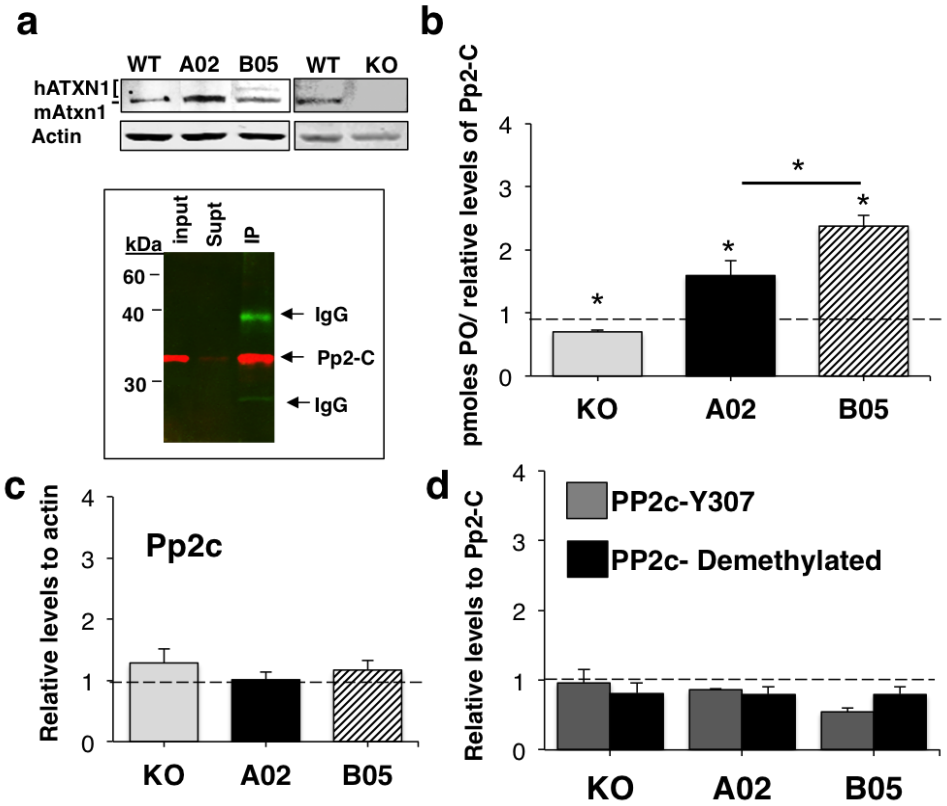
Guan Y, Gorenshteyn D, Burmeister M, Wong AK, et al. (2012) Tissue-Specific Functional Networks for Prioritizing Phenotype and Disease Genes. PLoS Comput Biol 8(9): e1002694. doi:10.1371/journal.pcbi.1002694
http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1002694

Human Molecular Genetics, 2013 **1–13**
doi:10.1093/hmg/ddt197

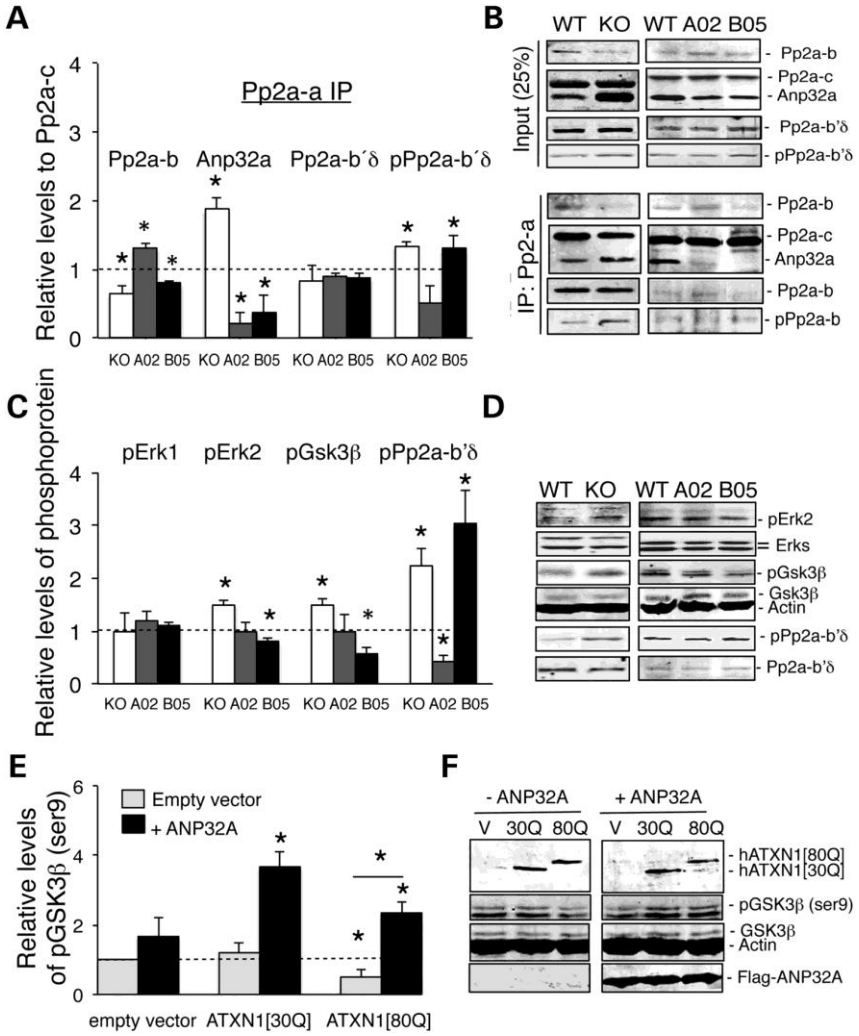
A novel function of Ataxin-1 in the modulation of PP2A activity is dysregulated in the spinocerebellar ataxia type 1

Ivelisse Sánchez[1,2,3], Patricia Piñol[1], Marc Corral-Juan[1], Massimo Pandolfo[4] and Antoni Matilla-Dueñas[1,2,*]





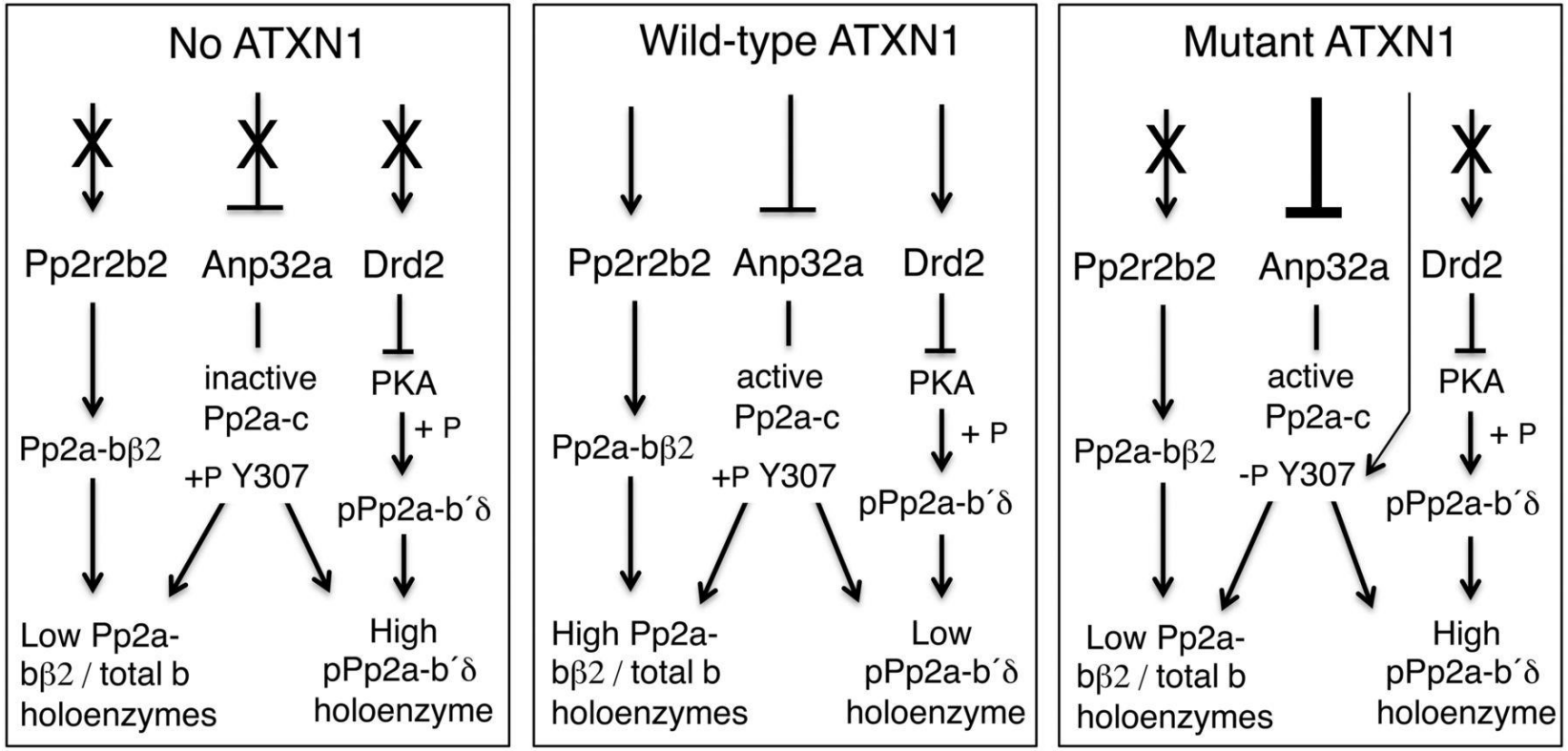
Pp2a holoenzyme composition and signalling are altered in SCA1.



Sánchez I et al. Hum. Mol. Genet. 2013;22:3425-3437

Human Molecular Genetics

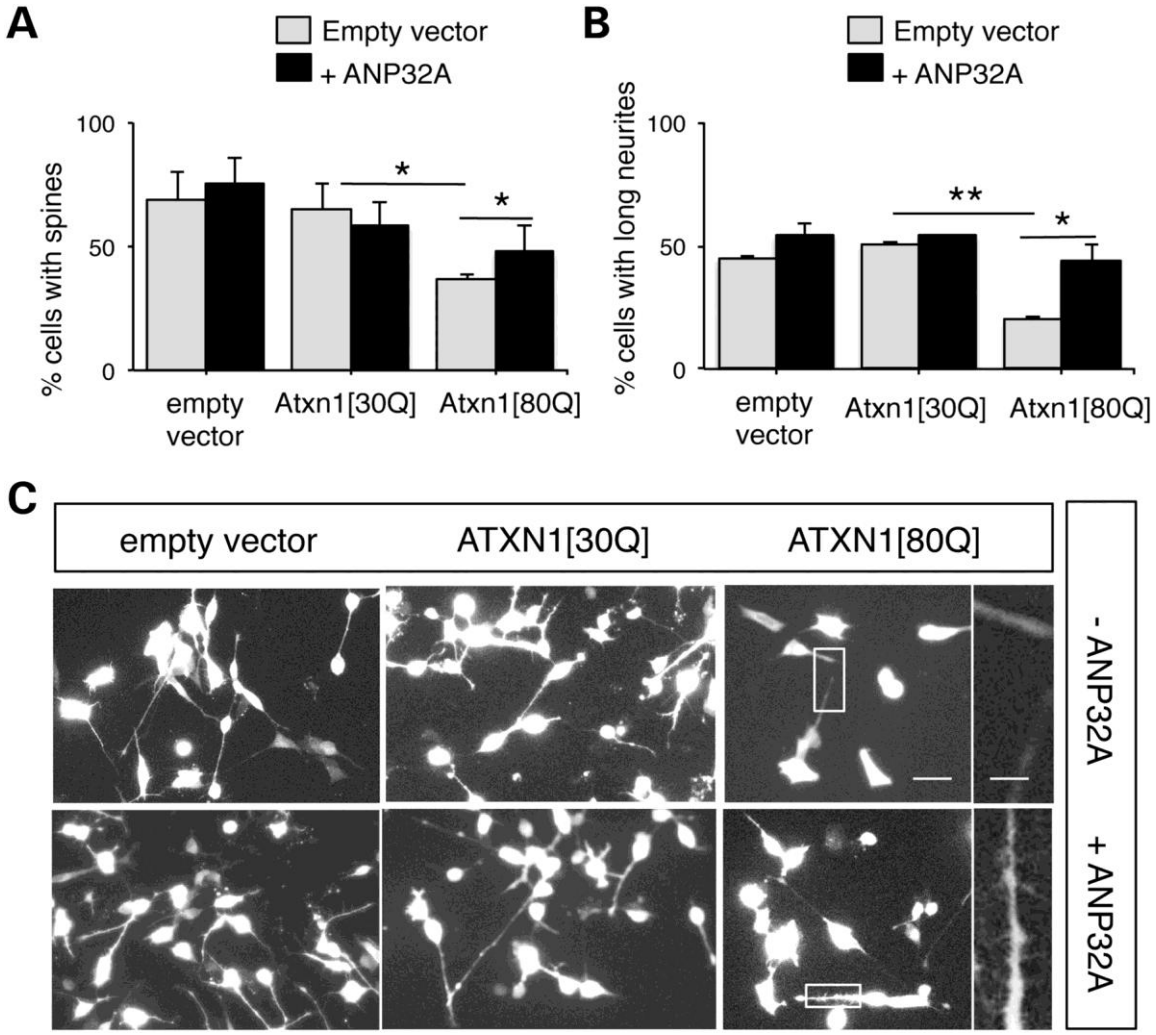
The proposed model of the ataxin-1 induced alterations of Pp2a activity and holoenzyme composition in the cerebellum of 5-week-old mice.



Sánchez I et al. Hum. Mol. Genet. 2013;22:3425-3437

Human Molecular Genetics

Neuronal morphological alterations in ATXN1[30Q] and ATXN1[80Q] expressing differentiated SH-SY5Y cells and the effects of ANP32A co-expression on neurite morphology.



Sánchez I et al. Hum. Mol. Genet. 2013;22:3425-3437

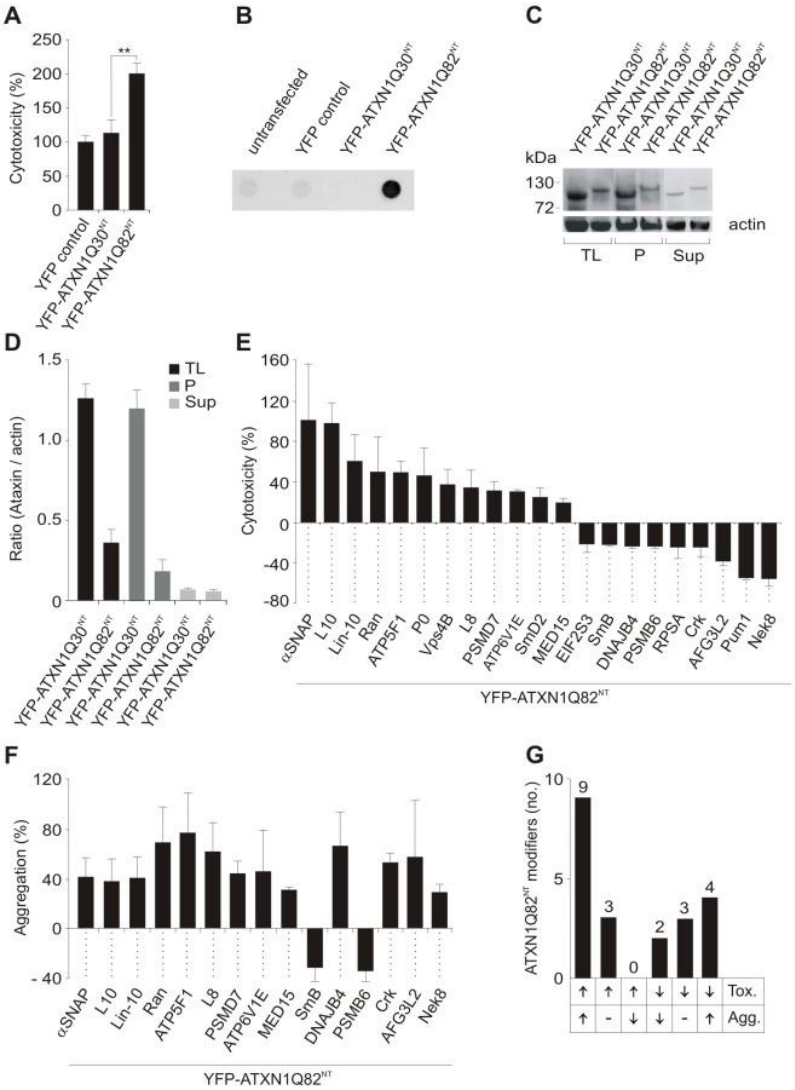
Human Molecular Genetics

OPEN ACCESS Freely available online PLOS MEDICINE

Lithium Therapy Improves Neurological Function and Hippocampal Dendritic Arborization in a Spinocerebellar Ataxia Type 1 Mouse Model

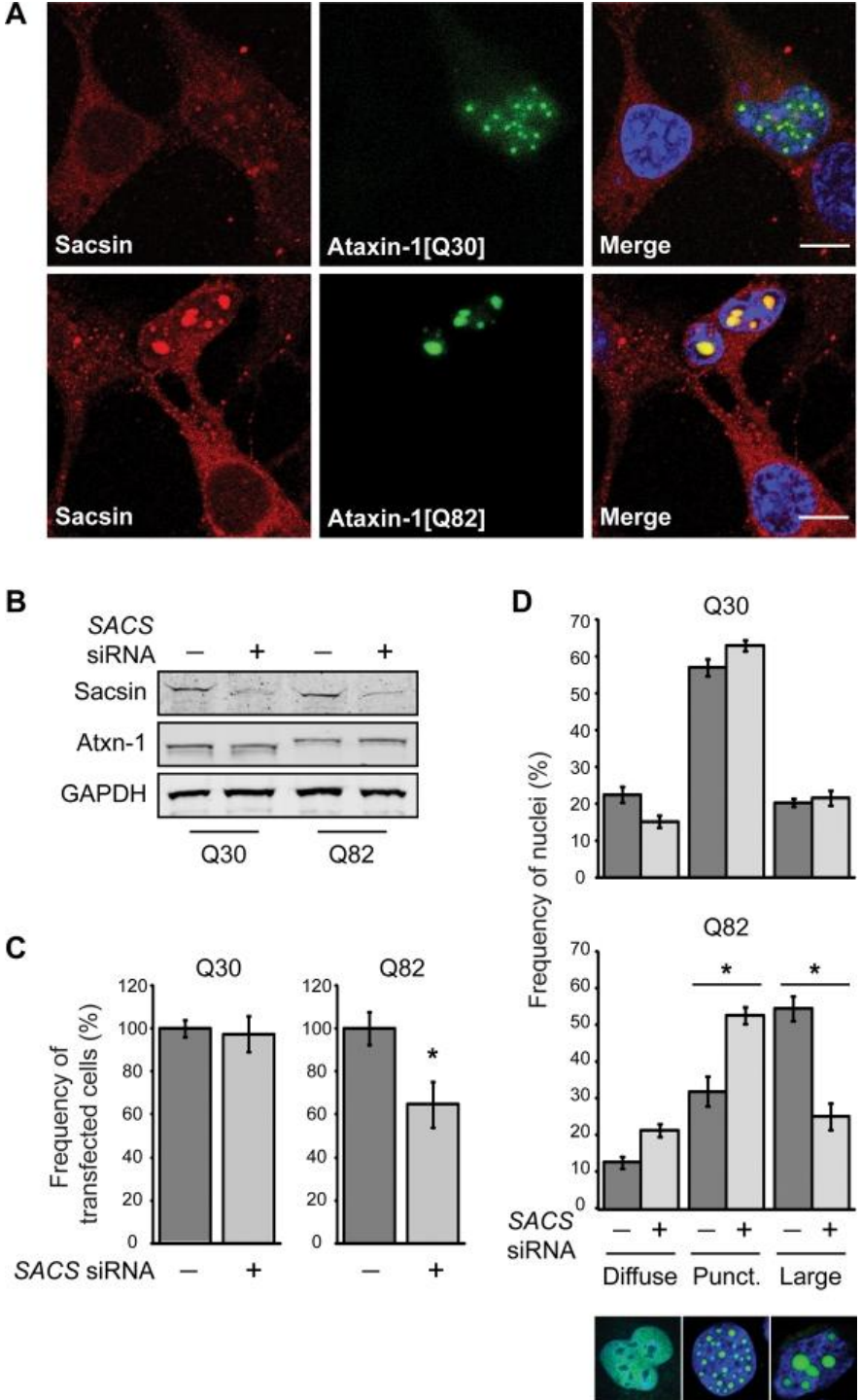
Kei Watase[1,2,3], Jennifer R. Gatchel[4], Yaling Sun[5], Effat Emamian[6], Richard Atkinson[4], Ronald Richman[2,3], Hidehiro Mizusawa[1], Harry T. Orr[6], Chad Shaw[4], Huda Y. Zoghbi[2,3,4,5*]

1 21st Century COE program on Brain Integration and Its Disorders, Tokyo Medical and Dental University, Tokyo, Japan, **2** Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, United States of America, **3** Howard Hughes Medical Institute, Baylor College of Medicine, Houston, Texas, United States of America, **4** Department of Neuroscience, Baylor College of Medicine, Houston, Texas, United States of America, **5** Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States of America, **6** Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota, United States of America



Identification of ATXN1 toxicity and aggregation modifiers using cell-based assays.
Petrakis et al. 2011

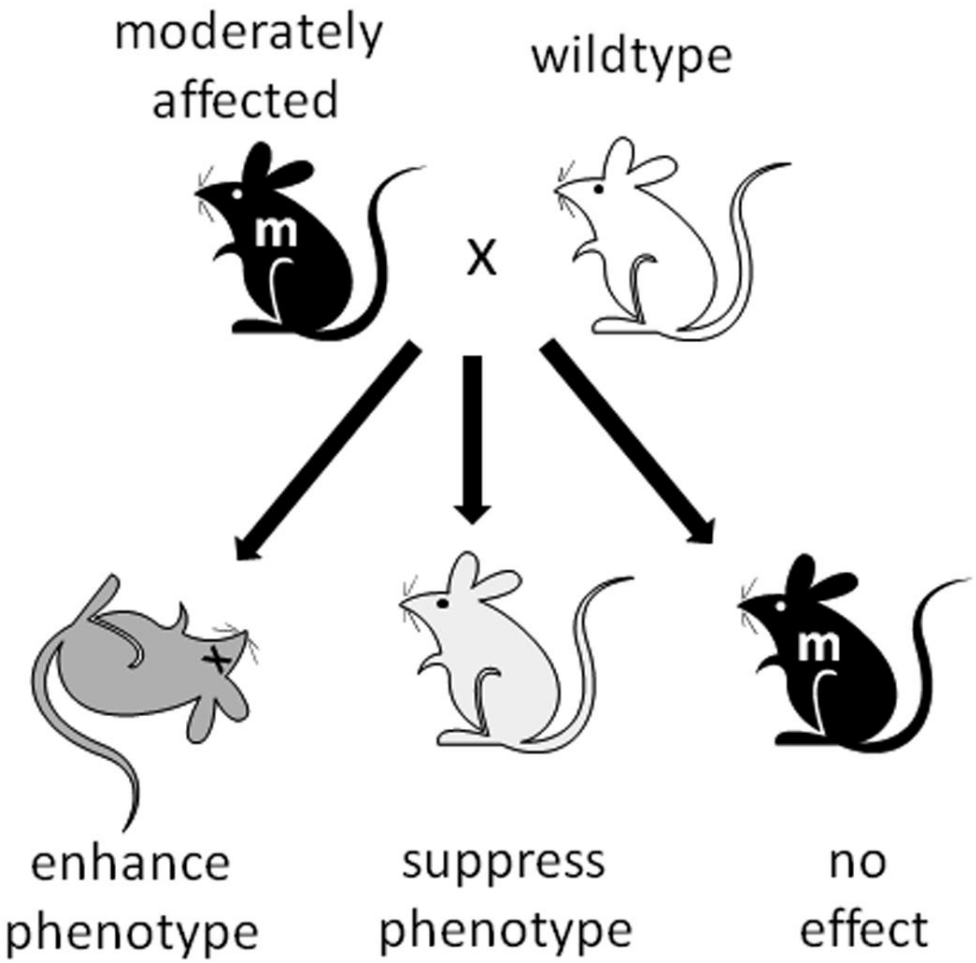
PLOS | GENETICS A peer-reviewed, open access journal

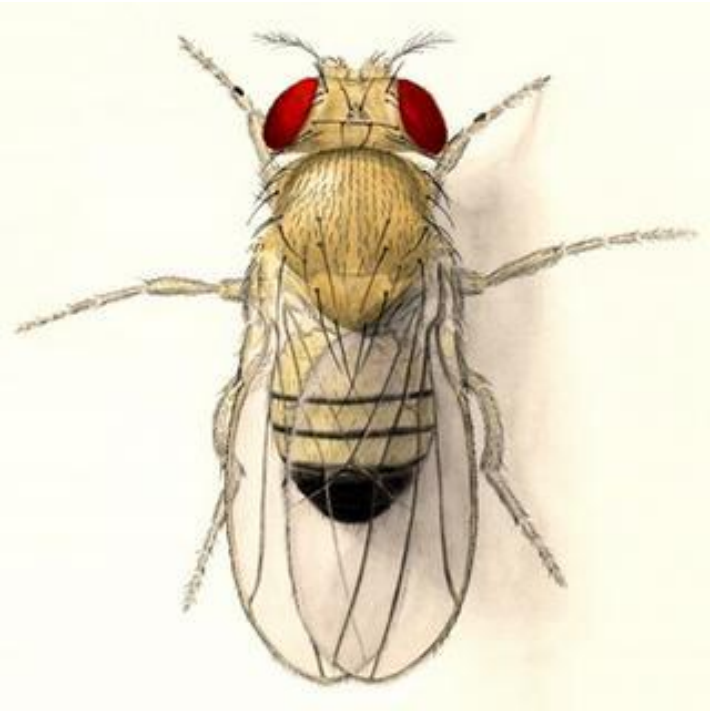


Sacsin knockdown reduces the incidence of cells with large nuclear inclusions of polyglutamine-expanded ataxin-1.

Hum Mol Genet. 2009 May 1; 18(9): 1556–1565.

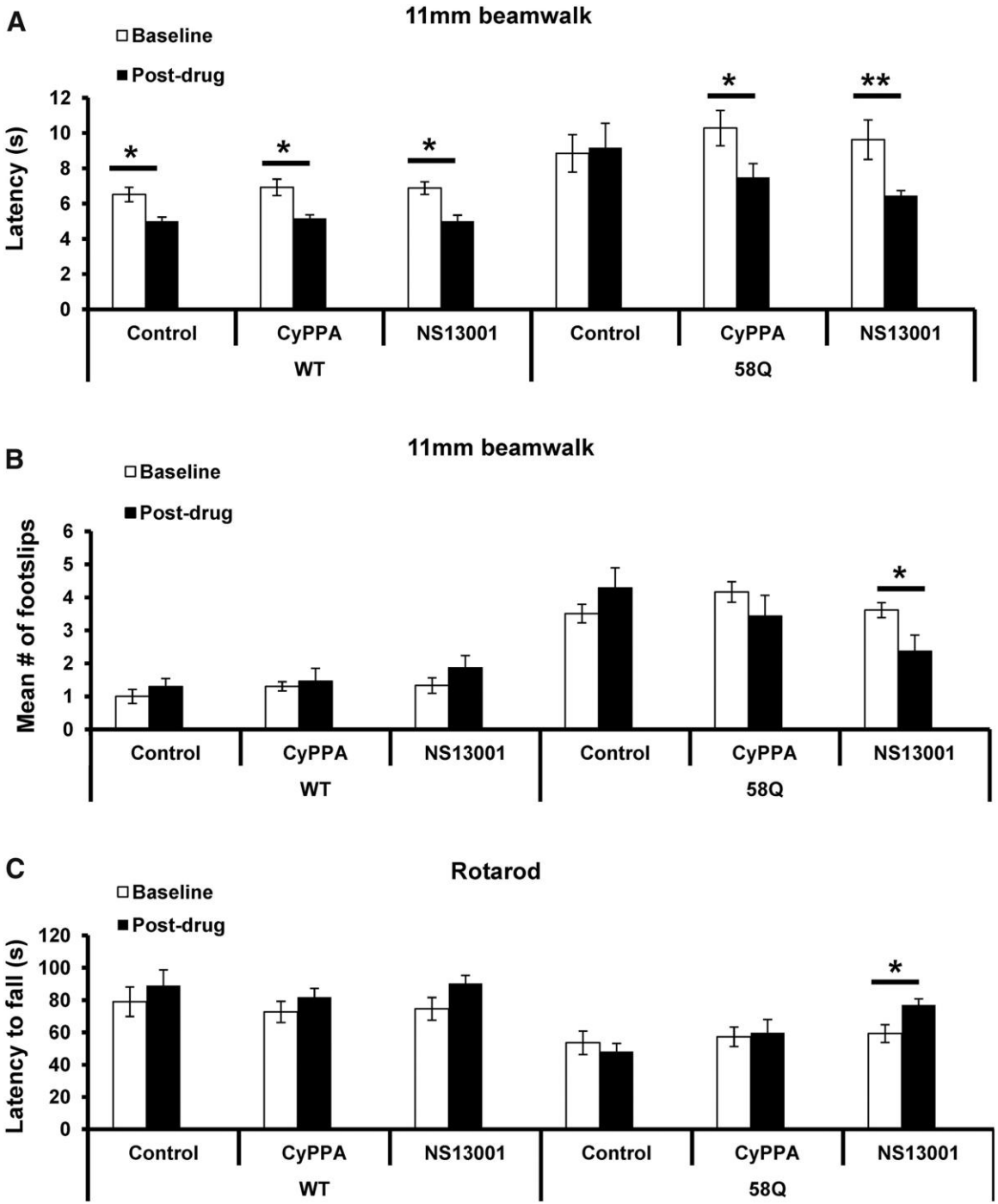
Cribados in vivo para identificar y/o validar moduladores fenotipo atáxico



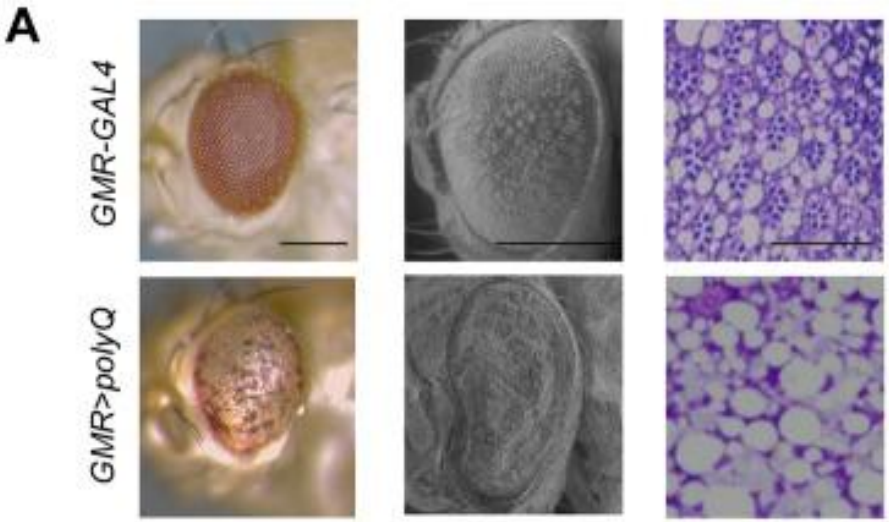


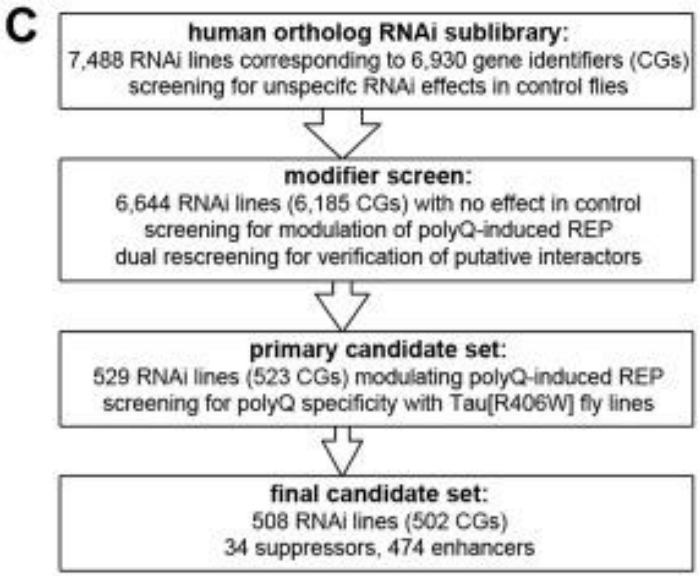
Selective Positive Modulator of Calcium-Activated Potassium Channels Exerts Beneficial Effects in a Mouse Model of Spinocerebellar Ataxia Type 2.

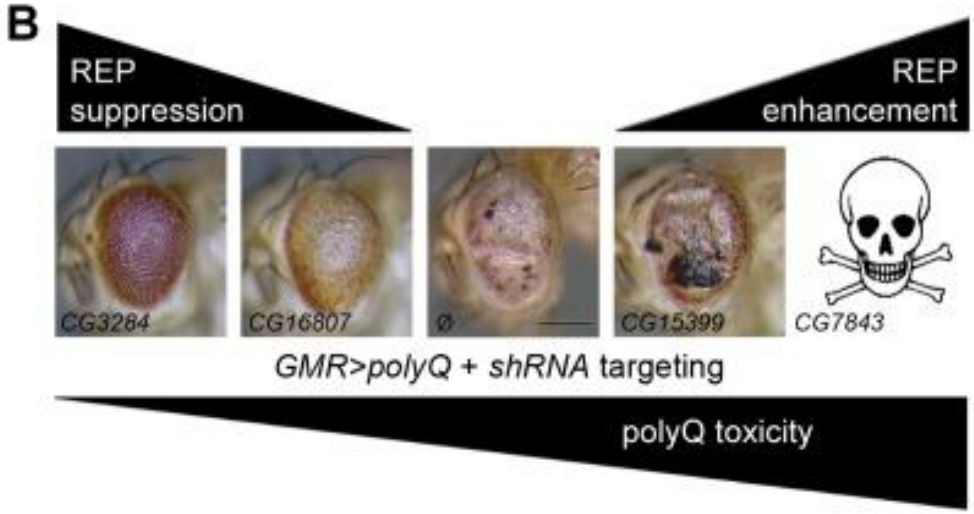
Chemistry & Biology Volume 19,
Issue 10 2012 1340 - 1353

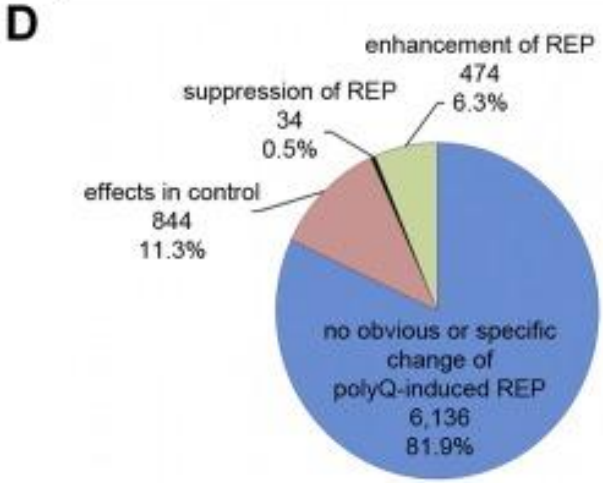


Large-Scale Screen for Modifiers of Ataxin-3-Derived Polyglutamine-Induced Toxicity in *Drosophila*

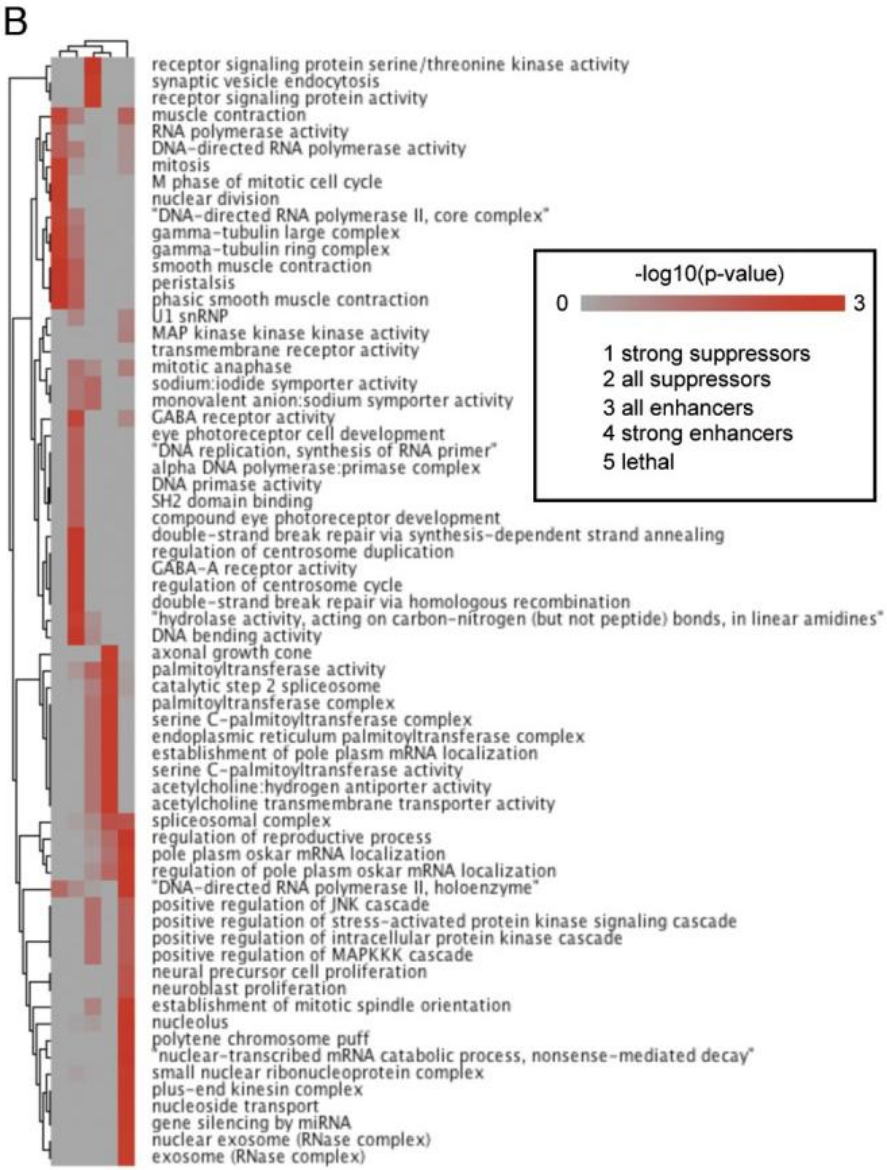


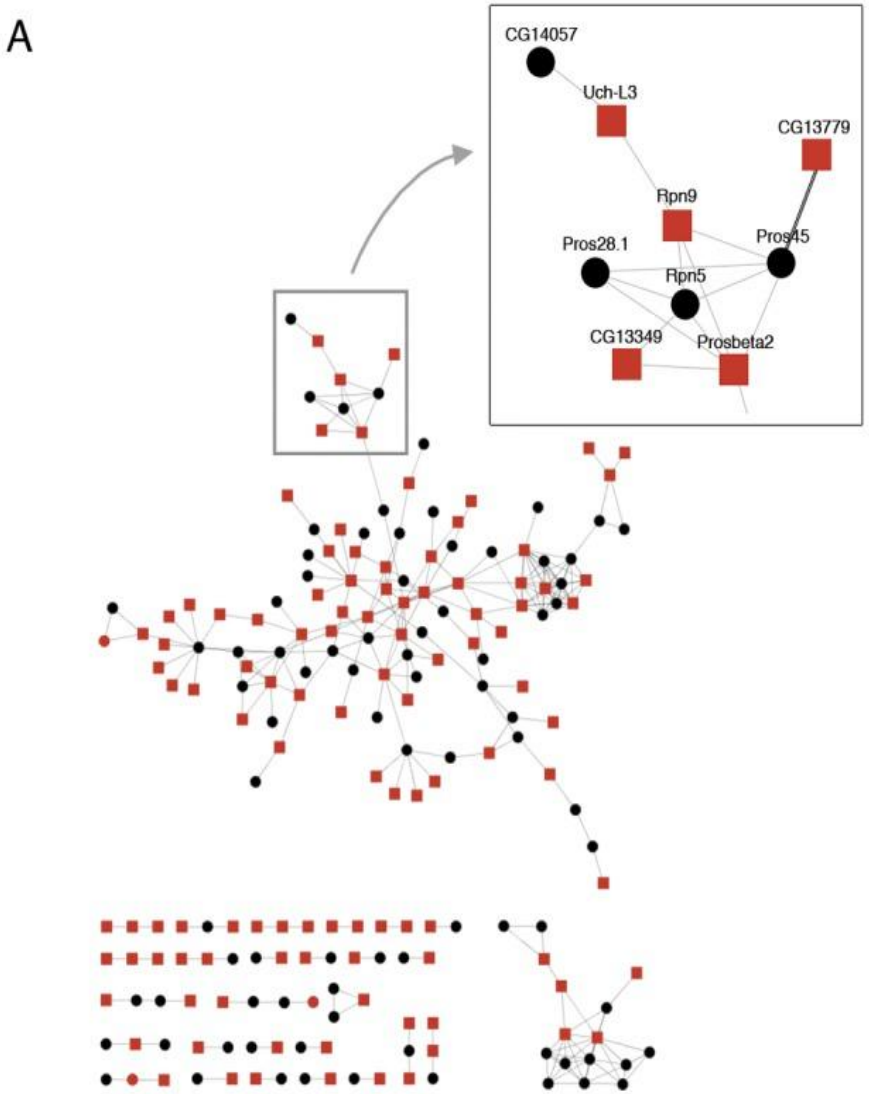






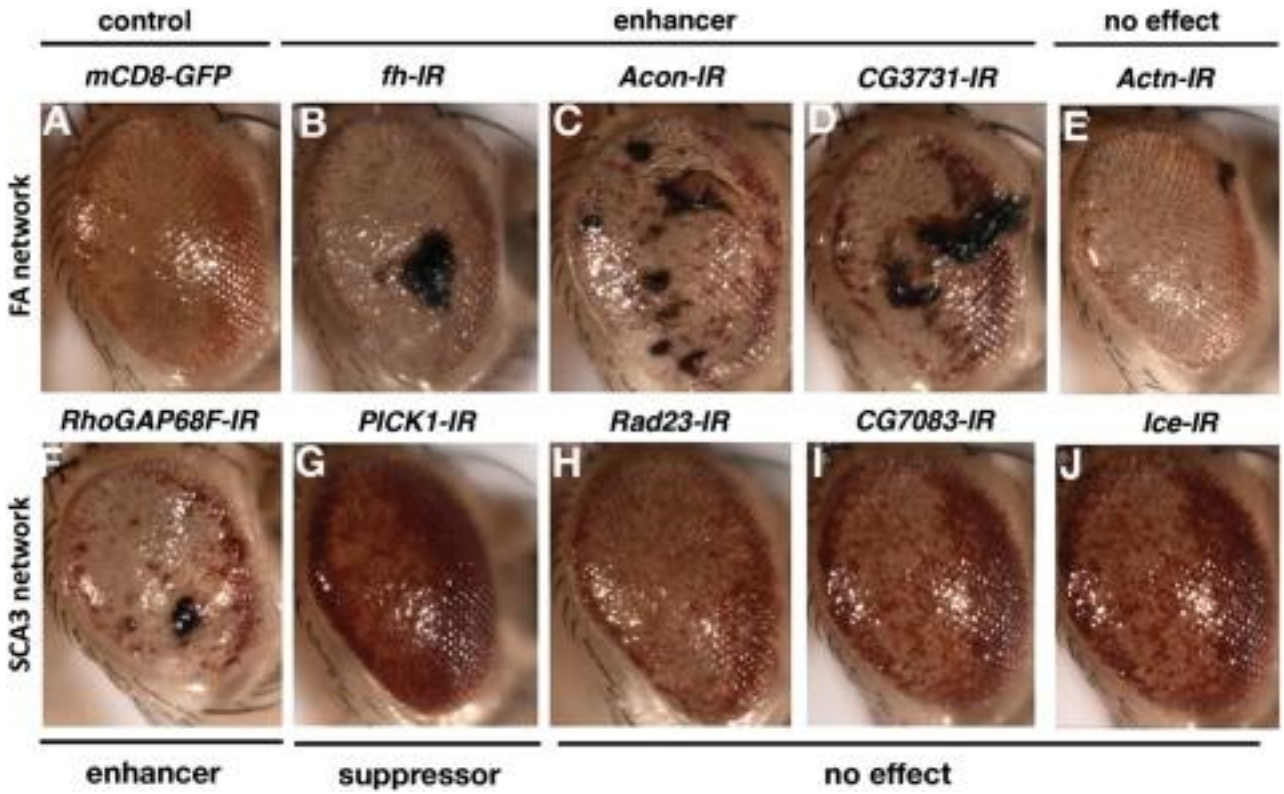
PLoS ONE 7(11): 2012





PLoS ONE 7(11): 2012

Modifiers of spinocerebellar ataxia 3-associated neurodegeneration in Drosophila



Hum Mol Genet. 2012 Jan 1;21(1):76-84. Epub 2011 Sep 23.

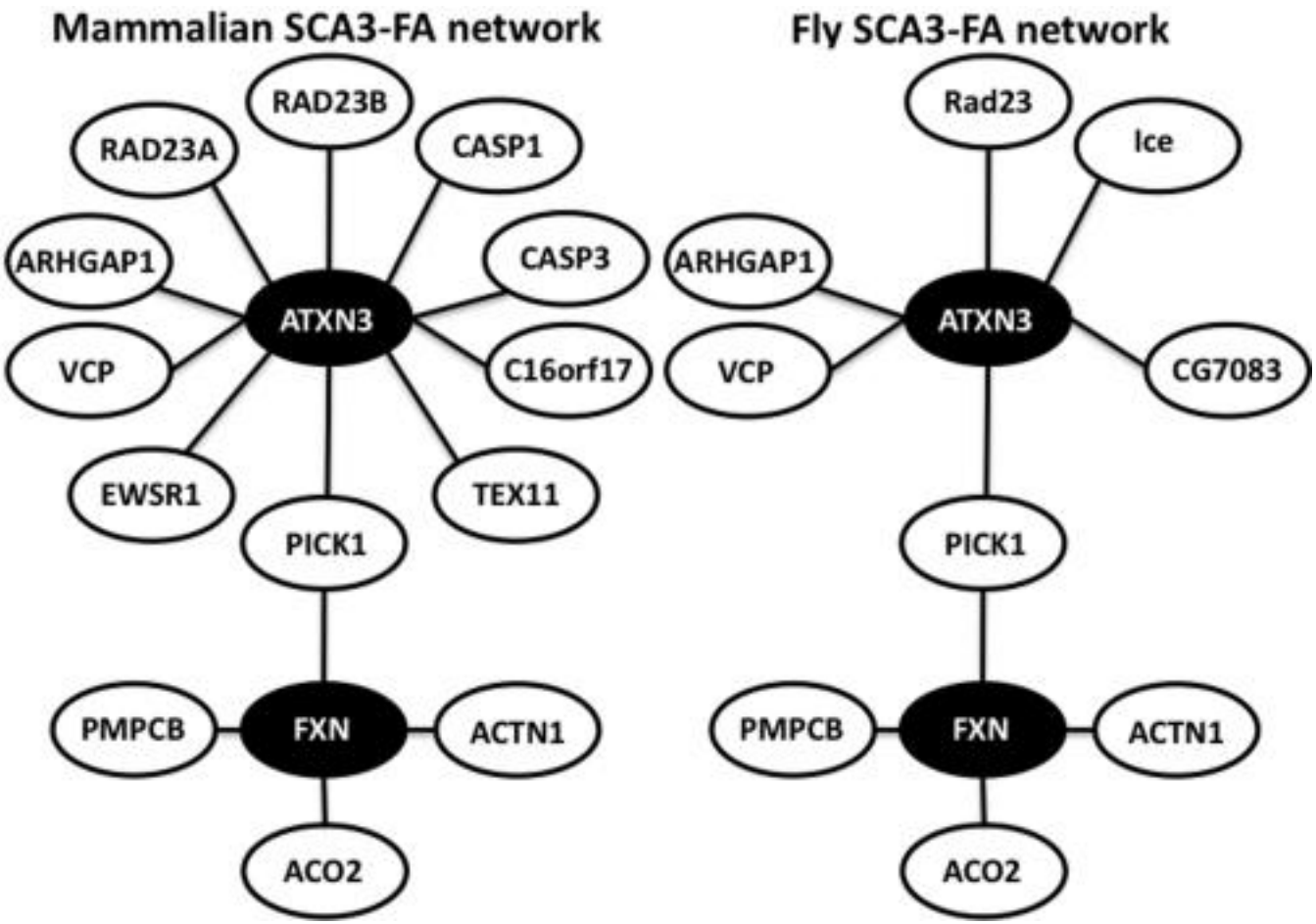
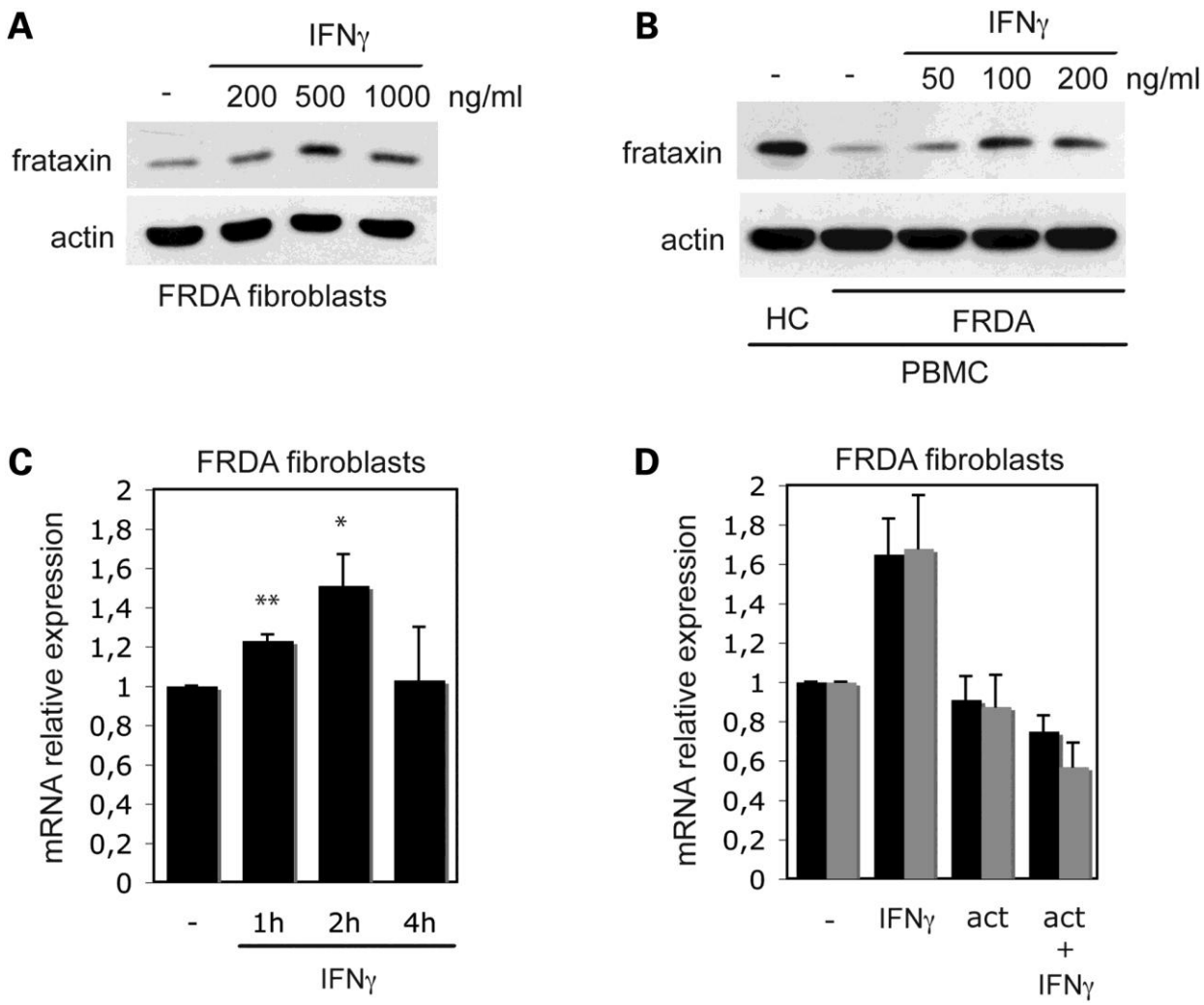

Mammalian SCA3-FA network
RAD23B
RAD23A
CASP1
ARHGAP1
CASP3
ATXN3
VCP
C16orf17
EWSR1
TEX11
PICK1
PMPCB
FXN
ACTN1
ACO2
Fly SCA3-FA network
Rad23
Ice
ARHGAP1
ATXN3
VCP
CG7083
PICK1
PMPCB
FXN
ACTN1
ACO2

Table 2. High-throughput screening for FRDA therapeutics

FRDA model	Readout	Activity or function targeted	Number of compounds screened	Hits	References
Human cells with dual luciferase reporter expression containing *FXN* minigene with about 800 GAA repeats	Dual luciferase assay	*FXN* expression	45,640	1200	Edward Grabczyk[a]
HEK293 cells expressing luciferase construct with 850 GAA or 30 GAA repeats	Luciferase assay	*FXN* expression	360,000 (NIH library)	255	Marek Napierala[a]
Cells expressing the *FXN* gene with about 300 GAA repeats coupled to luciferase gene	Luciferase assay	*FXN* expression	88 preselected compounds with HDACi-like structure	7	Michele Lufino[a]
HeLa cells expressing the full *FXN* locus coupled to EGFP	EGFP assay	*FXN* expression	n.a.	n.a.	Joe Sarsero[a]
Yfh1-depleted yeast	Cell viability (tetrazolium assay)	Sensitivity to oxidative stress	242,000 (MLSCN library)	400	Robert Wilson[a]
Diamide-treated patient fibroblasts	Cell viability (calcein-AM assay)	Sensitivity to diamide treatment	1060	40	Sunil Sahdeo[a]

[a]Personal communication, as presented at the 4th International Friedreich's Ataxia Conference (http://www.curefa.org/conference.html); HDACi, histone deacetylase inhibitor; MLSCN, Molecular Libraries Screening Centers Network; n.a., information not available; NIH, National Institutes of Health.

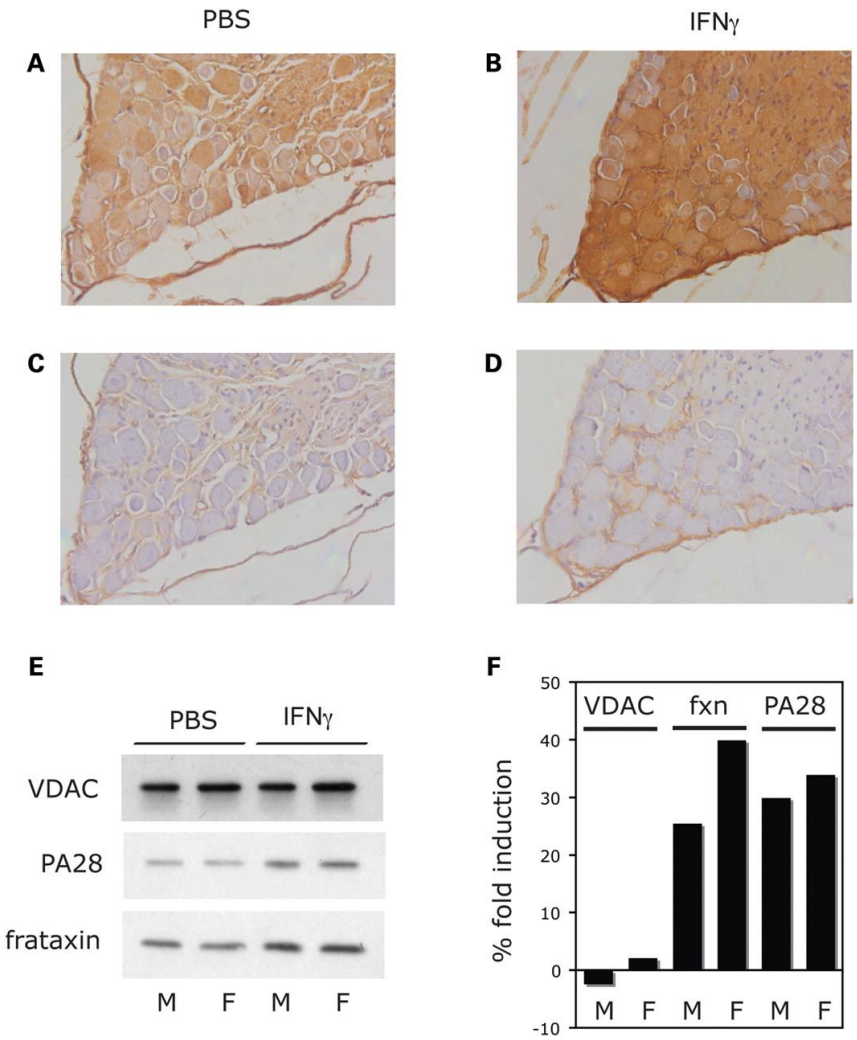
IFNγ induces frataxin accumulation in FRDA cells.



Tomassini B et al. Hum. Mol. Genet. 2012;21:2855-2861

Human Molecular Genetics

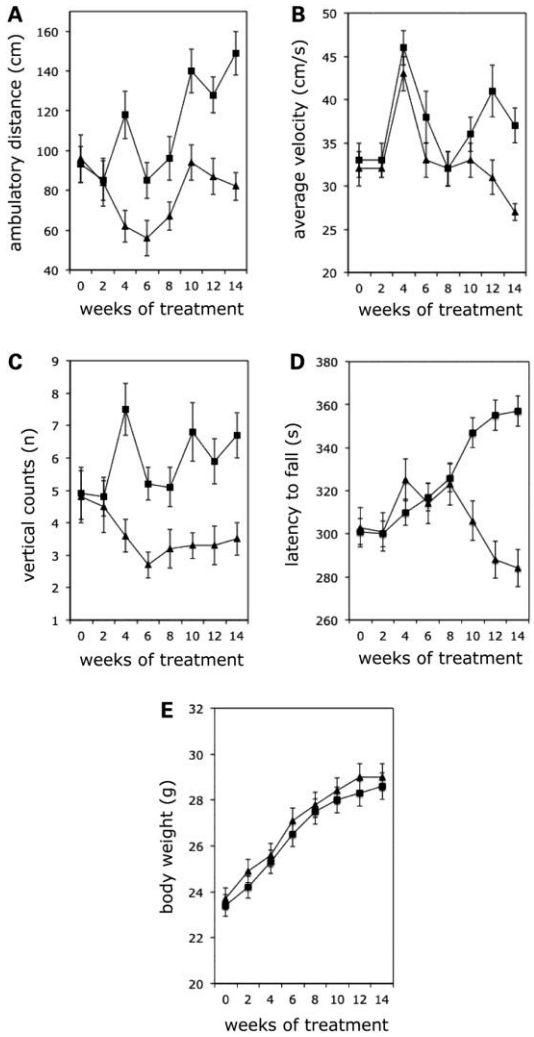
In vivo IFNγ treatment upregulates human frataxin in DRG of FRDA mice.

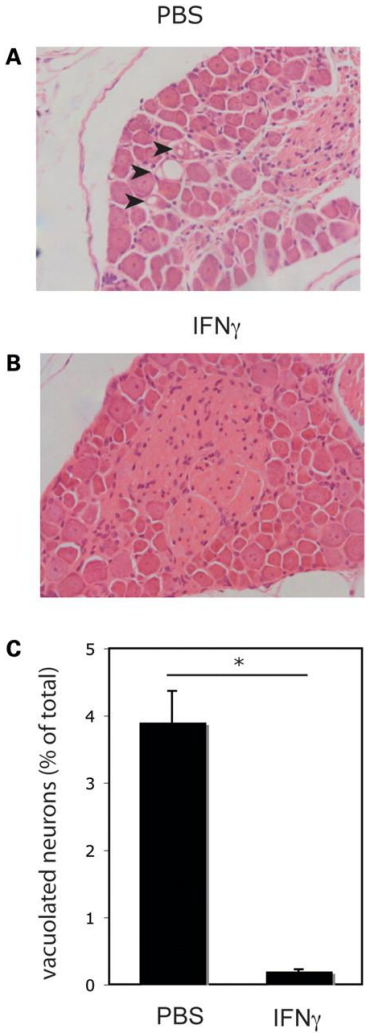


Tomassini B et al. Hum. Mol. Genet. 2012;21:2855-2861

Human Molecular Genetics

In vivo IFNγ treatment improves locomotor and motor coordination performances and prevents neurodegeneraton in FRDA mice.





Tomassini B et al. Hum. Mol. Genet. 2012;21:2855-2861

Human Molecular Genetics

Science News

... from universities, journals, and other research organizations

New Gene Therapy Strategy Boosts Levels of Deficient Protein in Friedreich's Ataxia

July 25, 2012 — A novel approach to gene therapy that instructs a person's own cells to produce more of a natural disease-fighting protein could offer a solution to treating many genetic disorders. The method was used to achieve a 2- to 3-fold increase in production of a protein deficient in patients with Friedreich's ataxia, as described in an article published in *Human Gene Therapy*.

The innovative gene therapy method described by Jacques Tremblay, Pierre Chapdelaine, Zoé Coulombe, and Joel Rousseau, Laval University, Quebec,and University of Quebec, Canada, takes advantage of the ability of a family of proteins called Tal effector (TALE) proteins to target specific DNA sequences. As a model of how this method could be used to treat genetic disease, the authors engineered TALE proteins to target the gene that codes for the frataxin protein, which is deficient in Friedreich's ataxia. The ability to induce cells to produce more frataxin could reduce symptoms of the disease and provide an effective, long-term therapeutic strategy, conclude the authors.

"This is a very clever approach to treat a recessive disease caused by decreased quantity of an otherwise normal protein," says James M. Wilson, MD, PhD, Editor-in-Chief, and Director of the Gene Therapy Program, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia.

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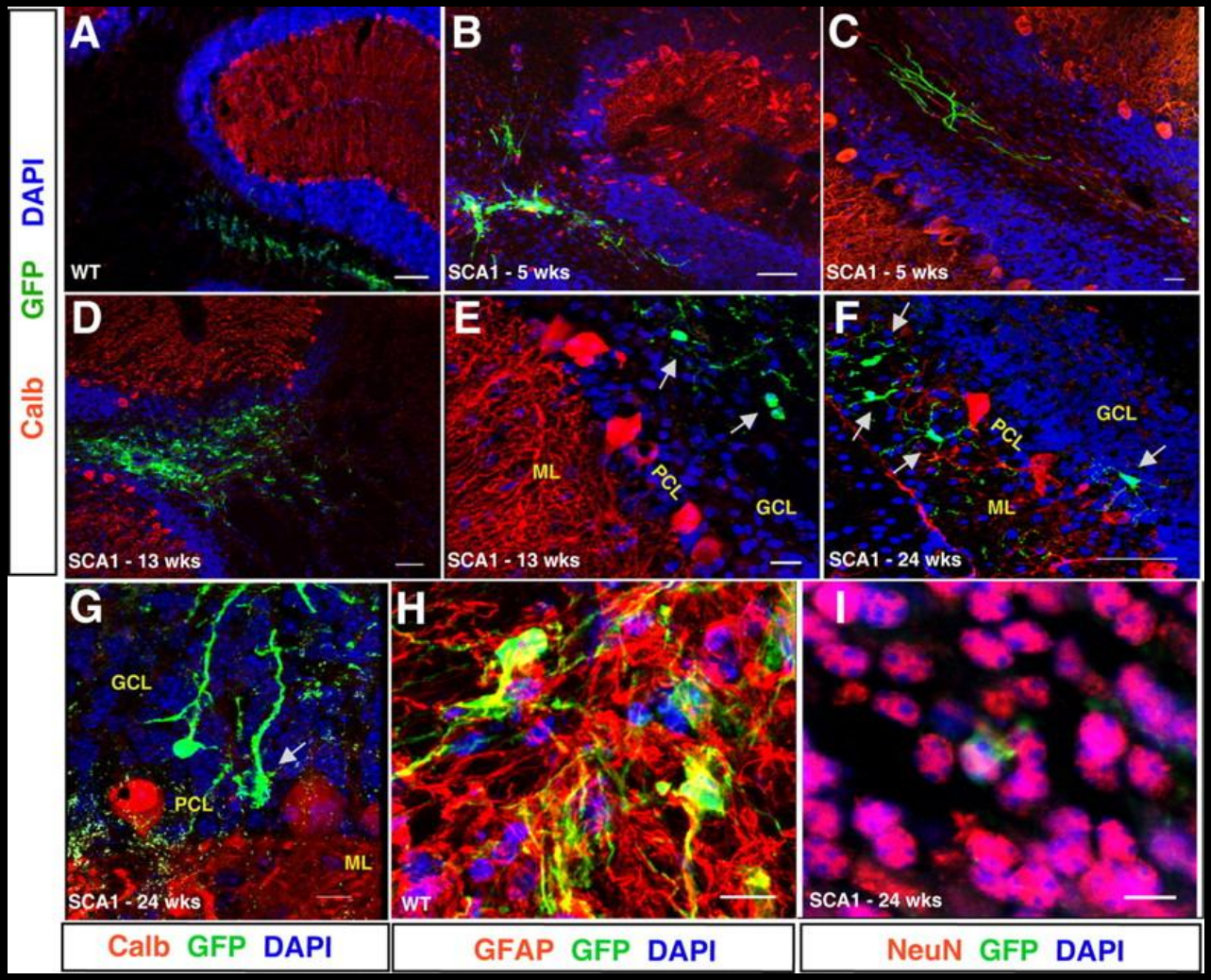
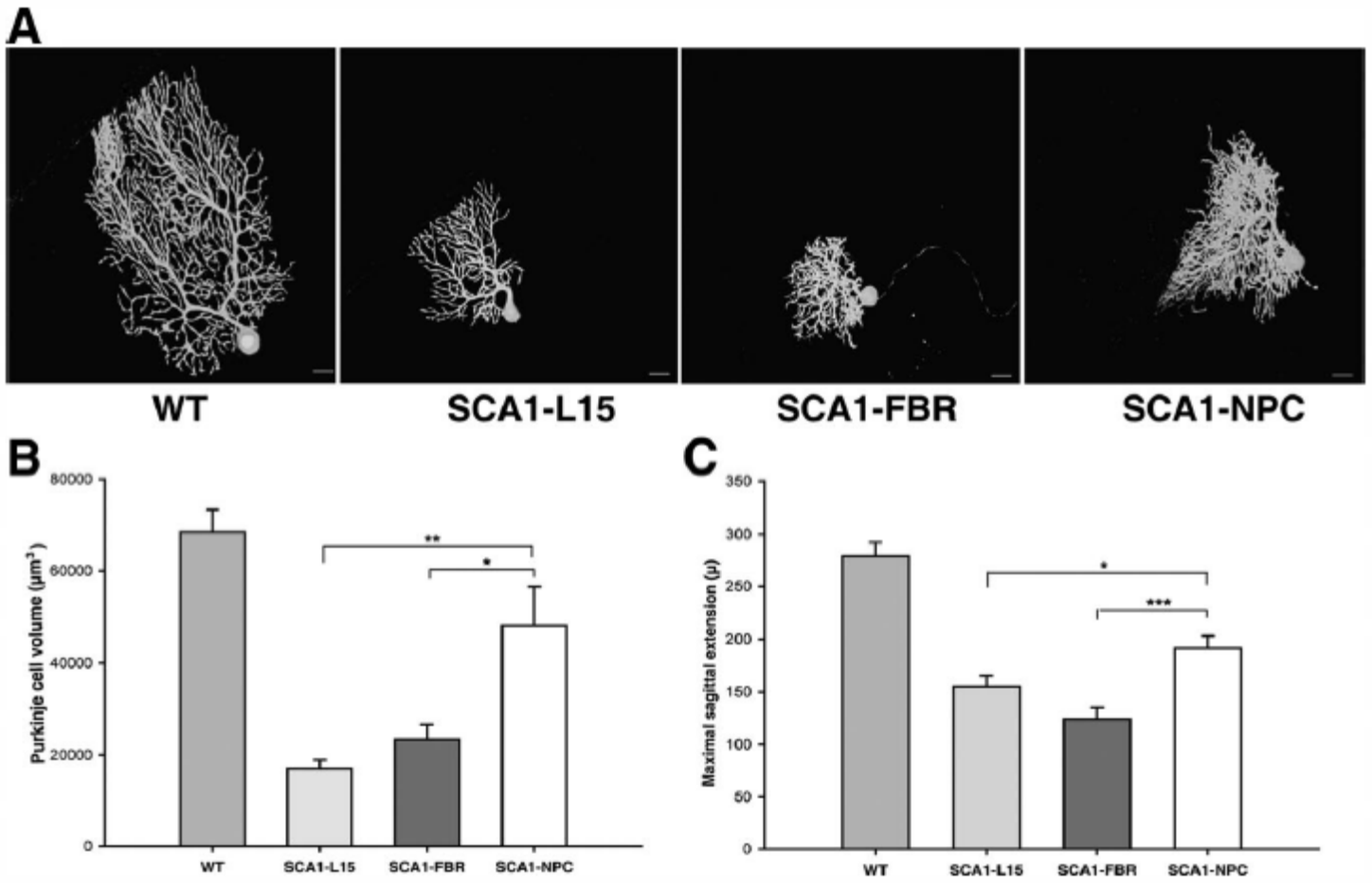
Injertos de Precursores neuronales en el cerebelo atáxico



Chintawar, S. et al. J. Neurosci. 2009;29:13126-13135



Pandolfo, M. *et al.* Grafting neural precursor cells promotes functional recovery in an SCA1 mouse model. The Journal of Neuroscience. 29, 13126-13135 (2009).

VIEWPOINT

We Cannot Cure Ataxia, We Can Only Eradicate It

Khalaf Bushara, MD, FRCP
Ataxia Center, University of Minnesota, Minneapolis.

The hereditary ataxias are a group of neurodegenerative progressive disorders for which there is currently no effective treatment. Since the discovery of the spinocerebellar ataxia type 1 gene,[1] there has been an explosion of gene discoveries and we are now at spinocerebellar ataxia type 36. Considerable effort and funds have been expended not only to discover new genes but also to explore the molecular mechanisms of ataxia with the hope of ultimately finding an effective treatment. However, finding a cure or even a marginally effective symptomatic treatment has been elusive despite 20 years of extensive research and billions of dollars of funding by both the National Institutes of Health and nongovernmental foundations.

Many of the approximately 200 000 patients with ataxia in the United States do participate in research and fundraising and strongly believe that their efforts will help science and future generations. However, despite the ongoing and exciting scientific discoveries, little has changed for the patients with ataxia and their physicians. Many patients have adapted to and accepted their disabilities but wish that their children will not have ataxia. Since most inherited ataxias manifest in adulthood, those who already have children hope that their children do not have the disease. In many cases, parents do not have to wait long to know because most of the autosomal dominant ataxias are nucleotide repeat disorders and exhibit the phenomenon of anticipation, with younger generations developing more severe symptoms at younger ages. Indeed, in certain ataxias such as spinocerebellar ataxia type 7, the nucleotide repeats can expand dramatically, leading to severe disease in infancy.[2]

implantation genetic diagnosis (PGD) are usually willing to go through this procedure if they can afford it. Preimplantation genetic diagnosis requires in vitro fertilization, testing the fertilized ova for the ataxia gene, and then implanting healthy embryos, thus guaranteeing that the ataxia gene from the mother or the father is not passed to the child.[4,5] The cost for PGD with in vitro fertilization is in the order of $10 000 to $15 000, and the procedure may need to be repeated if the initial implantation is not successful. Yet, from a strict financial point of view, this seems cost-effective when considering the cost of ataxia in terms of both a patient's lifelong care and post–gene discovery research funds. Therefore, directing our efforts to improving the technique and availability of PGD with in vitro fertilization with the aim of eradicating at least the known autosomal dominant ataxias seems logical. The same logic applies to other inherited disabling neurological disorders.

Preimplantation genetic diagnosis has been initially applied to select the sex of the newborn to primarily avoid X-linked disorders.[6] However, the potential nonclinical applications of the technique such as selecting certain characteristics of the newborn including sex has led to the controversy surrounding PGD and the public concern about the ethics of such practice. Nonetheless, in cases of ataxia, PGD is ethically acceptable to most affected parents. Indeed, PGD is likely to be more acceptable than prenatal diagnostic procedures such as amniocentesis because it avoids having to make the difficult decision of terminating a pregnancy of an affected fetus. Therefore, there seems to be little ethical concern about using PGD in a disabling disease such as

Corresponding

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Basic, Translational and Neurogenetics Research Unit in Neurodegeneration
BTN Unit

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Dr. Iñaki de Diego

sin ciencia NO hay tratamientos

GRÀCIES!
GRACIAS!