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Novel variants in *ATM* causing mild Ataxia-Telangiectasia: from benchside to bedside and back again

Josefina Perez Maturo, Bsc [1,2]; Marcela Gonzalez Cid, PhD [3]; Lucia Zavala, MD [1]; Sergio Rodriguez Quiroga, MD [1,4], Marcelo Andres Kauffman , MD, PhD [1].

1 Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

2 Programa de Medicina de Precisión y Genómica Clínica, Instituto de Investigaciones en Medicina Traslacional, Facultad de Ciencias Biomédicas, Universidad Austral-CONICET, Pilar, Argentina

3 Laboratorio de Mutagénesis, Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina, Buenos Aires, Argentina.

4 Área de Trastornos del Movimiento, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

Corresponding author

Dr. Marcelo Kauffman,

Consultorio de Neurogenética - División Neurología. Hospital JM Ramos Mejía

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mdc3.13013

Urquiza 609 (1221) Buenos Aires-Argentina

marcelokauffman@gmail.com

+541141270280

Text word Count: 500 words

Title character count: 98 characters (with spaces)

Running Title: Novel variants in *ATM*

Keywords:

Ataxia Telangiectasia, Autosomal Recessive ataxias, Mild phenotype, NGS ataxia panel, Cerebellar Ataxia.

Ataxia-telangiectasia (A-T) is one of the most frequent recessive ataxias worldwide. The disease results from biallelic pathogenic variants in *ATM* gene, coding for a high-molecular-weight protein kinase involved in double-strand breaks (DSBs) repair. It is usually characterized by childhood-onset cerebellar ataxia, oculocutaneous telangiectasia and early mortality [1]. Its molecular diagnosis is challenging because of the unusually large sequence of *ATM*, the extensive allelic heterogeneity with more than 600 reported pathogenic variants[2] and the increasing recognition of atypical phenotypic presentations such as mild and slow progressing variants which defy the

classical picture of an invariably deadly disorder of childhood [3]. Here, we describe the case of a 21-year-old patient with an early onset mildly progressive cerebellar ataxia, where a confirmatory diagnosis of A-T caused by two novel *ATM* pathogenic variants could be done by the combination of next generation sequencing (NGS) and ATM functional studies.

This 21 year-old woman was referred to our neurogenetic unit at the age of 17 for the study of a slowly progressive childhood-onset ataxia. She was born from nonconsanguineous healthy parents (Fig.1A). At the age of 5, frequent falls and a progressive incoordination in her gait led her parents to consult a pediatric neurology unit. The results of an MRI showing cerebellar atrophy (Fig.1B) and the finding of mild lower limb ataxia and dysarthria led to a diagnosis of likely genetic ataxia at that time. Our first evaluation showed in a fully unassisted ambulatory patient, a mild axial and appendicular ataxia (SARA score:7). She presented a fractionated smooth-pursuit and slow and hypometric horizontal and vertical saccades. There was no evidence of oculo-motor apraxia and other movement disorders were absent. Noteworthy, ocular or skin telangiectasias were absent. The disorder evolved during the next four years with a mild progression of ataxia (SARA score:10) and the appearance of billateral distal chorea and a subtle left–hand dystonia in upper limbs (Video S1). The biochemical workup highlighted the presence of elevated serum alpha-fetoprotein (fifteen times normal values) and reduced levels of immunoglobulins A and E. A NGS panel for Ataxias revealed the presence of two novel variants in compound heterozygous form in the *ATM* gene: (NM_000051) c.1373G>A(p. Cys458Tyr) and c.8785_8788delAGGT(p. Arg2929Metfs * 2) (Fig.1C). To increase the diagnostic certainty of this finding, we functionally assessed the ATM

repairing capacity of DSBs by means of an etoposide-induced DNA damage in lymphocytes assay (Supplemental-Material). We found an increased frequency of chromosomal aberrations after ex-vivo treatment with etoposide (Fig.1D) confirming a deficiency in the DNA damage repair mechanisms.

The case reported here highlights the importance of combining information from clinical, genetic and functional assays in the diagnostic exercise of progressive and complex ataxias. Although there have been initial descriptions of variant A-T phenotypes [3, 4], only after the recent widespread availability of molecular studies of *ATM* there has been an increasing recognition of atypical phenotype[5] such as the reported. In addition, the description of the pathogenic effect of two novel variants in *ATM* expands the spectrum of known causative mutations of A-T.

Author Roles

JPM: 1A, 1C, 3A

MGC: 1C, 3A, 3B

LZ: 1C, 3A

SRQ: 1A, 1B, 1C, 3A

MK: 1A, 1B, 1C, 3B

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

Disclosures

Funding Sources and Conflict of Interest

No specific funding was received for this work.

The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months

Josefina Perez Maturo has received scholarship support from Argentinean National Science Council (CONICET). Marcelo Kauffman and Marcela Gonzalez Cid have received grant support from Ministry of Health of Buenos Aires City, Argentinean National Science Council (CONICET). Marcelo Kauffman has received grant support from Argentinean Ministry of Science and Technology and serves as Associate Editor of the journal Neurología Argentina. The rest of the authors declare that they have no conflict of interest.

Ethical Compliance Statement

This study was approved by the Institutional Ethics Committee of the Hospital JM Ramos Mejia of Buenos Aires, Argentina. We 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. The authors confirm that the patient provided verbal and written consent. for this work but because this article is a case report no IRB approval was necessary.

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Legends for figures

Figure 1. (A) Pedigree Chart. Arrow indicates index case. Numbers over figures corresponded to current age/age at onset**. (B)** MRI Sagital T1-weighted image showing cerebellar atrophy **(C)** Alignment showing identified variants in the patient. (**D)** Chromosomal aberrations (both break and exchange type) following acute treatment with etoposide Representative image metaphase containing chromosomal aberrations is shown.

Legends for Supplemental files

Supplemental Material. Additional details about methodology.

Video S1. This video shows main findings during neurological examination in the case reported. Segment 1 shows the presence of fractionated smooth pursuit, slow and hypometric horizontal and vertical saccades. Segment 2-4 shows the presence of mild lower and upper limb ataxia at the SARA scale. Segment 5-6 shows mild impairment in gait and stance predominant visible when walking or stand in tandem. Segment 7 shows the presence of bilateral distal choreic movements and subtle left-hand dystonia in upper limbs**.**

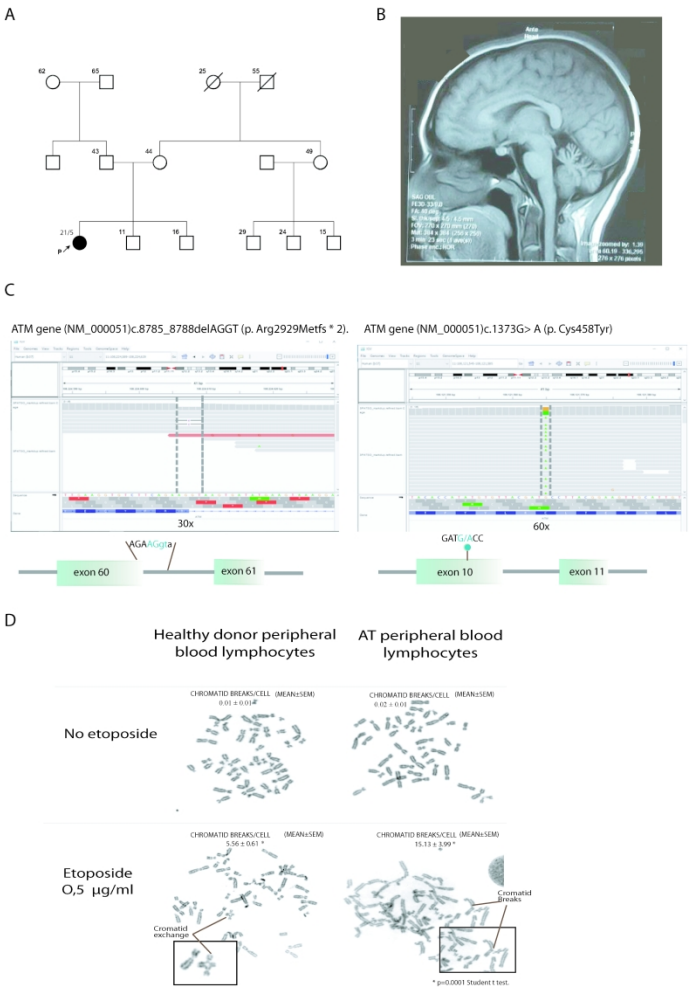

Figure 1

286x351mm (300 x 300 DPI)