Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

A Novel Variant in *SQSTM1* Gene Causing Neurodegeneration with Ataxia, Dystonia, and Gaze Palsy in a Peruvian Family

Cesar Chacaltana-Vinas, MD,[1] Patricia Ramirez-Pajares, MD,[1,2] Alid Manrique-Palomino, BS,[1] Amanda R. Clause, PhD,[3] Aditi Chawla, PhD,[3] Erin Thorpe, MS,[3] Ryan Taft, PhD,[3] Andrea Rivera-Valdivia, MD,[1,4] Elison Sarapura-Castro, MD,[1,4,*] Jeny Bazalar-Montoya, MD,[1,5] and Mario Cornejo-Olivas, MD[1,4]

Neurodegeneration with ataxia, dystonia and gaze palsy (NADGP), is an autosomal recessive disorder caused by disease-causing variants in the *SQSTM1* gene. There are at least 30 cases with NADGP reported worldwide. The classical phenotype includes progressive ataxia, dystonia, gaze palsy and learning difficulties,[1–4] however, clinical symptoms can vary even within the same family.

We present a Peruvian family with three affected siblings of non-consanguineous parents with an early-onset ataxia plus syndrome (Fig. 1). The proband (II-2) experienced difficulties walking and climbing stairs, and recurrent falls from age 6. She also complained about difficulties with picking up objects. She did not complete high school because of mild learning difficulties. She experienced slurred speech and muscle cramps since age 14. Neurological examination performed at 18 years showed muscle weakness and atrophy on both hypothenar eminences, hyperreflexia in her lower limbs, bilateral Babinski sign, gait and limb ataxia and dysarthria. She shows facial dystonia resembling a "grimacing", choreoathetosis in both arms with episodic limb jerk movements, and mild dystonic postures in both legs (Video 1). Restricted vertical gaze with abnormal saccades, and multidirectional nystagmus and vestibulo-ocular reflexes were also noted. Ancillary tests demonstrated increased LDH (535 U/L) and CK levels (82 U/L). Electromyography revealed a myopathic pattern. Brain MRI revealed mild cerebellar atrophy (Fig. S1). No iridoplegia nor anisocoria was identified. Molecular diagnosis performed by clinical whole genome sequencing (cWGS), identified a homozygous variant in the *SQSTM1* gene, NM_003900.5:c.1A > G (p. Met1?), which was classified as likely pathogenic (ACMG). Both clinically unaffected parents were heterozygous for this variant.

The proband's younger 12-year-old brother (II-4) experienced progressive walking, writing and drawing difficulties, as well as difficulty climbing stairs and running since age 7. He presented with jerky movements in his head and upper limbs and speech difficulties since age 8. He had moderate learning difficulties at school. On neurological examination he had weakness and atrophy on both hypothenar eminences, gait and limb ataxia and dysarthria. He shows "facial grimacing", mild generalized choreoathetosis with some jerk limb movements (Video 1). Downbeat nystagmus and vertical gaze restriction were also noted. Ancillary tests revealed elevated CK levels (201 U/L). Electromyography found a myopathic pattern. cWGS identified the same homozygous *SQSTM1* variant.

The proband's older 23-year-old sister (II-1) has a history of gait and walking instability with occasional falls since age 7. Swallowing difficulties and cramps since age 9 were reported. Neurological examination (video 1) revealed truncal and limb ataxia with dysarthria, orofacial dyskinesias with appearance of grimacing, mild generalized choreoathetosis, vertical gaze palsy, pes cavus and hammer toes with mild weakness for plantar dorsiflexion/flexion. Electromyography revealed myopathic pattern. She did not pursue genetic testing yet.

We present a family with NADGP phenotype carrying a homozygous *SQSTM1* variant. The wild-type *SQSTM1* protein regulates apoptosis and NRF2 activation, preventing oxidative stress and removing damaged mitochondria by autophagy.[5] Individuals with biallelic loss-of-function variants typically present with ataxia, dysarthria, cognitive decline, gaze palsy, dystonia, dyskinesia and chorea known as NADGP. By contrast, individuals with heterozygous *SQSTM1* missense or truncating variants present with FTD/ALS, distal myopathy with rimmed vacuoles and Paget disease.[5,6] NADGP should be considered within differential diagnosis among 100 early-onset dystonia-ataxic syndromes.[7]

Three affected siblings experienced early-onset ataxia with ophthalmoparesis, cognitive impairment, and hyperkinetic

[1]*Neurogenetics Research Center, Instituto Nacional de Ciencias Neurológicas, Lima, Peru;* [2]*Unidad Funcional de Genética y Biología Molecular, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru;* [3]*Illumina, Inc., San Diego, California, USA;* [4]*Neurogenetics Working Group, Universidad Científica del Sur, Lima, Peru;* [5]*School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru*

***Correspondence to:** Dr. Elison Sarapura-Castro, Neurogenetics Research Center, Instituto Nacional de Ciencias Neurologicas, 1271 Ancash St, 15003, Lima, Peru; E-mail: elison.sarapura.c@incngen.org.pe
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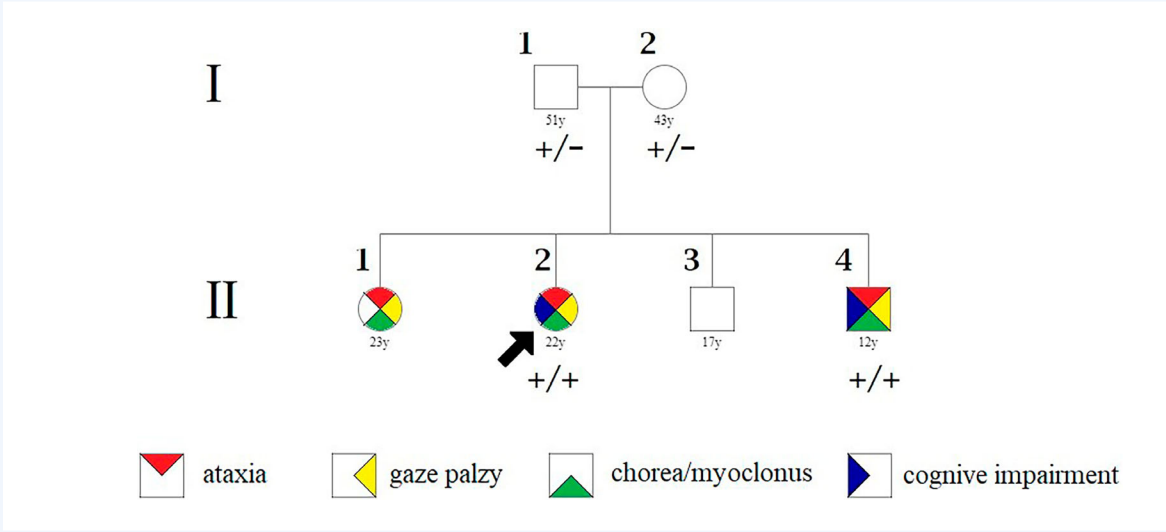
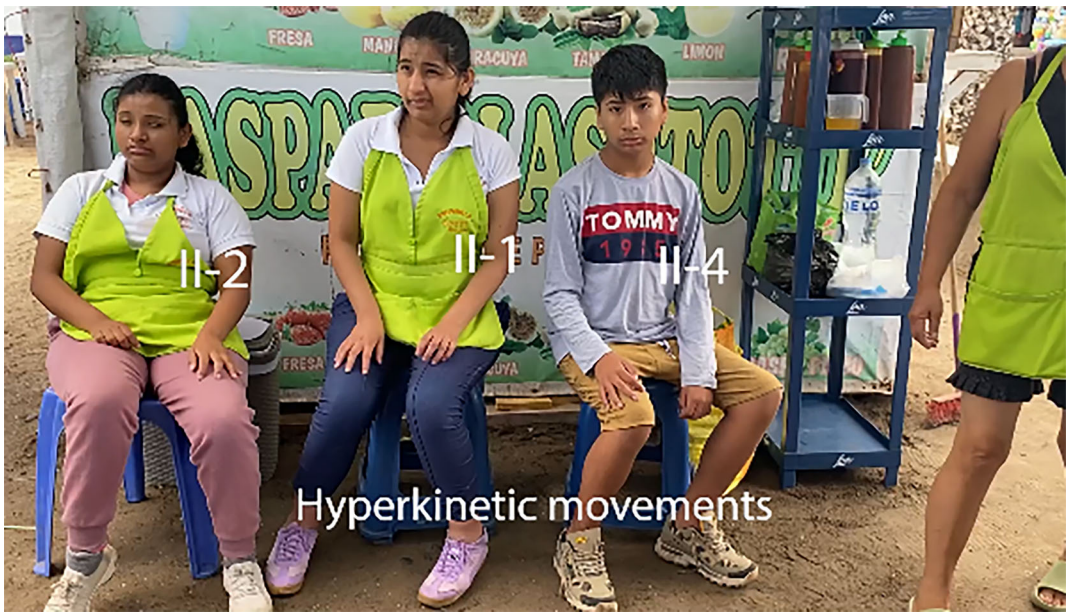


Figure 1. Pedigree of the family affected with the c.1A > G (p.Met1?) mutation in *SQSTM1* gene. The different colors represent the symptoms of affected family members. "+": Positive test for a *SQSTM1* c.1A > G variant, "−": wild type.



Video 1. Neurological examination of the three affected siblings with NADGP.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14025

movements, consistent with previous reports of individuals with NADGP.[1–4] The combination of vertical gaze impairment, dystonia "facial grimacing" and ataxia have been reported in few disorders like Niemann-Pick type C and GM1-gangliosidosis type 3.[8,9] Two siblings (II-1, II-2) also experienced dysautonomic symptoms, considered less frequent symptoms of NADGP. All three affected individuals in this family presented with myopathy. Brain MRI in NADGP may be normal or show mild cerebellar atrophy as our proband and, in some cases, bilateral pallidal SWI susceptibility.[10] The association with myopathy to date has only been described in individuals with heterozygous *SQSTM1* variants but not in cases harboring biallelic variants.[11]

To the best of our knowledge, the *SQSTM1* c.1A > G variant has not been previously described. It is rare, with a minor allele frequency of 0.00005684 in the African/African American population and only one allele in the Admixed American population. Biallelic inactivating variants in *SQSTM1* are known to cause NADGP, and the c.1A > G variant disrupts the translation initiation codon in the transcript encoding protein isoform 1. Studies of fibroblasts from individuals harboring a different nucleotide change affecting the same initiation codon, c.2 T > A showed a severe reduction in *SQSTM1* mRNA steady-state levels and absence of the *SQSTM1* protein, suggesting complete loss of function.[10]

In conclusion, we report a Peruvian family with NADGP becoming the second family of Latin American origin. This report contributes to better understanding variable expressivity of NADGP and provides evidence for a novel disease-causing variant associated with NADGP. We highlight the importance of whole genome sequencing in the diagnosis of rare neurodegenerative disorders.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Case compilation; (2) Manuscript preparation: A. Writing of the first draft, B. Review and Critique.

C.C.-V.: 1A, 1B, 1C, 2A, 2B
P. R.-P.: 1A, 1B, 1C, 2A, 2B
A.M.-P.: 1A, 1B, 1C, 2A, 2B
A.R.C.: 1A, 1B, 1C, 2B
A.C.: 1A, 1B, 1C, 2B
E.T.: 1A, 1B, 1C, 2B
A.R.-V.: 1A, 1B, 1C, 2B
E. S.-C.: 1A, 1B, 1C, 2B
J. B.-M.: 1A, 1B, 1C, 2B
M.C.-O.: 1A, 1B, 1C, 2B

Disclosures

Ethical Compliance Statement: This work was reviewed and approved by the local IRB at Instituto Nacional de Ciencias Neurologicas. Nro. 1271-CIEI-INCN-2023. Appropriate written Informed patient consent was obtained for this study. The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Proband's Brain MRI (sagital Flair) showing mild cerebellar atrophy.