EXAMPLE OF A SUCCESSFUL R&D COLLABORATION: THE RIBERMOV LATIN-AMERICAN NETWORK ON MOVEMENT DISORDERS.

Antoni Matilla Dueñas
Director Functional and Translational Neurogenetics Unit
RIBERMOV Coordinator
Genetics Section Editor "The Cerebellum"
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Universitat Autònoma de Barcelona
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What is RIBERMOV?

www.ribermov.org

Argentina:

Brazil:

Chile:

UNIVERSIDAD DE CHILE

Cuba:

Centro para la Investigación y Rehabilitación de las Ataxias Hereditarias

Ecuador:

Peru:

Portugal:

INSTITUTO DE BIOLOGIA MOLECULAR E CELULAR
INSTITUTE FOR MOLECULAR AND CELL BIOLOGY

Spain:

Health Research Institute
Germans Trias i Pujol

MINISTERIO
DE ECONOMÍA
Y COMPETITIVIDAD

Instituto
de Salud
Carlos III

GENERAL OBJECTIVES

Clinical:

- Clinical Registry of patients.
- Unified Clinical Research Protocol.
- Biological Samples.
- Clinical-Genetic correlations.

Epidemiological:

- Estimate incidence and prevalence of studied diseases.

Genetics:

- Develop and implement new tools to facilitate diagnosis.
- Identify and characterise underlying genetic and molecular causes.

Translational:

- Identify and characterise new molecular pathways.
- Elucidate pathophysiological mechanismes.
- Translate the new knowledge to implement therapies.

MAIN OBJECTIVES

- To standardize methodologies to implement clinical and interventional studies.
- To generate a record of clinical information with natural histories and to collect DNA samples for each registered individual.
- To analyze the epidemiological impact and risk factors for these diseases in each participating country.
- To provide genetic diagnosis and counseling as preventive measures.
- To carry out familiar studies using genetic linkage, disequilibrium, and association analysis to identify new disease causal deficits.
- To complement clinical investigations with basic research studies aimed to elucidate the underlying physiopathological molecular mechanisms.
- To identify new risk factors including modifier genes aimed at understanding the clinical variability with direct towards the prognosis.
- To identify new molecular pathways and biomarkers using molecular tools of structural biology, proteomics and transcriptomics studies to assist the diagnosis, prevention, and the design and development of effective therapeutic strategies.

SPECIFIC AIMS

1. To promote **Clinical Research**. To standardize methodologies in order to implement clinical, epidemiological and interventional studies. Information systems will be implemented to include the Hospital records of clinical information with natural histories and epidemiological data. DNA samples for each registered individual will be collected and a BioBank for Biological samples was created for the study of these pathologies.

2. To analyze the **epidemiological impact**, the prevalences, and risk factors for these diseases in each participating country.

3. To implement **diagnosis and genetic counseling** as preventive measures. Family studies were carried out using genetic linkage, disequilibrium and wide association studies to identify new disease genes and causal deficits. Modifier genes were also identified. Genotype-phenotype correlations were performed for causal molecular defects and potential neurophysiological biomarkers.

4. To complement clinical studies with **basic research** aimed to increase our knowledge of the underlying physiopathological molecular mechanisms. New risk factors including modifier genes were identified to explain the clinical variability with subsequent applications for the prognosis.

SPECIFIC AIMS

5. To identify new **molecular pathways and biomarkers** using molecular tools, structural biology, proteomics and transcriptomics studies to increase our knowledge of the underlying mechanisms to assist in diagnosis, prevention, and the design and establishment of therapeutic strategies.
6. To promote the design and establishment of **pre-clinical and clinical assays**.
7. To **promote training and exchange of specialists**, the **transfer of knowledge and technology** among the participating countries in the various disciplines of Clinical, Epidemiology, Genetics, and Basic Research. European standards were implemented in the Ibero-American participating groups for genetic and clinical protocols as well as in the regulations on consent and confidentiality in data processing, and for the usage and shipment of biological samples.
8. To generate a **website and an interactive platform** for the exchange and dissemination of knowledge, results, ideas, and for discussing projects or needs of each group and that of other groups in Latin-American countries.

RIBERMOV Activities

Meetings	65
Training: 4 RIBERMOV TC	53 Fellowships
Workshops	58
Books	3
Book chapters	10
Guides	2
Publications	51
Scientific conferences	81
Projects	18
Extra-mural grant funding	22

4 fellowships to attend III RIBERMOV TC in Lima, Peru, September 2012:

1. Raphael Machado de Castilhos (Brasil)
2. Juan Cristobal Núñez Fuster (Chile)
3. Denny Almaguer Gotay (Cuba)
4. Isabel Alonso (Portugal)

Scientific Meetings

XVIII Curso Internacional de Neurociencias,
Sociedad Peruana de Neurología, Agosto 2013

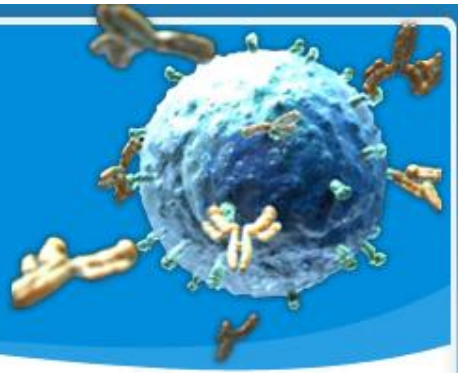
1ST Bilateral Workshop CUBA-SPAIN, March 2011

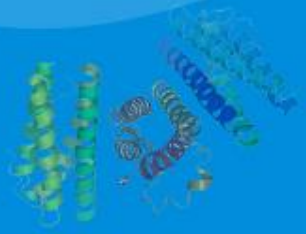
Salón de Conferencias
Hotel Rio Sol de Mares

DrC Luis Velázquez
(Cuba)

DrC Jose A Obeso
(España)

Immuno pharmacology 2011





IV International Symposium on Hereditary Ataxias

Themes in IV International Symposium on Hereditary Ataxias

1. Preclinical and Clinical Trials in SCA2 Patients and Other Polyglutamine Diseases.
2. Neuropharmacogenetics.
3. Neurodegenerative Diseases due to Proteinopathies: From SCA2 to Other Related Conditions (Huntington Disease, Amyotrophic Lateral Sclerosis, Parkinson Disease, Alzheimer Disease, Prion Diseases).
4. Neurochemistry and Immunology as Therapeutic and Diagnostic Tools for Hereditary Ataxias.
5. New Insights into the Molecular Characterization of Hereditary Ataxias.
6. Pathophysiological and Neuroprotective Mechanisms in Polyglutamine Diseases.
7. New Ataxias Electrophysiological Biomarkers.
8. Molecular Neuroepidemiology of Hereditary Ataxias.
9. Ethical and Psychological Aspects in the Diagnosis of Neurodegenerative Diseases.
10. Neuroinformatic and Neurosciences.
11. Hereditary Ataxias Seen Through the Experience of Patients and Relatives.

4th International Symposium on Inherited Ataxias, Varadero, Cuba, June 2011

AWARD RAFAEL ESTRADA in memoriam

Varadero, Cuba 2011

Los 5 premiados con el presidente del Jurado

Jonas Saute (Brasil) recibiendo el premio

IGTP
Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol

SEMINARI NEUROCIÈNCIES

TÍTOL: **OXIDACIÓN DE DOPAMINA Y NEURODEGENERACIÓN DE NEURONAS EN LA ENFERMEDAD DE PARKINSON.**

PONENT: **PROF. JUAN SEGURA AGUILAR**
PROGRAMA DE FARMACOLOGÍA CLÍNICA Y MOLECULAR, UNIVERSIDAD DE CHILE,
RED IBEROAMERICANA MULTIDISCIPLINAR PARA EL ESTUDIO DE LOS TRASTORNOS DEL MOVIMIENTO (RIBERMOV)-CYTED

DATA: **DIVENDRES 11 MARÇ 2011**

HORA: **12.00**

LLOC: **AULA POLIVALENT,**
INSTITUT D'INVESTIGACIÓ EN CIÈNCIES DE LA SALUT GERMANS TRIAS I PUJOL (IGTP)

HOSTE: **DR. ANTONI MATILLA, NEUROCIÈNCIES, COORDINADOR RIBERMOV**

RIBERMOV
CYTED

Congreso Europeo de Neurociencias,
Barcelona,
Julio 2012

Congreso Internacional de
Huntington, Septiembre 2013

Visit to the National Institutes of Health, USA, May 2013

Annual Meeting of the American Neurology Society, San Diego, USA, 2013

Scientific Achievements

http://lattes.cnpq.br/4353623807142918

Laura Bannach Jardim, MD, PhD

e-mail: ljardim@hcpa.ufrgs.br

Médica.

Professora do Departamento de Medicina Interna, da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul.

Chefe do Serviço de Genética Médica do Hospital de Clínicas de Porto Alegre

Coordenadora da Rede Neurogenética da UFRGS.

Áreas de interesse:

Neurogenética, Erros Inatos do Metabolismo e Aconselhamento Genético.

Atua principalmente em pesquisa clínica, sobre os seguintes temas: doenças neurogenéticas, como as ataxias espinocerebelares, e doenças neurometabólicas, como as esfingolipidoses e a adrenoleucodistrofia ligada ao X.

JOINT PUBLICATIONS

OPEN ACCESS Freely available online

PLoS one

Ancestral Origin of the ATTCT Repeat Expansion in Spinocerebellar Ataxia Type 10 (SCA10)

Teresa Almeida[1], Isabel Alonso[1], Sandra Martins[2], Eliana Marisa Ramos[1], Luísa Azevedo[2], Kinji Ohno[3], António Amorim[2,4], Maria Luiza Saraiva-Pereira[5], Laura Bannach Jardim[5], Tohru Matsuura[3], Jorge Sequeiros[1,6], Isabel Silveira[1]*

February 2009 | Volume 4 | Issue 2 | e4553

JOINT PUBLICATIONS

Cerebellum
DOI 10.1007/s12311-011-0316-8

REVIEW ARTICLE

Ataxia Rating Scales—Psychometric Profiles, Natural History and Their Application in Clinical Trials

Jonas Alex Morales Saute · Karina Carvalho Donis · Carmen Serrano-Munuera · David Genis · Luís Torres Ramirez · Pilar Mazzetti · Luis Velázquez Pérez · Pilar Latorre · Jorge Sequeiros · Antoni Matilla-Dueñas · Laura Bannach Jardim · On behalf of the Iberoamerican Multidisciplinary Network for the Study of Movement Disorders (RIBERMOV) Study Group

Abstract We aimed to perform a comprehensive systematic review of the existing ataxia scales. We described the disorders for which the instruments have been validated and used, the time spent in its application, its validated psychometric properties, and their use in studies of natural history and clinical trials. A search from 1997 onwards was performed in the MEDLINE, LILACS, and Cochrane databases. The web sites ClinicalTrials.gov and Orpha.net were also used to identify the endpoints used in ongoing randomized clinical trials. We identified and described the semiquantitative ataxia scales (ICARS, SARA, MICARS, BARS); semiquantitative ataxia and non-ataxia scales (UMSARS, FARS, NESSCA); a semiquantitative non-ataxia scale (INAS); quantitative ataxia scales (CATSYS

JOINT PUBLICATIONS

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

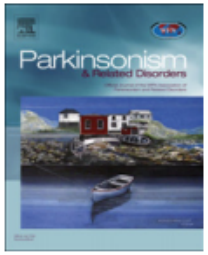
JOINT PUBLICATIONS

Parkinsonism and Related Disorders 17 (2011) 629–631

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 [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]

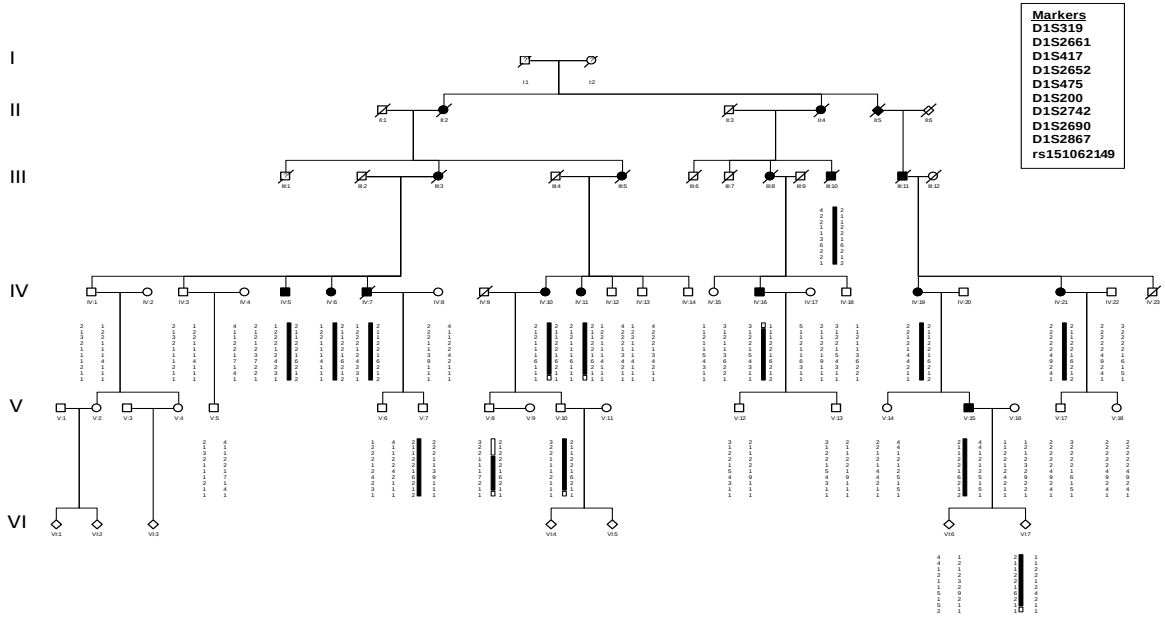
JAMA Neurology

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



Science News

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

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.

The results have been published online on April 29 in the journal *JAMA Neurology*.

The cause of ataxia is a diverse genetic alteration. For this reason it is classified in subtypes. The new subtype identified described by the researchers has been called SCA37. The study has found this subtype in members of the same family living in Barcelona, Huelva and Madrid and Salamanca (Spain). The finding will allow in the medium term that these families and all who suffer the genetic alteration identified will have personalized therapies and diagnostics prior to the development of the disease. The study was funded by La Marató de TV3 (the Catalan public TV) in 2009, dedicated to rare diseases.

Related Topics

Health & Medicine
- Today's Healthcare
- Diseases and Conditions
- Personalized Medicine

Mind & Brain
- Alzheimer's
- Disorders and Syndromes
- Stroke

Articles
- Rett syndrome
- Neurology
- Huntington's disease
- Traumatic brain injury
- Transmissible spongiform encephalopathy
- Multiple sclerosis

Related Stories

Dysfunction in Cerebellar Calcium Channel Causes Motor Disorders and Epilepsy (Mar. 21, 2013) — A dysfunction of a certain calcium channel, the so called P/Q-type channel, in neurons of the cerebellum is sufficient to cause different motor diseases as well as a special type of ...
> *read more*

New Genetic Disorder of Balance and Cognition

Just In:
Hidden Genetic Code for Better Designer Genes
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... from NewsDaily.com

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- Climate panel forecast: Higher seas, temperatures

sistemas genómicos BIOMÉDICA

Targeted Exome Sequencing NEUROLOGICAL DISEASES: 400 genes (Neurogene Profile®)

Functional and Translational Neurogenetics Unit IGTP

MYASTHENIAS
NEUROPATHIES

- Demyelinating
- Axonal
- Intermedium
- AD, AR, LX

- **88 GENES**

ATAXIAS
LEUCODISTROPHIES

- Spinocerebellar
- Episodic
- Spastic
- Telangiectasia
- Friedreich
- Syndromic

- **99 GENES**

DEMENTIAS
ALS
PARKINSON TREMOR

- Late Onset
- Early Onset
- Dementia with Parkinsonism

- AD
- AR
- **99 GENES**

PARAPLEGIAS

- AD
- AR
- LX
- Syndromic

- **89 genes**

DIOSTROPHIES
MIOPATHIES

- Emery Dreyfuss
- Waist
- Distroglycans
- D Merosin

- M. Disproportion fiber
- Miotubular
- Nemalinic
- Minicore

- **74 genes**

ALGORITHM FOR THE GENETIC DIAGNOSIS OF INHERITED ATAXIAS

AUTOSOMAL DOMINANT

EXPANSION DETECTION: SCAs 1, 2, 3, 6, 7, 10, 12, 17, 36, DRPLA

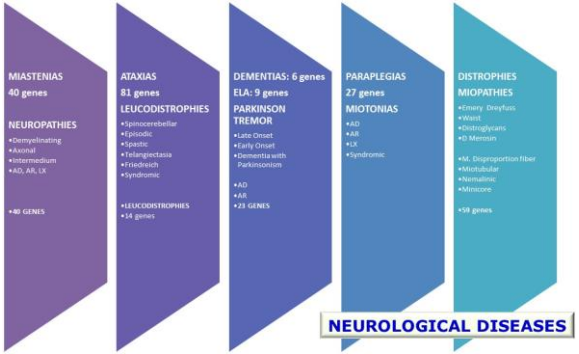
AUTOSOMAL RECESSIVE

GAA EXPANSION: Friedreich Ataxia

Negative

MULTIGENE PANEL ATAXIAS: 99 GENES

Negative



X-LINKED INHERITANCE

Negative

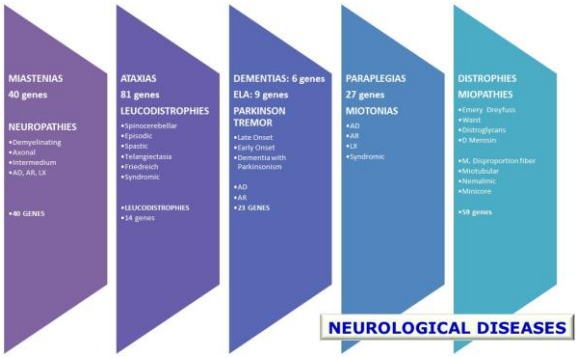
EXOME SEQUENCING RESEARCH

ALGORITHM FOR THE DIAGNOSIS OF INHERITED NEUROPATHIES

MLPA: 5 genes

Negative

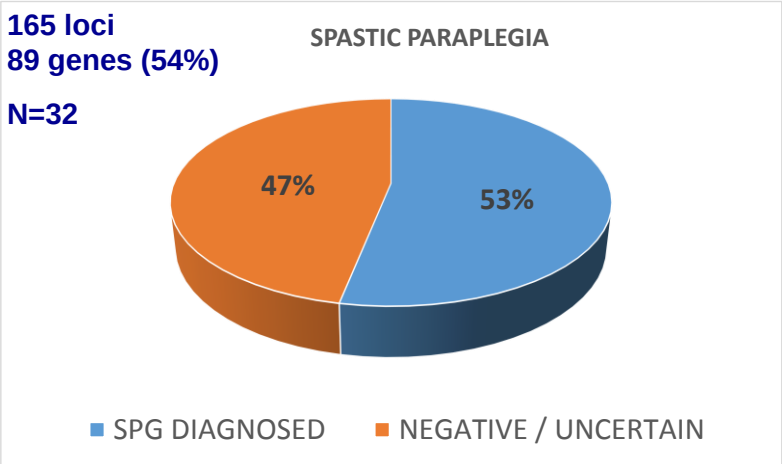
MULTIGENE PANEL CMT: 88 genes

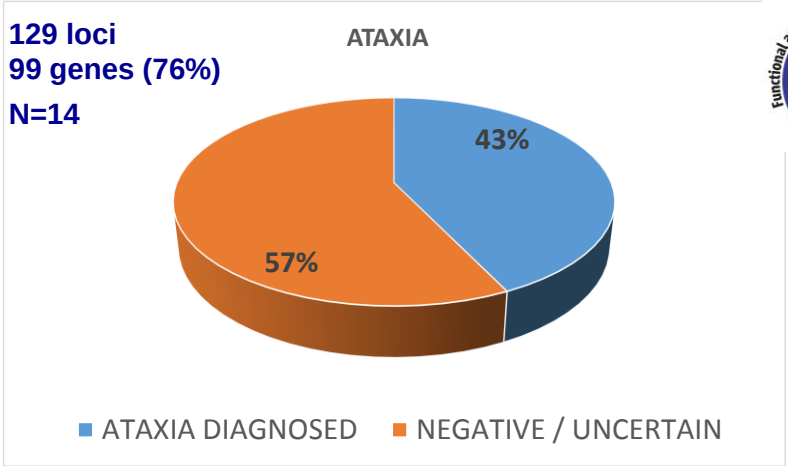


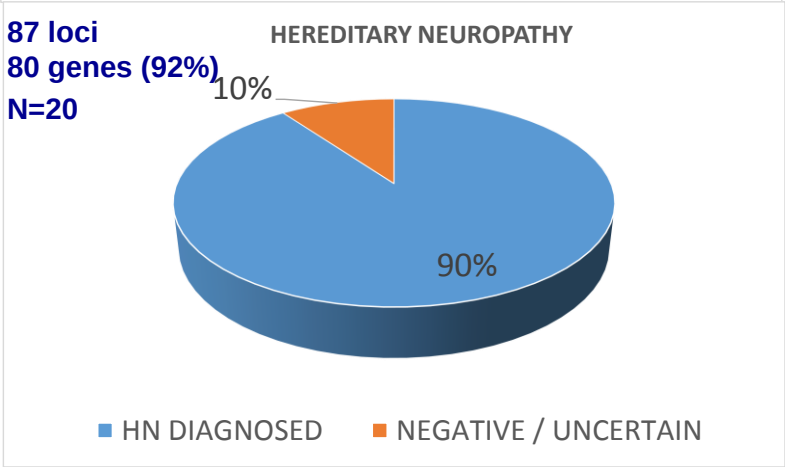
Negative

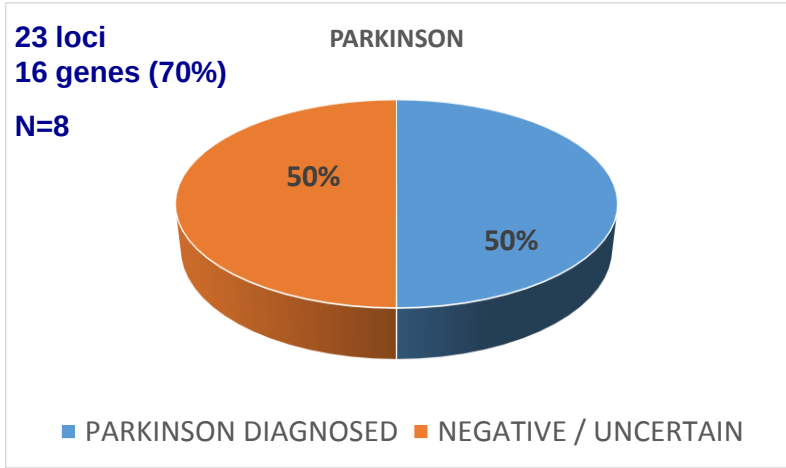
EXOME SEQUENCING

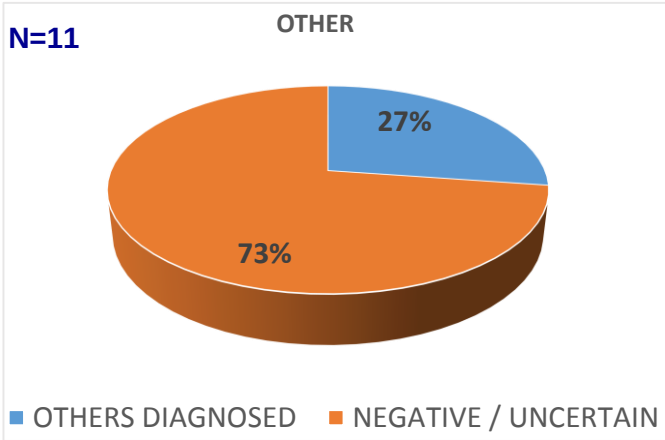
RESEARCH


165 loci
89 genes (54%)
N=32
SPASTIC PARAPLEGIA
47%
53%
SPG DIAGNOSED
NEGATIVE / UNCERTAIN


129 loci
99 genes (76%)
N=14
ATAXIA
43%
57%
ATAXIA DIAGNOSED
NEGATIVE / UNCERTAIN

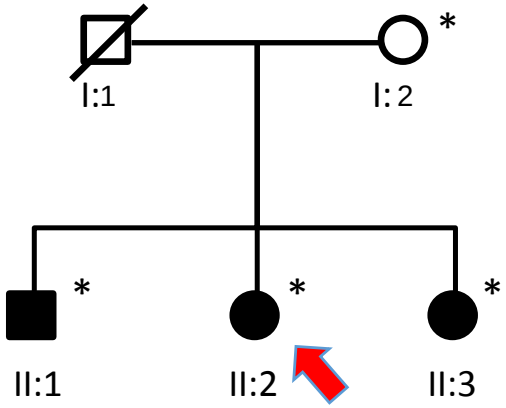

87 loci
80 genes (92%)
N=20
HEREDITARY NEUROPATHY
10%
90%
HN DIAGNOSED
NEGATIVE / UNCERTAIN


23 loci
16 genes (70%)
N=8
PARKINSON
50%
50%
PARKINSON DIAGNOSED
NEGATIVE / UNCERTAIN

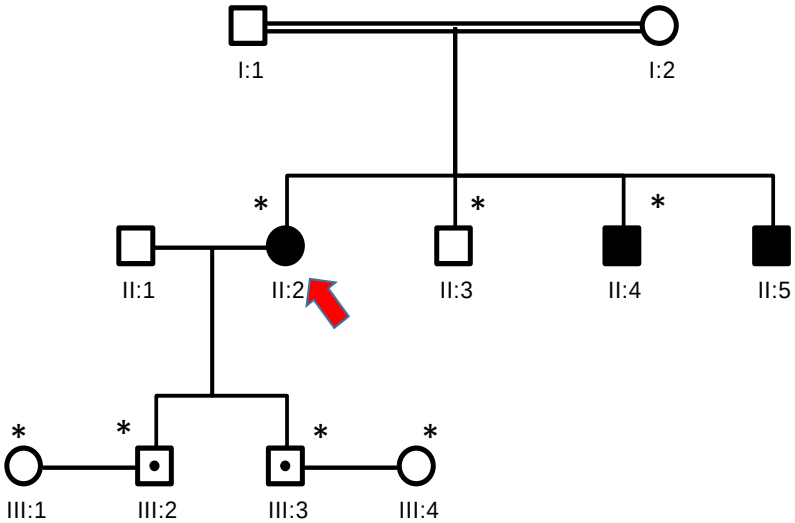

N=11
OTHER
27%
73%
OTHERS DIAGNOSED
NEGATIVE / UNCERTAIN

METHODOLOGY	SAMPLE	SYMPTOMS	INHERITANCE	ANALYSED GENES	MUTATED GENE	MUTATIONS		GENETIC DIAGNOSIS	PROTEIN PREDICTION	COMMENTS
NGS AMPLICONS	AT-1	ATAXIA	AR	APTX	*SACS*	Het. c.9938delC (Exón 10)	p.Pro3313Glnfs*11	ARSACS	READING FRAME ALTERATION & PREMATURE STOP CODON	NOVEL
				SETX						
				SACS		Het. c.11375C>T (Exón10)	p.Arg3792*		PREMATURE STOP CODON	(Bouhlal *et al.* 2008)
	AT-2	ATAXIA WITH TREMOR	AD	CACNA1A	*CACNA1A*	Het. c.11375C>T (Exón 8)	p.Glu362Ser	EA2	PREMATURE STOP CODON	NOVEL
PANEL	AT-3	SCA5/15/26/29?	AD	ATAXIAS PANEL	*ITPR1*	Het. c.4218C>G (Exón 32)	p.His1406Gln	SCA15/29	PROBABLY PATHOGENIC	NOVEL (MAF G=0.0062/31)
	AT-4	ATAXIA TELANGIECTASIA	AR	ATM, ATR, MRE11A	*ATM*	Homo c.1199T>C (Exón 7)	p.Leu400Pro	AT	PROBABLY PATHOGENIC	NOVEL
	AT-5	ATAXIA WITH OCULOMOTOR APRAXIA	AR	ATAXIAS PANEL	*ATM*	Compound Het. c.6679C>T (Exón 48)	p.Arg2227Cys	AT	PROBABLY PATHOGENIC	(Sandoval *et al.* 1999)
						Compound Het c.7328G>A (Exón 52)	p.Arg2443Gln		PROBABLY PATHOGENIC	NOVEL
	AT-6	ATAXIA WITH TREMOR	AD	ATAXIAS PANEL	*CACNA1A*	Het. c.37G>A (Exón 1)	p.Gly13Arg	EA2	PROBABLY PATHOGENIC	NOVEL
	AT-7	ATAXIA	AR	PANEL	*FA2H*	Compound Het. c.771C>G (Exón 5)	p.His257Gln	HETEROGENIC SPG35	PROBABLY PATHOGENIC	NOVEL
						Compound Het. c.1055C>T (Exón 7)	p.Thr352Ile		PROBABLY PATHOGENIC	NOVEL
EXOME SEQUENCING	AT-8	ATAXIA	AR	EXOME	*SYNE1*	Homo. c.16933C>T (Exón 90)	p.Gln5645*	SCAR8	PREMATURE STOP CODON	NOVEL
	AT-9	ATAXIA, HEARING LOSS, EARLY MENOPAUSE	AR	EXOME	*C10ORF2*	Compound Het. c.85C>T (Exón 1)	p.Arg29*	IOSCA	PREMATURE STOP CODON	(Goh *et al.* 2011)
						Compound Het. c.1886C>T (Exón 5)	p.Ser629Phe		PROBABLY PATHOGENIC	NOVEL
	AT-10	ATAXIA, SPASTIC PARAPLEGIA, MYOCLONIC TREMOR	AR	EXOME	*RNF170*	Homo. c.702_705delCTTT (Exón 7)	p.Phe234Leufs*17	DIFFERENTIATED PHENTOYPE	PREMATURE STOP CODON	NOVEL

Familia AT-9



Familia AT-10



LIMITATIONS

1. Heterogeneity in resources in participating groups
    - Funding resources
    - Human resources
    - Methodologies, etc
2. Different country regulations:
    - Biobank
    - Biological samples
    - Consentment forms for Genetics studies
    - Patient Data Protection
    - Intellectual Property
    - Etc.

CONCLUSIONS

1. Latin-American Collaborative Networks and Projects are needed and welcome
2. More Funding and Resources to Latin-American Groups to make them possible
3. Identify problems and limitations to overcome them
4. Successful interactions
5. Training is highly benefited: human resources
6. Translation and Exploitation of Results
7. Collaboration with Industry
8. Latin-American groups are very well trained, very eager to collaborate, but have limitations and resources and funding.

Barcelona, Spain, 2013

Thank you for your attention!!