HIGH-LEVEL WORKSHOP

The U.S.-Cuba Exchange on Neurodegenerative Diseases: Experiences in the Hereditary Ataxias Field

Prof. Luis C. Velázquez Pérez
President of the Cuban Academy of Sciences
Founding Director of the Pan-American Ataxias Network

2023

Global SCAs

- Spinocerebellar ataxias are progressive, neurodegenerative, and heterogeneous diseases that are characterized by gait impairment, incoordination of eye and limb movements, and dysarthria.

- Progressive deterioration of patients SCAs has a major impact on the health-related quality of life.

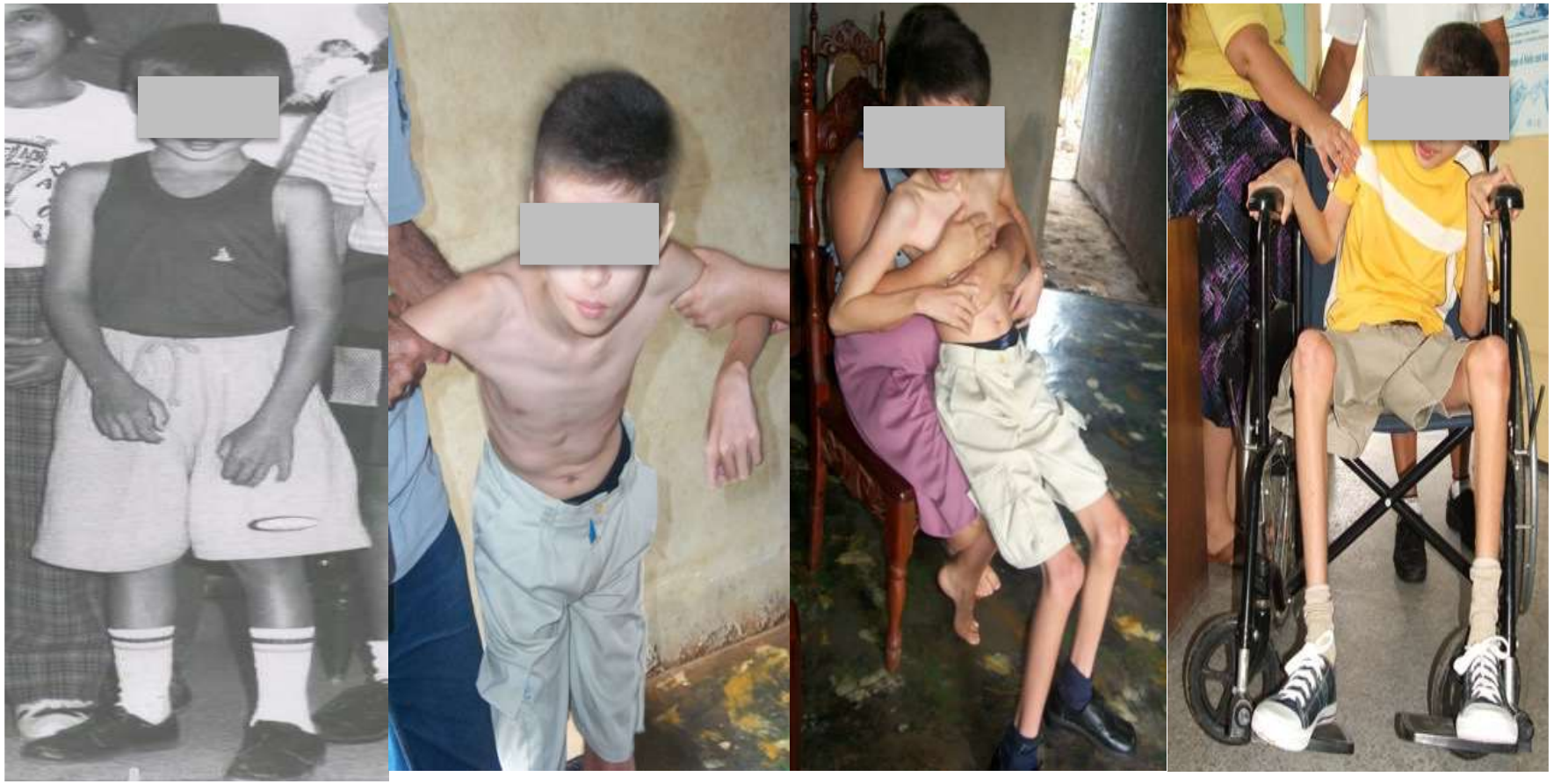
- SCAs often appear in adults, but also in the paediatric age group.

Slight gait ataxia **External aid** **Wheelchair** **Confinement to bed**

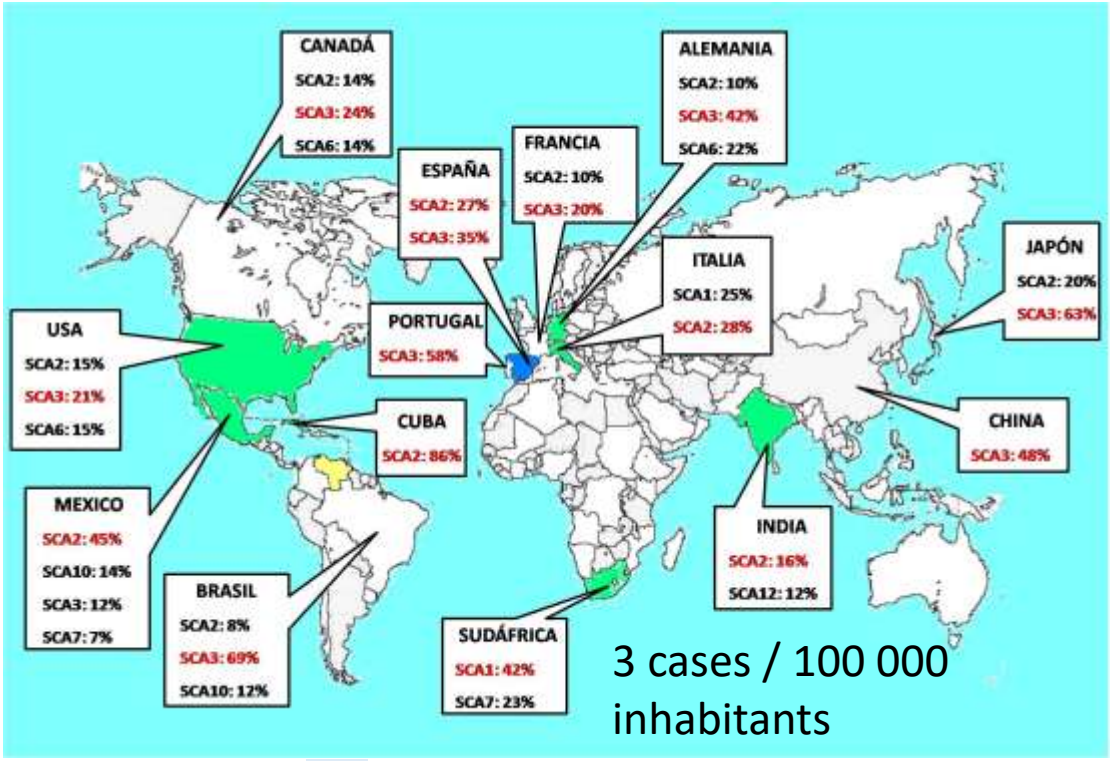
SARA: 3 - 15 points ***SARA: 15 - 25 points*** ***SARA: 26 - 35*** ***SARA: + 35 points***

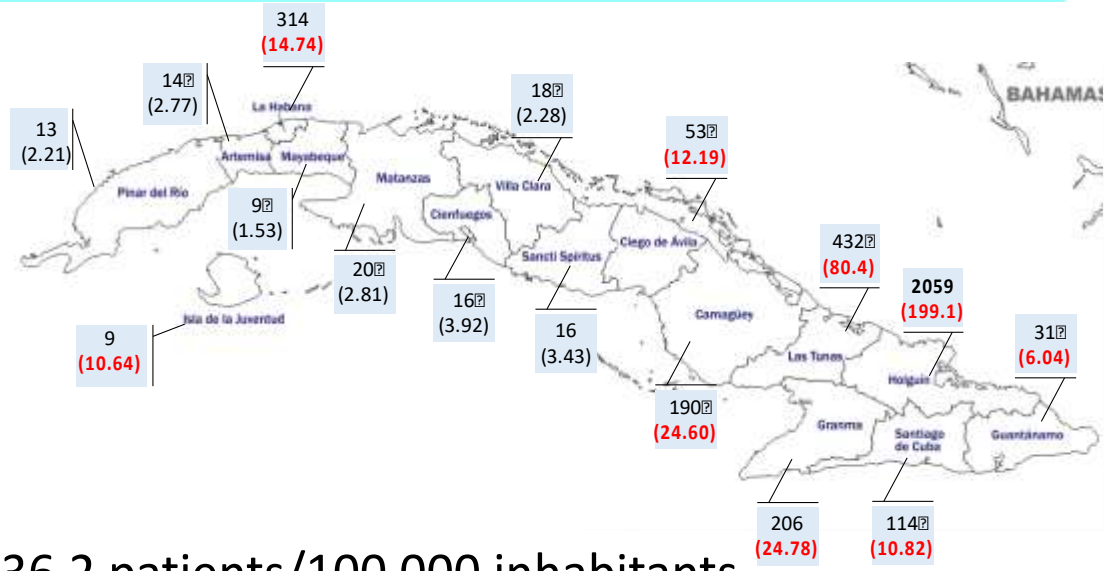
The Cerebellum (2020) 19:252–264

Progression of the Disease in the Paediatric Onset



Global Epidemiology





36.2 patients/100 000 inhabitants

The Cerebellum (2020) 19:252–264

Center for Research and Rehabilitation of Hereditary Ataxias









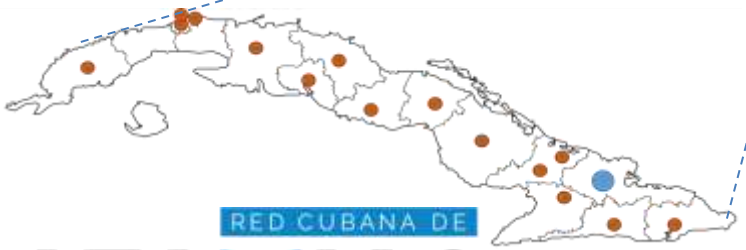
Networks for the Research of Hereditary Ataxias

GLOBAL NETWORK OF SPINOCEREBELLAR ATAXIAS

SCA Global

PAN-AMERICAN NETWORK OF HEREDITARY ATAXIAS

PANHA



RED CUBANA DE ATAXIAS HEREDITARIAS

CUBAN NETWORK OF HEREDITARY ATAXIAS

CUBA-USA Relationships in Ataxia Research

- 1 Multinational network (PanAmerican Network of Hereditary Ataxias

pahan
pan american hereditary ataxia network

- 7 papers in high-impact journals (Brain, Neurology, JAMA, Mov Disord, etc)
- 287 cites


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

RESEARCH ARTICLE

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

- Bilateral academic/teaching formation

Main topics of collaboration:

- ❖ Molecular researches
- ❖ Biomarkers
- ❖ Epidemiology

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

Nature, 1996, IF: 69.504Citation rate: 35/year

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

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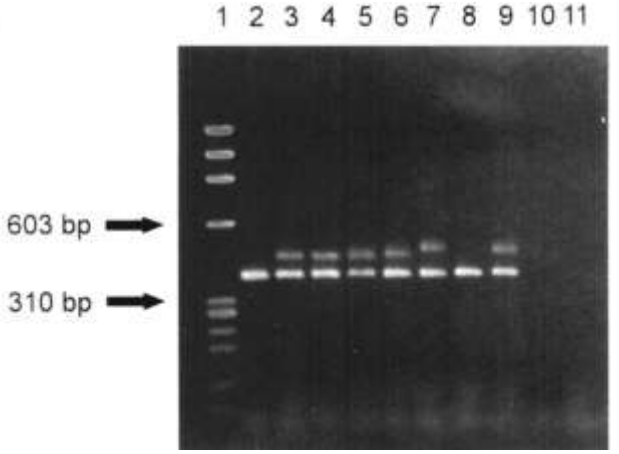
[2]*Department of*

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 $(CAG)_{37}$, 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.










Modifier Genes

IF: 15.255

Citation rate: 9.6/year

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,[4] Dai Wang,[4,5] Huiying Yang,[4,5] Duong Huynh,[1,2] Luis Velazquez[4] and K. Pattie Figueroa[1]

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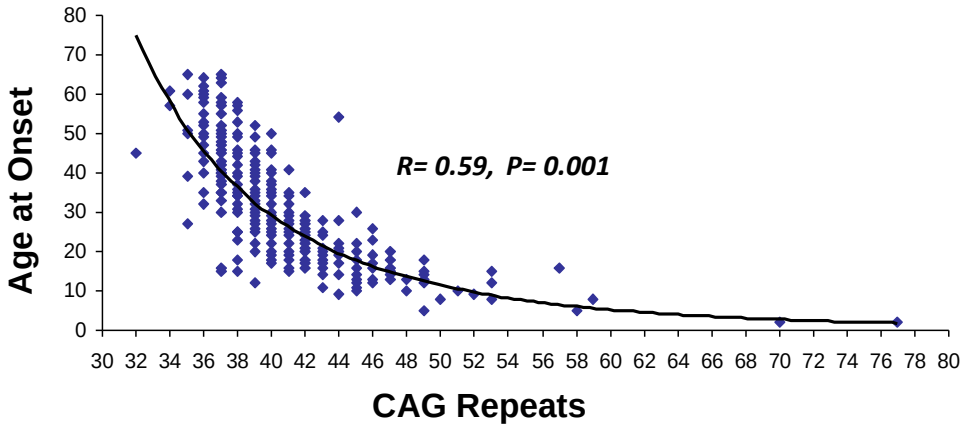
Nine neurodegenerative diseases, collectively referred to as polyglutamine (polyQ) diseases, are caused by expansion of a coding CAG DNA trinucleotide repeat. PolyQ diseases show a strong inverse correlation between CAG repeat length and age of disease onset (AO). Despite this, individuals with identical repeat expansion alleles can have highly variable disease onset indicating that other factors also influence AO. We examined AO in 148 individuals in 57 sibships from the SCA2 founder population in Cuba. The mutant CAG repeat allele explained 57% of AO variance. To estimate heritability of the residual variance after correction for



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OBSERVATION

Mitochondrial Complex I Gene Variant Associated With Early Age at Onset in Spinocerebellar Ataxia Type 2

David K. Simon, MD, PhD; Kangni Zheng, MD; Luis Velazquez, MD, PhD; Nieves Santos, MD; Luis Almaguer, MD; K. Pattie Figueroa, MS; Stefan-M. Pulst, MD

Background: A common mitochondrial complex I gene polymorphism (10398G) is reported to be inversely associated with the risk of Parkinson disease. We hypothesized that this variant might have a protective effect on the central nervous system and therefore might delay the onset of symptoms in spinocerebellar ataxia type 2 (SCA2).

Objective: To assess the association of the 10398G polymorphism with age at onset in Cuban patients with SCA2.

Design: Genetic association study.

Setting: Holguin, Cuba.

Patients: Forty-six Cuban patients with SCA2.

Main Outcome Measures: Presence or absence of the 10398G polymorphism was determined in 46 Cuban patients with SCA2 and early or late onset of symptoms, defined as at least 2 SDs lower than or higher than the mean age at onset for patients with a similarly sized triplet repeat expansion.

Results: The polymorphism was present in 11 of 27 Cuban patients with SCA2 and early onset (41%) vs 2 of 19 with late onset (11%) (Fisher exact test; P=.04).

Conclusion: Contrary to our prediction of a later onset of SCA2 in patients with the 10398G polymorphism, we find that this variant is associated with an earlier age at onset in Cuban patients with SCA2.

Arch Neurol. 2007;64(7):1042-1044

Impacts: clinical trials assessing the efficacy of calcium/potassium homeostasis stabilizers in SCA2 pathogenesis (Ex. dantrolene, riluzole) as well as antioxidant drugs

Transgenic mouse model of the SCA2

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SCIENCE DIRECT

Neuroscience Letters 392 (2006) 202–206

Neuroscience Letters

www.elsevier.com/locate/neulet

Ubiquitous expression of human SCA2 gene under the regulation of the SCA2 self promoter cause specific Purkinje cell degeneration in transgenic mice

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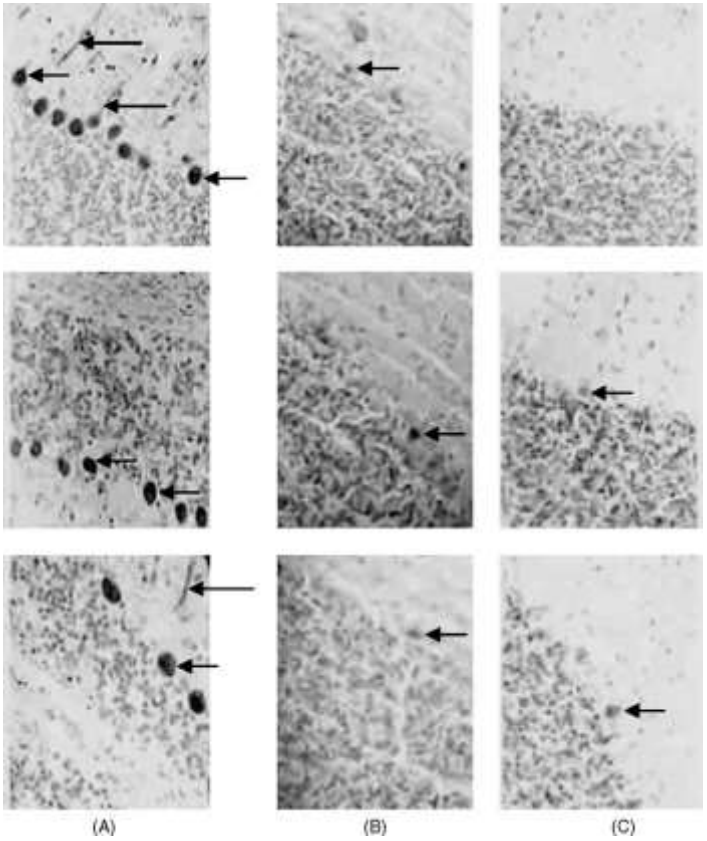
We are grateful to Dr. Stefan Pulst and Dr. Duong Huynh for providing the human SCA2 cDNA that contains the normal 22 CAG repeat, and the expansions of 40, 58 and 104 CAG repeats. We thank Dr. Oscar Díaz-Horta, for the critical review of the manuscript. We are indebted to Rafael Maura and Victor Patterson for their excellent technical assistance. This work has been supported by the Center for Genetic Engineering and Biotechnology (CIGB), Havana, Cuba.



non-transgenic mouse

founder F050

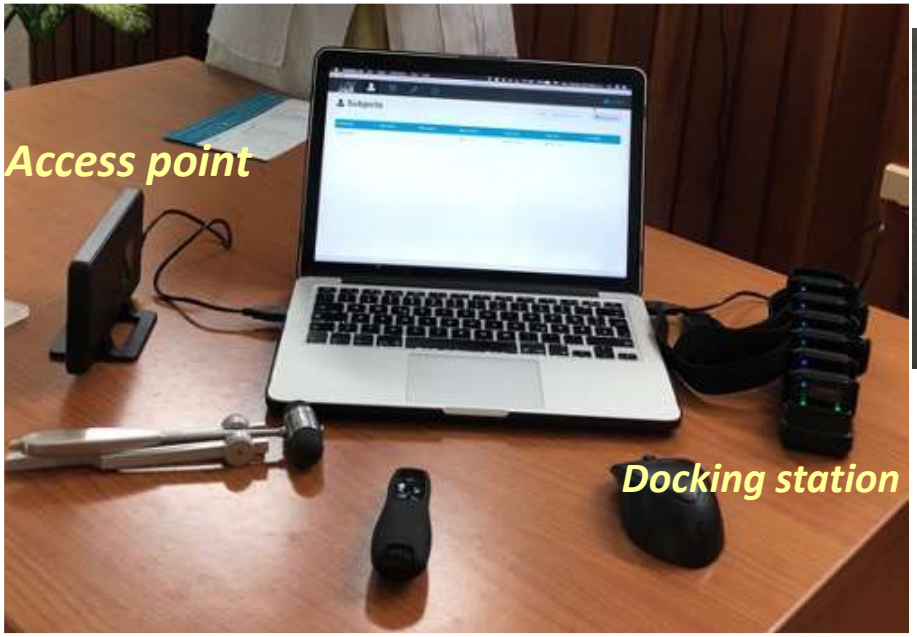
founder F066

Preclinical trial in Transgenic mouse

Erythropoietin in SCA2: A Randomized Controlled Study, Mov Dis 2022

NESCA Study: Phase III, placebo-controlled, randomized, double-blind

Biomarkers



- **Chicago University**

RESEARCH ARTICLE

Gait Variability in Spinocerebellar Ataxia Assessed Using Wearable Inertial Sensors

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[10]Cuban Academy of Sciences, La Habana, Cuba

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] Yaamani González-Garcés, BSc,[1] Eduardo Arrufat-Pie, MD,[4] Reidenis Torres-Vega, BSc,[1] Jacqueline Medrano-Montero, PhD,[1] Beatriz Ramírez-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]

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[10]Department of Neurology, University of Chicago, Chicago, Illinois, USA

Binational (CUBA-US) cohort of:

- 163 patients
- 42 preclinical carriers
- 96 controls

Cuban cohort of

- 30 preclinical carriers
- 30 controls

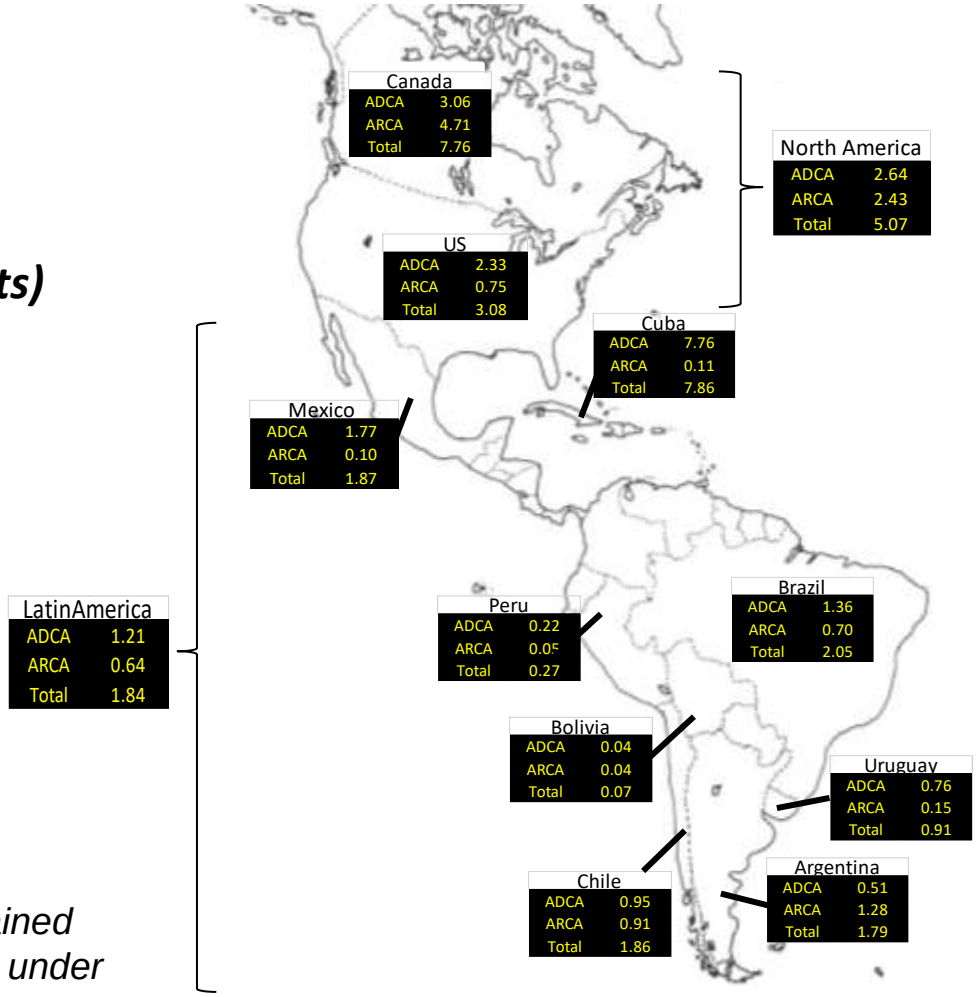
Description of objective indicators of motor deficits that can be used as surrogate markers of preclinical status, disease progression and molecular damage in SCAs

Clinical Trials

Movement Disorders, 2021, 2022

Hereditary Ataxias in the American Continent

Prevalence estimates (cases/100.000 inhabitants)



- *Prevalence estimates were obtained only with the number of patients under care*
- *Only Cuban data comes from national studies, the rest is from regional studies*

Bannach Jardim et al., 2022

Cumulative Number of Ataxia Diagnoses done in the last 20 years

Ataxia Families **Ataxia Patients**

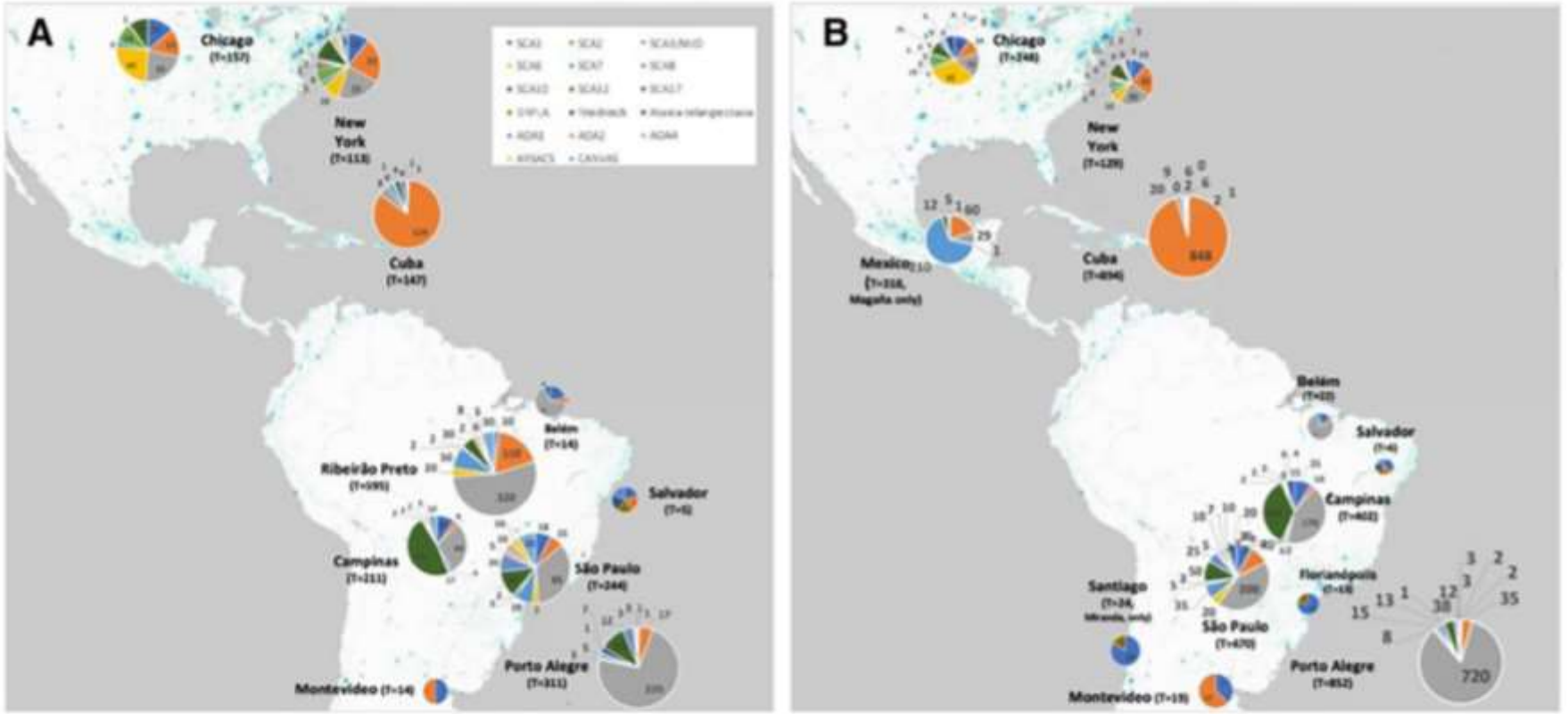
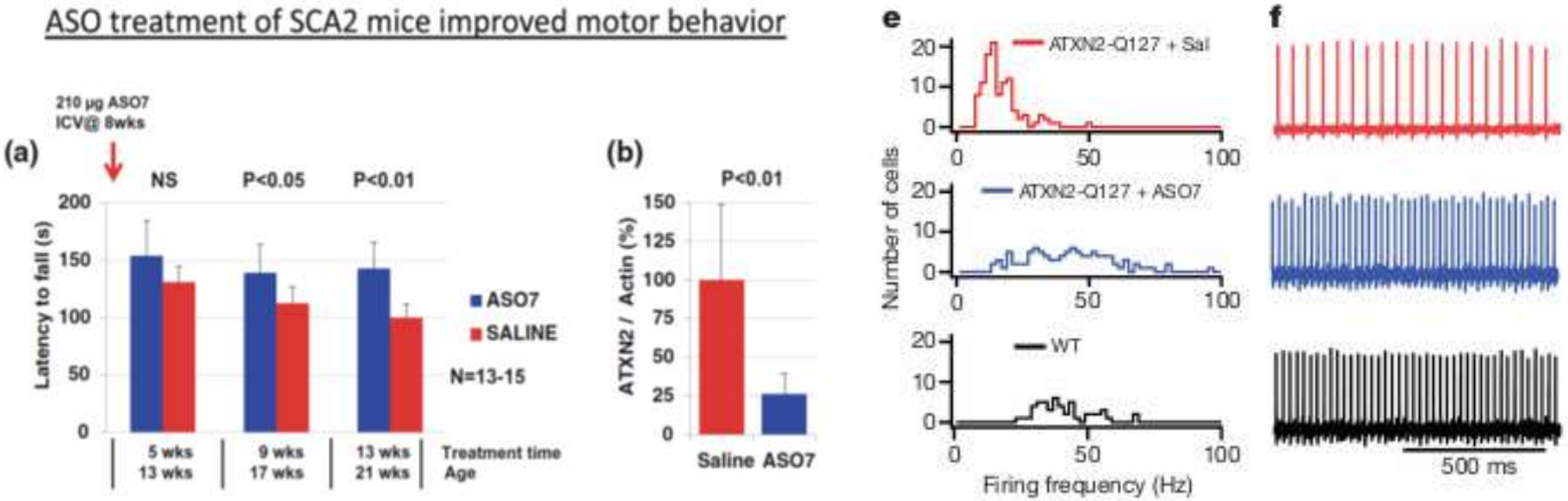


Fig. 3 Cumulative numbers of specific diagnoses done in the last 20 years, according to the information given by the participants of the survey. **A** Data obtained on the number of ataxia families. **B** Data obtained on the number of ataxia subjects

*The Cerebellum, 2022. (**On Behalf of the PAHAN)***

Therapies aimed at blocking the expression of the mutated protein that causes the disease



Scoles, DR, et al. Nature 2017; Pulst S and Scoles, 2018

U.S. National Library of Medicine

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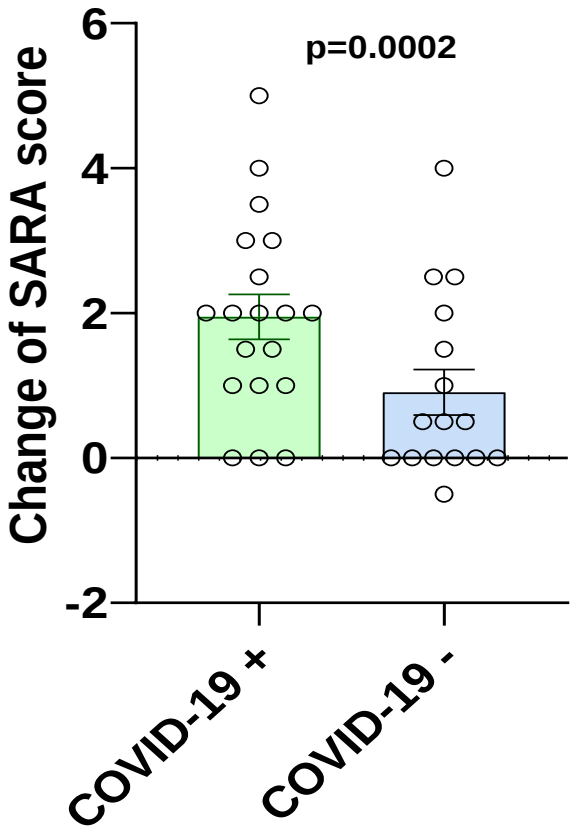
A Pharmacokinetics and Safety Study of BIIB132 in Adults With Spinocerebellar Ataxia 3

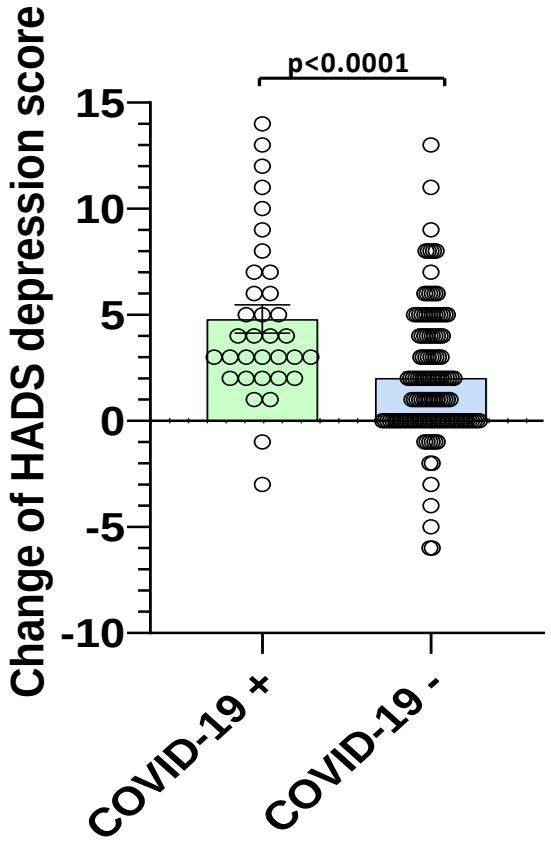
ClinicalTrials.gov Identifier: NCT05160558

Challenges: COVID-19 and Cerebellar Functioning

SARA Score

Annual SARA Score increase: 1.49





- N: 208 SCAs patients (24 preclinical subjects)
- 43 subjects developed COVID-19 disease (COVID-19+), while 159 became uninfected (COVID-19 -)

Thinking Loud:
How to follow?, Strengths, New Challenges

- The U.S.-Cuba collaboration on the Ataxia project has been successful.
- Facing new challenges for collaboration in ASOs therapy.
- Developing more sensitive biomarkers.

Building a lasting bridge between Cuba and the U.S. through scientific collaboration.

Thank you very much