ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

# First AGI Regional Meeting – Latin America and the Caribbean

## Building a Clinical Trial Network for Hereditary Ataxias: Perspectives from the Cuban Ataxia Project

**Luis Velázquez Pérez, MD, PhD, D.Sc, Dr.hc**
President of the Cuban Academy of Sciences
Senior Professor of Medical University of Havana
Emeritus Researcher of the Cuban Academy of Sciences

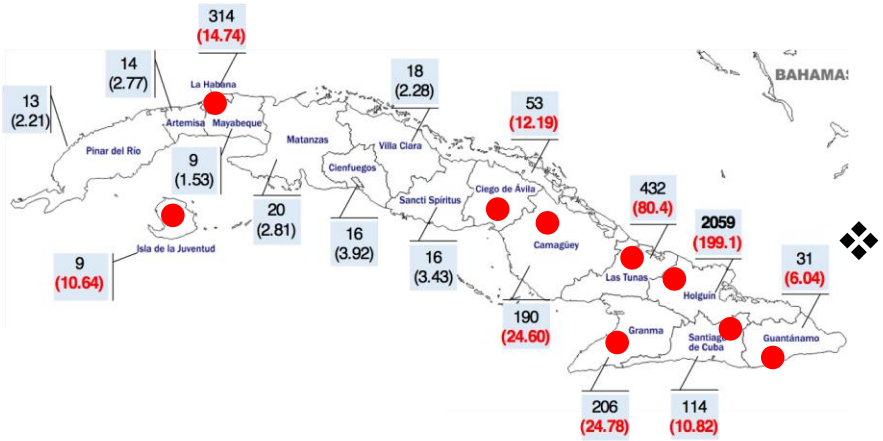
RED CUBANA DE ATAXIAS HEREDITARIAS

# Overview of SCA2

- Cuba has the world's highest concentration of SCA2 subjects, which is caused by a CAG repeat expansion in the *ATXN2* gene and to date, over 2,000 patients have been diagnosed and 10,000 descendants at risk

- Each year, 35 new cases are diagnosed and 20 patients die from the disease and the time to death is abot 16 to 20 years after disease onset

- Approximately 25% of cases had juvenile onset and the clinical course to disability is approximately 10 years.

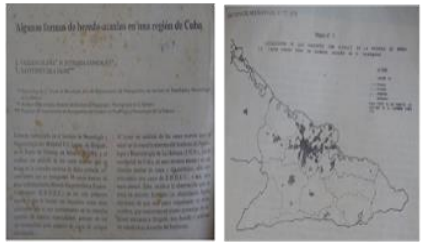



- Families affected by SCA2 have spread across the whole country.


**Aim:** To provide medical care and conducting basic-to traslational researches

*Neurosci Let, 2009, The Cerbellum, 2011, Clin Genet, 2008*

# I. Key Contributions of Epidemiological and Molecular Studies





Epidemiología de la ataxia hereditaria cubana

Neuroscience Letters

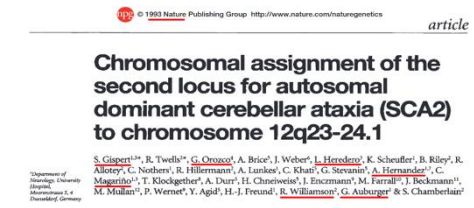
Molecular epidemiology of spinocerebellar ataxias in Cuba: Insights into SCA2 founder effect in Holguin

ORIGINAL PAPER

Hereditary Ataxias in Cuba: A Nationwide Epidemiological and Clinical Study in 1001 Patients

- Initial observations of a large HA population come from the 1970s, with the first study in eastern Cuba followed by a second survey in 1998 in Holguín province (Vallés, 1978; Velázquez et al, 1998).
- Nationwide epidemiological studies were conducted in 2003 and 2018, covering the whole country.
- Also, we have developed epidemiological studies in other countries.
- These findings emphasize Cuba's leading role in the epidemiology of SCAs and highlight the significant public health impact of these disorders across different countries.

# Key Molecular Contributions



article

Chromosomal assignment of the second locus for autosomal dominant cerebellar ataxia (SCA2) to chromosome 12q23-24.1

S. Gispert[1,3*], R. Twells[2*], G. Orozco[1], A. Brice[3], J. Weber[4], L. Heredero[1], K. Scheufler[1], B. Riley[2], R. Allotey[1], C. Nothen[1], R. Hillermann[1], A. Lunkes[1], C. Khati[3], G. Stevanin[3], A. Hernandez[1,], C. Magariño[1,3], T. Klockgether[4], A. Durr[3], H. Chneiweiss[4], I. Enczmann[4], M. Farrall[2,], J. Beckmann[1], M. Mullan[2], P. Wernet[4], Y. Agid[3], H.-J. Freund[1], R. Williamson[2], G. Auburger[4] & S. Chamberlain[2]

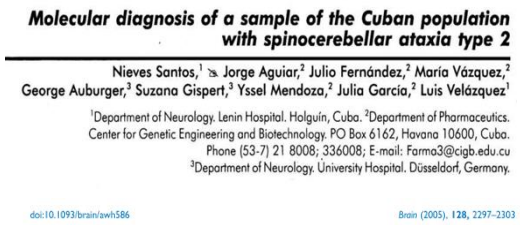
article

The causal gene: Ataxin-2 (ATXN2)

Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2

Stefan-M. Pulst[1], Alex Nechiporuk[1*], Tamilla Nechiporuk[1*], Suzana Gispert[2], Xiao-Ning Chen[3], Jacia Lopes-Cendes[4], Susan Pearlman[5], Sidney Starkman[5], Guillermo Orozco-Diaz[2], Astrid Lunkes[2], Pieter DeJong[3], Guy A. Rouleau[6], Georg Auburger[2], Julie R. Korenberg[7], Carla Figueroa[1] & Soodabeh Sahba[1]

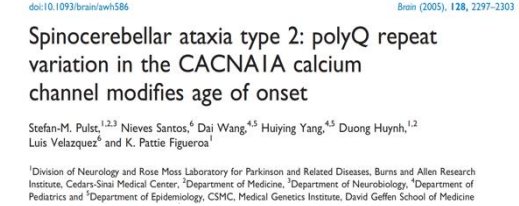
The gene for spinocerebellar ataxia type 2 (SCA2) has been mapped to 12q24.1. A 1.1-megabase contig in the candidate region was assembled in P1 artificial chromosome and bacterial artificial chromosome clones. Using this contig, we identified a CAG trinucleotide repeat with CAA interruptions that was expanded in patients with SCA2. In contrast to other unstable trinucleotide repeats, this CAG repeat was not highly polymorphic in normal individuals. In SCA2 patients, the repeat was perfect and expanded to 36–52 repeats. The most common disease allele contained $(CAG)_{22}$, one of the shortest expansions seen in a CAG expansion syndrome. The repeat occurs in the 5′-coding region of *SCA2* which is a member of a novel gene family.



Molecular diagnosis of a sample of the Cuban population with spinocerebellar ataxia type 2

Nieves Santos,[1] Jorge Aguiar,[2] Julio Fernández,[2] María Vázquez,[2] George Auburger,[3] Suzana Gispert,[3] Yssel Mendoza,[2] Julia García,[2] Luis Velázquez[1]

[1]Department of Neurology. Lenin Hospital. Holguín, Cuba. [2]Department of Pharmaceutics. Center for Genetic Engineering and Biotechnology. PO Box 6162, Havana 10600, Cuba. Phone (53-7) 21 8008; 336008; E-mail: Farma3@cigb.edu.cu [3]Department of Neurology. University Hospital. Düsseldorf, Germany.

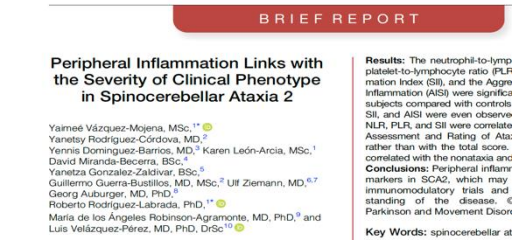


doi:10.1093/brain/awh586 Brain (2005), 128, 2297–2303

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

Stefan-M. Pulst,[1,2,3] Nieves Santos,[6] Dai Wang,[4,5] Huiying Yang,[4,5] Duong Huynh,[1,2] Luis Velazquez[6] and K. Pattie Figueroa[1]

[1]Division of Neurology and Rose Moss Laboratory for Parkinson and Related Diseases, Burns and Allen Research Institute, Cedars-Sinai Medical Center, [2]Department of Medicine, [3]Department of Neurobiology, [4]Department of Pediatrics and [5]Department of Epidemiology, CSMC, Medical Genetics Institute, David Geffen School of Medicine



BRIEF REPORT

Peripheral Inflammation Links with the Severity of Clinical Phenotype in Spinocerebellar Ataxia 2

Yairneé Vázquez-Mojena, MSc,[1*] Yanetsy Rodríguez-Córdova, MD,[2] Yennis Domínguez-Barrios, MD,[3] Karen León-Arcia, MSc,[1] David Miranda-Becerra, BSc,[4] Yanetza Gonzalez-Zaldivar, BSc,[5] Guillermo Guerra-Bustillos, MD, MSc,[2] Ulf Ziemann, MD,[6,7] Georg Auburger, MD, PhD,[5] Roberto Rodríguez-Labrada, PhD,[1*] María de los Ángeles Robinson-Agramonte, MD, PhD,[8] and Luis Velázquez-Pérez, MD, PhD, DrSc[10]

**Results:** The neutrophil-to-lymp platelet-to-lymphocyte ratio (PLR mation Index (SII), and the Aggre Inflammation (AISI) were significa subjects compared with controls SII, and AISI were even observe NLR, PLR, and SII were correlate Assessment and Rating of Ata: rather than with the total score. correlated with the nonataxia and **Conclusions:** Peripheral inflamr markers in SCA2, which may immunomodulatory trials and standing of the disease. Parkinson and Movement Disor

**Key Words:** spinocerebellar at

- Localization of the locus for SCA2 disease on the long arm of cromosome number 12 (Gisper, 2013).
- Identifying the specific mutation that causes SCA2 ataxia (Pulst, 1996).
- Longer alleles of the SCA6 gene have been found to modify the age of onset in patients with SCA2 (Pulst, 2005).
- Creating an animal model of SCA2 expressing the gene with 75 CAG repeats (Aguiar, 2006).
- Evidencing that long normal alleles are the main source of new SCA2 mutations explaining the high prevalence of SCA2 in Cuba (Laffita, 2011).
- Elevated peripheral inflammation markers in SCA2 patients were associated with cognitive deficits (Vázquez, 2024, 2025).
- The implementation of predictive diagnostic programs benefited over 2,000 individuals from more than 150 families.

# II.- Comprehensive Phenotype Characterization

- Cerebellar disorders (100%)
  - Ataxia of the gait
  - Intention tremor
  - Dysmetria
  - Incoordination of the upper and lower limbs
  - Cerebellar dysarthria

- Non-cerebellar signs:
  - Slowing of saccadic eye movements (95%)
  - Peripheral neuropathy (73%)
  - Amyotrophy (30%)
  - Sleep disturbances (90%)
  - Cognitive disorders (48%)

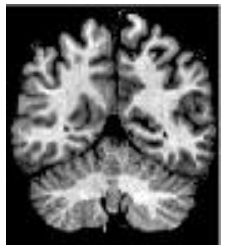
- Final Stage:
  - Severe weight loss
  - No speech/anarthria
  - Severe disphagia

*Velázquez-Pérez L, et al. Cerebellum 10:184–198, 2011.*
*Velázquez-Pérez L, et al. Neuros Letter, 2009*

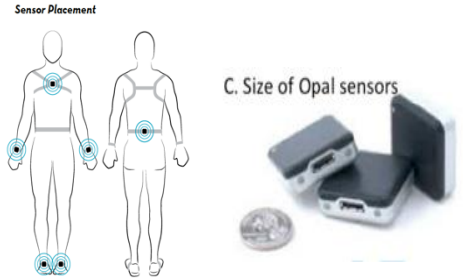
# III.- Indentification of Biomarkers

Biomarkers are classified according to the nature of the measurement and include Clinical, genetic, biochemical, imaging, electrophysiological and digital biomarkers.

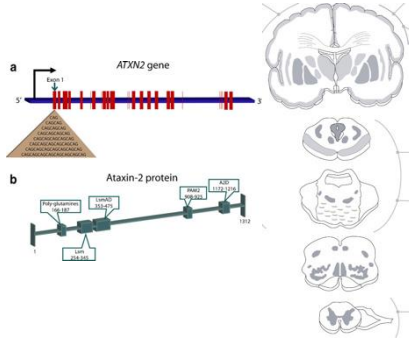
**Clinical Biomarkers**



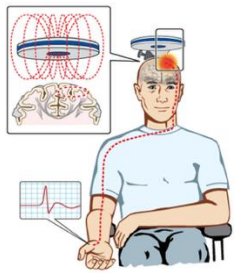
**Imaging Biomarkers**



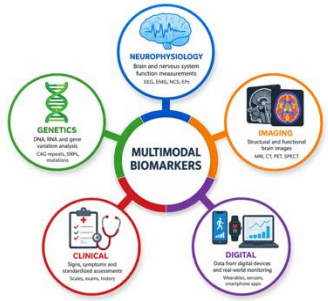

**Digital Biomarkers**




**Genetic damage Biomarkers**



**Electrophysiological Biomarkers**




**Multimodal Biomarkers**

*Biomarkers Definitions Working Group, 2001*
*Velázquez-Pérez L, et al. Clinical Neurophysiology 135 (2022) 1–12*

# Digital Biomarkers

RESEARCH ARTICLE

Gait Variability in Spinocerebellar Ataxia Assessed Using Wearable Inertial Sensors

Vrutangkumar V. Shah, PhD,[1*] Roberto Rodriguez-Labrada, PhD,[2,3] Fay B. Horak, PhD, PT,[1,4] James McNames, PhD,[4,5] Hannah Casey, BS,[6] Kyra Hansson Floyd, BA,[6] Mahmoud El-Gohary, PhD,[4] Jeremy D. Schmahmann, MD,[7] Liana S. Rosenthal, MD, PhD,[8] Susan Perlman, MD,[9] Luis Velázquez-Pérez, MD, PhD,[2,10] and Christopher M. Gomez, MD, PhD[1,6]

**Binational (CUBA-US):**

- 163 patients
- 42 preclinical carriers
- 96 controls

**Main Results:** Identification novel gait biomarkers able to differentiate subtle gait abnormalities in SCAs subjects from healthy controls.

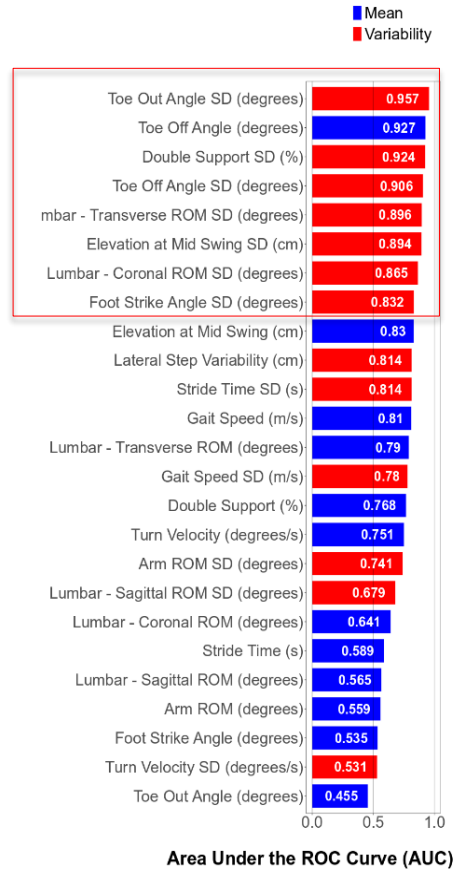
Increased gait variability is the most distinctive digital signature of SCA.

These digital gait markers correlate with ataxia severity and disease duration, supporting their value for progression monitoring and clinical trials.

RESEARCH ARTICLE

Prodromal Spinocerebellar Ataxia Type 2 Subjects Have Quantifiable Gait and Postural Sway Deficits

Luis Velázquez-Pérez, DSc,[1,2*] Roberto Rodriguez-Labrada, PhD,[1,3] Yasmani González-Garcés, BSc,[1] Eduardo Arrufat-Pie, MD,[4] Reidenis Torres-Vega, BSc,[1] Jacqueline Medrano-Montero, PhD,[1] Beatriz Ramirez-Bautista, MD,[5] Yaimeé Vazquez-Mojena, MSc,[1,3] Georg Auburger, MD,[6] Fay Horak, PhD,[7] Ulf Ziemann, PhD,[8,9] and Christopher M. Gomez, PhD[10]




*Movement Disorders, 2021, 2022*

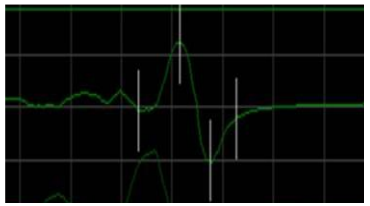
# Electrophysiological Biomarkers

Electrophysiological measures are useful parameters to assess the neurodegeneration of non-cerebellar system in pre-ataxic and ataxic stages of SCA2.

Saccade Velocity is Controlled by Polyglutamine Size in Spinocerebellar Ataxia 2

Luis Velázquez-Pérez, MD,[1] Carola Seifried, MD,[2] Nieves Santos-Falcón,[1] Michael Abele, MD,[3] Ulf Ziemann, MD,[2] Luis Enrique Almaguer, PhD,[1] Edilberto Martínez-Góngora, MD,[1] Gilberto Sánchez-Cruz, MD,[1] Nalia Canales, MD,[1] Ruth Pérez-González, MD,[1]

*Ann Neurol 2004;56:444–447*

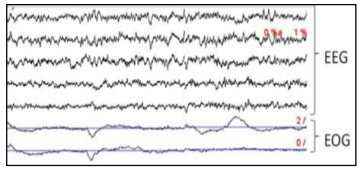


**Transcraneal Magnetic Stimulation**
Increasing of the CMC (93%)

ELSEVIER — Journal of the Neurological Sciences 263 (2007) 158–164

Electrophysiological features in patients and presymptomatic relatives with spinocerebellar ataxia type 2

Luis Velázquez Pérez *, Gilberto Sánchez Cruz, Nalia Canales Ochoa, Roberto Rodríguez Labrada, Julio Rodríguez Díaz, Luis Almaguer Mederos, José Laffita Mesa

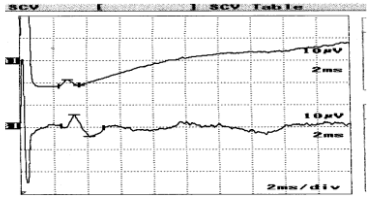



**Video-Polysomnography**
REM Sleep pathology (84%)

Contents lists available at ScienceDirect — Clinical Neurophysiology — journal homepage: www.elsevier.com/locate/clinph

Saccade velocity is reduced in presymptomatic spinocerebellar ataxia type 2

L. Velázquez-Pérez[a], C. Seifried[b], M. Abele[c], F. Wirjatijasa[b], R. Rodríguez-Labrada[a], N. Santos-Falcón[a], G. Sánchez-Cruz[a], L. Almaguer-Mederos[a], R. Tejeda[a], N. Canales-Ochoa[a], M. Fetter[d], U. Ziemann[b], T. Klockgether[c], J. Medrano-Montero[a], J. Rodríguez-Díaz[a], J.M. Laffita-Mesa[a], G. Auburger[b,*]

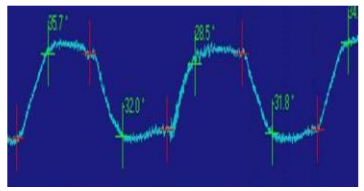



**Sensory Nerve Conduction Studies**
Decrease of the sensory nerve amplitude (92%)

Contents lists available at ScienceDirect — Journal of the Neurological Sciences — journal homepage: www.elsevier.com/locate/jns

Progression markers of Spinocerebellar Ataxia 2. A twenty years neurophysiological follow up study

Luis Velázquez-Perez[a,*,1], Roberto Rodríguez-Labrada[a], Nalia Canales-Ochoa[a], Gilberto Sanchez-Cruz[a], Juan Fernandez-Ruiz[b,c], Jacqueline Medrano Montero[a], Raúl Aguilera-Rodríguez[a], Rosalinda Diaz[b], Luis E. Almaguer-Mederos[a], Agustín Palomino Truitz[d]




**Electronystagmography**
Saccade Slowing (95.1%)

Original Paper

Neurodegenerative Diseases

Neurodegenerative Dis 2011;8:447–454 — DOI: 10.1159/000324374

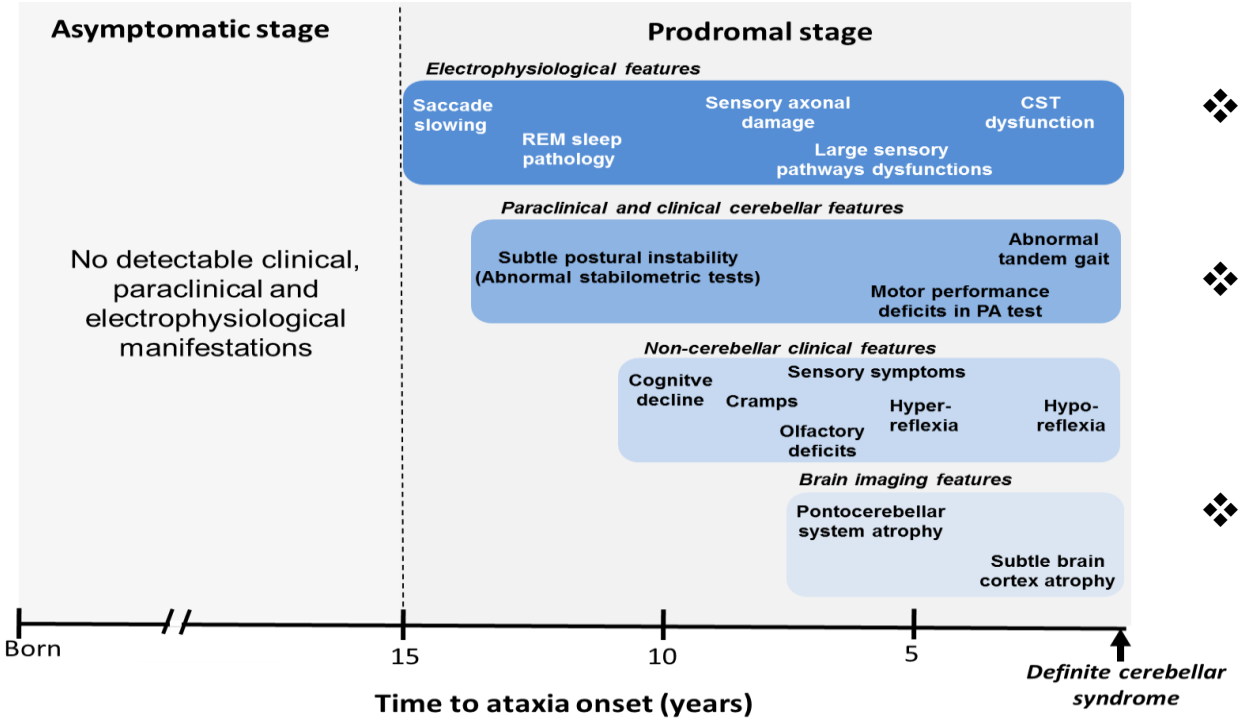
Received: June 26, 2010 — Accepted after revision: January 13, 2011 — Published online: April 15, 2011

Luis Velázquez-Pérez[a] Ursula Voss[b,c] Roberto Rodríguez-Labrada[a] Georg Auburger[b] Nalia Canales Ochoa[a] Gilberto Sánchez Cruz[a] Lourdes Galicia Polo[a] Reyes Haro Valencia[a] Raúl Aguilera Rodríguez[a] Jacqueline Medrano Montero[a] Jose M. Laffita Mesa[a] Inka Tuin[b,d]

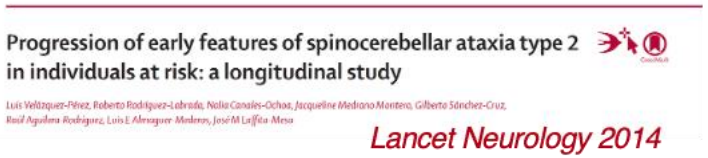
Velázquez-Pérez L, et al. Clin Neurophysiol 2009, 2016
Rodríguez-Labrada R, et al. Mov Dis, 26(2):347-350, 2011.
Velázquez-Pérez L, et al. J Neurol Sci, 2007
*Velázquez-Pérez L,, et al. Clinical Neurophysiology 135 (2022) 1–12*

# IV.- Prodromal Stage in SCA2

## Chronological order of prodromal disease stage abnomalities according to time to ataxia onset

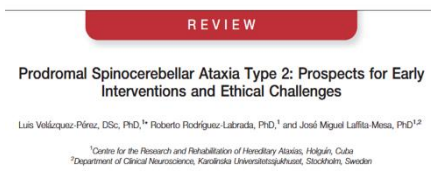



- **Earliest stage:** saccade slowing and REM sleep abnormalities.
- **Intermediate stage:** subtle postural instability, abnormal tándem gait, sensory pathway damage, corticospinal dysfunction, cognitive and reflex changes.
- **Near ataxia onset:** MRI evidence of pontocerebellar and mild cortical atrophy.


Progression of early features of spinocerebellar ataxia type 2 in individuals at risk: a longitudinal study

Luis Velázquez-Pérez, Roberto Rodríguez-Labrada, Nolia Canales-Ochoa, Jacqueline Medrano-Montero, Gilberto Sánchez-Cruz, Raúl Aguilera-Rodríguez, Luis E Almaguer-Mederos, José M Laffita-Mesa

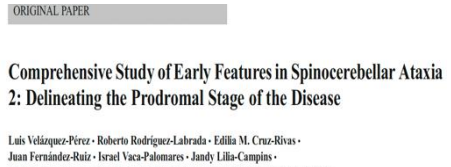
Lancet Neurology 2014


REVIEW

Prodromal Spinocerebellar Ataxia Type 2: Prospects for Early Interventions and Ethical Challenges

Luis Velázquez-Pérez, DSc, PhD,[1]* Roberto Rodríguez-Labrada, PhD,[1] and José Miguel Laffita-Mesa, PhD[1,2]

[1]Centre for the Research and Rehabilitation of Hereditary Ataxias, Holguín, Cuba
[2]Department of Clinical Neuroscience, Karolinska Universitetssjukhuset, Stockholm, Sweden


ORIGINAL PAPER

Comprehensive Study of Early Features in Spinocerebellar Ataxia 2: Delineating the Prodromal Stage of the Disease

Luis Velázquez-Pérez · Roberto Rodríguez-Labrada · Edilia M. Cruz-Rivas · Juan Fernández-Ruiz · Israel Vaca-Palomares · Jandy Lilia-Campins · Bulmaro Cisneros · Arnov Peña-Acosta · Yaimeé Vázquez-Mojena · Rosalinda Díaz ·

# V. Contributions to Therapeutic Approaches

- Nine clinical interventions involving nearly 300 patients and 31 preclinical individuals have been developed in Cuba SCA2 subjects.
- NeuroEPO was safe and exhibited a small clinical effect on motor and cognitive abnormalities after 6 months.
- The rehabilitation treatment improves subtle coordination deficits in prodromal SCA2 and reduces SARA scores in symptomatic patients.
- Rehabilitation should be integrated with future disease-modifying therapies.
- The Cuban SCA2 population represents one of the world's most valuable human platforms for hereditary ataxia trials.


RESEARCH ARTICLE

Erythropoietin in Spinocerebellar Ataxia Type 2: Feasibility and Proof-of-Principle Issues from a Randomized Controlled Study

Roberto Rodriguez-Labrada, PhD,[1,2] Ricardo Ortega-Sanchez, MD,[1] Patricia Hernández Casaña, PhD,[3] Orestes Santos Morales, MD,[3] Maria del Carmen Padrón-Estupiñan, MD,[4] Maricela Batista-Nuñez, MD,[5] Daise Jiménez Rodríguez, MSc,[6] Nalia Canales-Ochoa, BSc,[1] Arnoy Peña Acosta, BSc,[1]


RESEARCH ARTICLE

Neurorehabilitation Therapy in Spinocerebellar Ataxia Type 2: A 24-Week, Rater-Blinded, Randomized, Controlled Trial

Julio Cesar Rodríguez-Díaz, BSc,[1] Luis Velázquez-Pérez, DSc,[1,2,3]* Roberto Rodríguez Labrada, PhD,[1,2,3] Raúl Aguilera Rodríguez, MD,[1] Dalina Laffita Pérez, BSc,[4] Nalia Canales Ochoa, BSc,[1] Jacqueline Medrano Montero, PhD,[1,3] Annelié Estupiñán Rodríguez, BSc,[1] Marcos Osorio Borjas, MD,[5] Mariela Góngora Marrero, MSc,[1] Lorenzo Reynaldo Cejas, BSc,[1] Yanetza González Zaldívar, BSc,[1] and Dennis Almaguer Gotay, MSc[1]


RESEARCH ARTICLE

Neurorehabilitation Improves the Motor Features in Prodromal SCA2: A Randomized, Controlled Trial

Luis Velázquez-Pérez, DSc,[1,2*] Julio C. Rodríguez-Diaz, BSc,[1] Roberto Rodríguez-Labrada, PhD,[1,2,3] Jacqueline Medrano-Montero, PhD,[1,3] Annety B. Aguilera Cruz, MD,[4] Lorenzo Reynaldo-Cejas, BSc,[1] Mariela Góngora-Marrero, MSc,[1] Annelié Estupiñán-Rodríguez, BSc,[1] Yaimeé Vázquez-Mojena, MSc[1,2,3] and Reidenis Torres-Vega, BSc[1]

# Key Messages

- The Cuban Ataxia Project is a model for the comprehensive management of neurodegenerative disorders that could be useful to other regions of the world.

- Cuba provides a homogenous cohort that has been well-studied, as well as organizational expertise and strategic vision to an international network.

# Acknowledgements


- SCA2 preclinical carriers
- Healthy controls

CIRAH´s research team

Habana research team

pahan

## International collaborators

Georg Auburger

Neurophysiology

Ulf Ziemann

TMS/Coherence

Kathrin Reetz

Imis Dogan

Sandro Romanzetti

MRI/Clinics -CARE project

Adam Vogel

Matthis Synofzik

Winfried Ilg

Disarthria/Swallowing

Christopher

Fay Horak

Movement analysis

Juan Fernandez

Jonathan Magañas

MRI/Visuomotor learning/Molecular features


Thank you !!!