

ORIGINAL ARTICLE

Epidemiology of variant transthyretin amyloidosis at a reference center in Argentina

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Abstract

Background: In Argentina, there is limited data of prevalence of variant transthyretin amyloidosis (ATTRv) and phenotype-genotype correlation. The laboratory of Hospital Italiano de Buenos Aires (HIBA) is a reference center for transthyretin (*TTR*) gene sequencing. The Institutional Amyloidosis Registry (RIA) enable us to characterize people with ATTRv. Our aim was to describe the prevalence of *TTR* mutations at a reference center in Argentina and the phenotypic presentations of patients with ATTRv included in an institutional registry.

Methods: Retrospective cohort study of consecutive patients with genetic variants in the *TTR* gene identified from 2012 to 2019 in the laboratory. We collected all phenotypic characteristics of patients who were clinically evaluated by HIBA doctors.

Results: Five hundred seventy-six patients tested, 141 positive: p.Val50Met 107, p.Thr80Ala 16, p.Ala117Ser 9, p.Phe84Leu 2, p.Ile127Val 2, p.Tyr134Cys 2, p.Ala56Pro 2, p.Val142Ile 1. Only 20 patients were clinically evaluated. The mean age at diagnosis was 54 years; 70% had family history with a pedigree median of 4. Mutations were p.Thr80Ala 9, p.Val50Met 6, p.Ala56Pro 2, p.Val142Ile 1, p.Phe84Leu 1, and p.Tyr134Cys 1. Eleven patients presented polyneuropathy, 11 had gastrointestinal compromise, six patients had autonomic compromise, six presented cardiac symptoms and four patients presented ocular involvement.

Conclusion: We present the first prevalence report of *TTR* mutations in a reference center of amyloidosis in Argentina. The most frequent genetic variant was p.Val50Met. Our data show considerable phenotypic heterogeneity in the patients with ATTRv.

KEYWORDS

amyloid cardiomyopathy, amyloid neuropathy, amyloidosis, amyloidosis hereditary transthyretin-related, transthyretin gene variants

1 | INTRODUCTION

Variant transthyretin amyloidosis (ATTRv) is the most prevalent inherited form of amyloidosis. ATTRv is an autosomal dominant, multisystemic, progressive, degenerative, and potentially fatal disease. It is characterized by misfolding of the *TTR* protein (Gertz, 2017), which results in a progressive disruption of the structure and functioning of the affected tissues and organs (Pepys, 2006). *TTR* is a homotetrameric protein consisting of four identical 127-amino acid β -sheet monomers. It is mainly synthesized in the liver, but also in the choroid plexus and retina. Transthyretin protein is encoded by *TTR* gene located in the 18th chromosome (*TTR*, MIM#176300) and it is known to be highly polymorphous, with more than 140 variants, 130 of which are amyloidogenic (Rowczenio et al., 2014). The p.Val50Met mutation is the most prevalent genetic variant of amyloidosis reported worldwide.

The phenotypic presentations may be predominantly neuropathic (known as familial amyloid polyneuropathy), predominantly cardiac (or transthyretin amyloid cardiomyopathy), or mixed (Maurer et al., 2016). The clinical picture of the disease, as well as the age of onset of symptoms, depend greatly on environmental factors, geographical region, and population type; it also varies even in patients with the same mutation, thus there is a significant degree of variability of phenotypes among patients (Gertz, 2017; González-Duarte et al., 2018).

Globally, the incidence of ATTRv is widely variable. In Portugal, Sweden, and Japan, the disease is considered endemic. In other areas, ATTRv cases are considered non-endemic. These non-endemic areas show the greatest genetic heterogeneity, which confers greater variability in its phenotypic presentations. However, an increase in the number of cases has been reported in the last few years (Parman et al., 2016), likely due to an increased awareness of this disease as well as better diagnostic methodology.

There is no epidemiological data of ATTRv in Argentina. Therefore, we have an unmet need for real world data and generation of evidence to be used for informed decision-making. The laboratory of Hospital Italiano de Buenos Aires (HIBA) is a reference center in Argentina for *TTR* gene sequencing. Since 2010, there has been an ongoing, active Institutional Amyloidosis Registry (RIA) with strict quality control rules. Understanding the epidemiology of ATTRv (as found in RIA) and its potential applications in real-world settings is crucial for patients, families, health professionals, and scientists.

1.1 | Purposes

To describe the prevalence of *TTR* mutations at a reference center in Argentina and the phenotypic presentations of patients with ATTRv included in the RIA of HIBA.

2 | MATERIALS AND METHODS

This study was conducted in accordance with the amended Declaration of Helsinki. This is an institutional research protocol ethics committee-approved study (approval number 5234).

2.1 | Design

Retrospective cohort study of consecutive patients with a *TTR* gene sequencing referred to HIBA laboratory from 2012 to 2019.

HIBA laboratory receives samples from patients clinically assessed at the hospital and samples referred for analysis from other facilities in the country. Since 2012, the lab has performed *TTR* gene sequencing and it is a reference center for the country. To the best of our knowledge, this is the only facility doing *TTR* sequencing in Argentina at the time of this study (2019).

Genomic DNA was extracted from whole blood treated with EDTA using Qiaamp DNA Blood Mini Kit (Qiagen). Exons 2 to 4 of the *TTR* gene (NCBI Reference Sequence NM_000371.4) were amplified by polymerase chain reaction (PCR) assay using Platinum™ Taq DNA polymerase (Invitrogen) under the following cycling conditions: 1 cycle of 95°C for 1 min; 30 cycles of 95°C for 15 s, 55°C for 30 s, and 72°C for 30 s; and a final extension step of 72°C for 7 min. The reaction mixture was 20 mmol/L Tris-HCl, 50 mmol/L KCl, 1.5 mmol/L MgCl₂ (pH 8.4) containing 0.2 mmol/L dNTP, 0.6 μ mol/L of each primer, 1.5 units polymerase, and 5 μ l of DNA template in a final volume of 50 μ l. The primer sequences were as follows: exon 2 5'-TCTTGTTCGCTCCAGATTTC-3' and 5'-CAGATGATGTGAGCCTCTCTC-3'; exon 3, 5'-CCTA CTTCTGACTTAGTTGAG-3' and 5'-ACTGTGCATTTCCCT GGAATGC-3'; exon 4, 5'-GTCATGTGTGCATCTGTAC-3' and 5'-CATATGAGGTGAAAACACTGC-3'. PCR products were purified using Illustra™ ExoProStar™ Enzymatic PCR and Sequence Reaction Cleanup Kit (GE Healthcare) according to the manufacturer's protocol and bidirectional capillary electrophoresis sequencing was carried out on ABI 3500 genetic analyzer (Thermo Fisher Scientific) using the primers previously described, as appropriate.

Additionally, the RIA belongs to the organizational structure of HIBA, and is dependent on the Institute of Translational Medicine and Biomedical Engineering (IMTIB). The institutional scope of RIA (NCT01347047) covers cases of amyloidosis, but does not exclude any areas within the hospital environment. Most patients have a diagnosis of amyloidosis confirmed by biopsy (80%) of nerve, skin, eye, salivary gland, or abdominal fat and are clinically assessed (signs and symptoms, familiar history, positive mutation). All patients are followed for treatment and prognosis.

2.2 | Participants

All patients with suspected ATTRv, whose blood samples were sent to HIBA laboratory for *TTR* gene sequencing during the period of interest, were included. Regarding the description of the phenotypic characteristics, we only included those patients with genetic variants and incorporated into the RIA (Website, n.d., <https://clinicaltrials.gov/ct2/show/NCT01347047>).

2.3 | Definitions

The presence of organ involvement was studied: cardiac involvement (development of congestive heart failure, arrhythmia attributable to amyloidosis, or biopsy positive for amyloidosis, imaging involvement (cardiac MRI with gadolinium, echocardiogram with strain)); neurological involvement (polyneuropathy, autonomic dysfunction attributable to amyloidosis or biopsy positive for amyloidosis); nephrologic involvement (kidney failure, nephrotic syndrome, urine protein attributable to amyloidosis, or biopsy positive for amyloidosis); and involvement of other organs attributable to amyloidosis or biopsy positive for amyloidosis (Aguirre et al., 2016).

2.4 | Statistical considerations

Consecutive sampling of patients with a *TTR* gene sequencing request. Descriptive continuous variables are shown as their absolute frequencies.

3 | RESULTS

3.1 | Prevalence of *TTR* mutations in the cohort of patients referred to HIBA laboratory

From 2012 to 2019, 576 tests have been performed looking for mutations in the *TTR* gene (Figure 1). Patients were

referred to HIBA laboratory with the suspicion of ATTRv for testing; 95% were referred by neurologists and 5% by cardiologists. Of these, 497 (86%) samples were sent from medical centers located in Ciudad Autónoma de Buenos Aires (CABA) and Gran Buenos Aires (Figure 2).

One hundred forty one (24%) of the patients tested were positive for at least one amylogenic mutation. Of these, 61 (43%) were women and 80 (57%) were men. Three patients were homozygous for p.Val50Met. Of the 435 patients with negative results, 156 were only sent for exon 2 sequencing of *TTR* gene.

Eight different mutations were found. The mutations found were p.Val50Met in 107 (76%) patients, p.Thr80Ala in 16 (11%) patients, p.Ala117Ser in 9 (6%) patients, p.Val142Ile in one patient, and p.Phe84Leu, p.Ile127Val, p.Tyr134Cys, p.Ala56Pro in two patients in each case (Figure 2).

3.2 | Clinical characteristics of positive patients included in the RIA of HIBA

Of the 141 patients showing *TTR* mutations, 20 (14%) were clinically assessed by an HIBA doctor. Of these, six (30%) patients were women and 14 (70%) were men. The mean age at diagnosis was 54 years; 70% had family history with a pedigree median of 4, see Table 1. The mutations found were p.Thr80Ala 9, p.Val50Met 6, p.Ala56Pro 2, p.Val142Ile 1, p.Phe84Leu 1, and p.Tyr134Cys 1. All the patients with p.Thr80Ala and p.Ala56Pro mutations came from other Latin American countries (Bolivia and Peru, respectively); nine patients were from Argentinian, five were from Gran Buenos Aires, three were from CABA, and one from Cordoba.

At the time of this study, 16 (80%) patients had disease-related symptoms and four were asymptomatic carriers. Eleven patients presented polyneuropathy, 11 had gastrointestinal symptoms, six patients had autonomic compromise, six presented cardiac symptoms, and four patients presented ocular involvement (Figure 3). No patient presented renal or dermatological compromise.

One patient died due to cardiac arrest in the intensive care unit after 56 months of follow-up since diagnosis.

4 | DISCUSSION

This paper exhibits the first analysis of laboratory data in Argentina of all patients undergoing *TTR* sequencing at our facility since *TTR* sequencing was included as a diagnostic tool. Additionally, 20 patients with genetic variants were clinically assessed at HIBA allowing the description of the clinical presentation in patients diagnosed with ATTRv. The patients evaluated at HIBA may not be representative

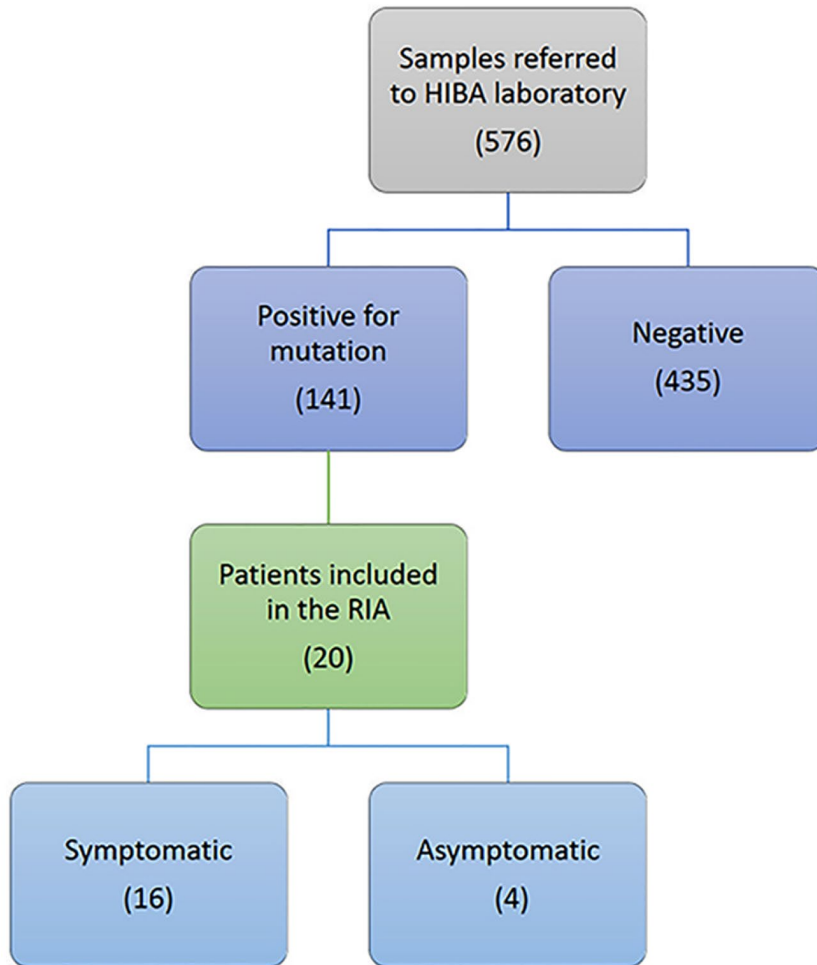


FIGURE 1 Study design.

Retrospective cohort study of consecutive patients with a *TTR* gene sequencing referred to HIBA laboratory from 2012 to 2019

of the country population with ATTRv. To the best of our knowledge, this is the largest population report of *TTR* gene sequence variants in our country (Chaves et al., 2016).

Since 2012, 576 samples have been sent for *TTR* gene sequencing to our laboratory, and 141 (24%) were positive for at least one mutation. Before that, the only available technique in Argentina was PCR to find point mutations (p.Val50Met; Pérez et al., 2008). Because of the availability of therapeutic agents, increased interest and awareness of the disease in the region, and due to the availability of diagnostic techniques such as *TTR* gene sequencing in the country, an increase in the number of patients studied in the last 4 years has been observed (Figure 2). Including genetic testing in the evaluation of patients suspected of having ATTRv is paramount. Different mutations are associated with different clinical manifestations, age at onset, and clinical progress of the disease (Parman et al., 2016).

Eight different mutations were identified, all of which were already reported in the online hereditary amyloidosis registry (Rowczenio et al., 2014). This shows the great heterogeneity of mutations, probably due to the significant heterogeneity of ethnicity and interbreeding. The most frequently found mutation among all the samples

referred to the laboratory was p.Val50Met, which was also the one mostly reported worldwide and the one more frequently associated with hereditary polyneuropathy (Coelho et al., 2013). These results are meant to be analyzed within the following context: (1) Most of the patients tested were evaluated by a neurologist for a differential diagnosis of hereditary polyneuropathy. Currently, treatment is approved in Argentina for patients with p.Val50Met mutation and ATTRv with neurologic involvement; (2) 36% of negative patients were referred only for partial sequencing tests (target search of p.Val50Met mutation); (3) Argentina is a country of immigrants. Its ethnic composition is mainly of European ancestry, to a lesser extent, Native Americans and some have African or Asian ancestry. Not surprisingly, p.Val50Met is the most frequent mutation in the population tested in Argentina until now; (4) We have described the geographical distribution of samples referred to the laboratory, which may differ from patient's birthplace; (5) The geographical distribution of mutations shows that most of the samples were sent from the central region of the country (86% from Ciudad Autónoma de Buenos Aires and Gran Buenos Aires). (6) We do not have any clinical or additional information of patients referred to the laboratory for sequencing purpose.

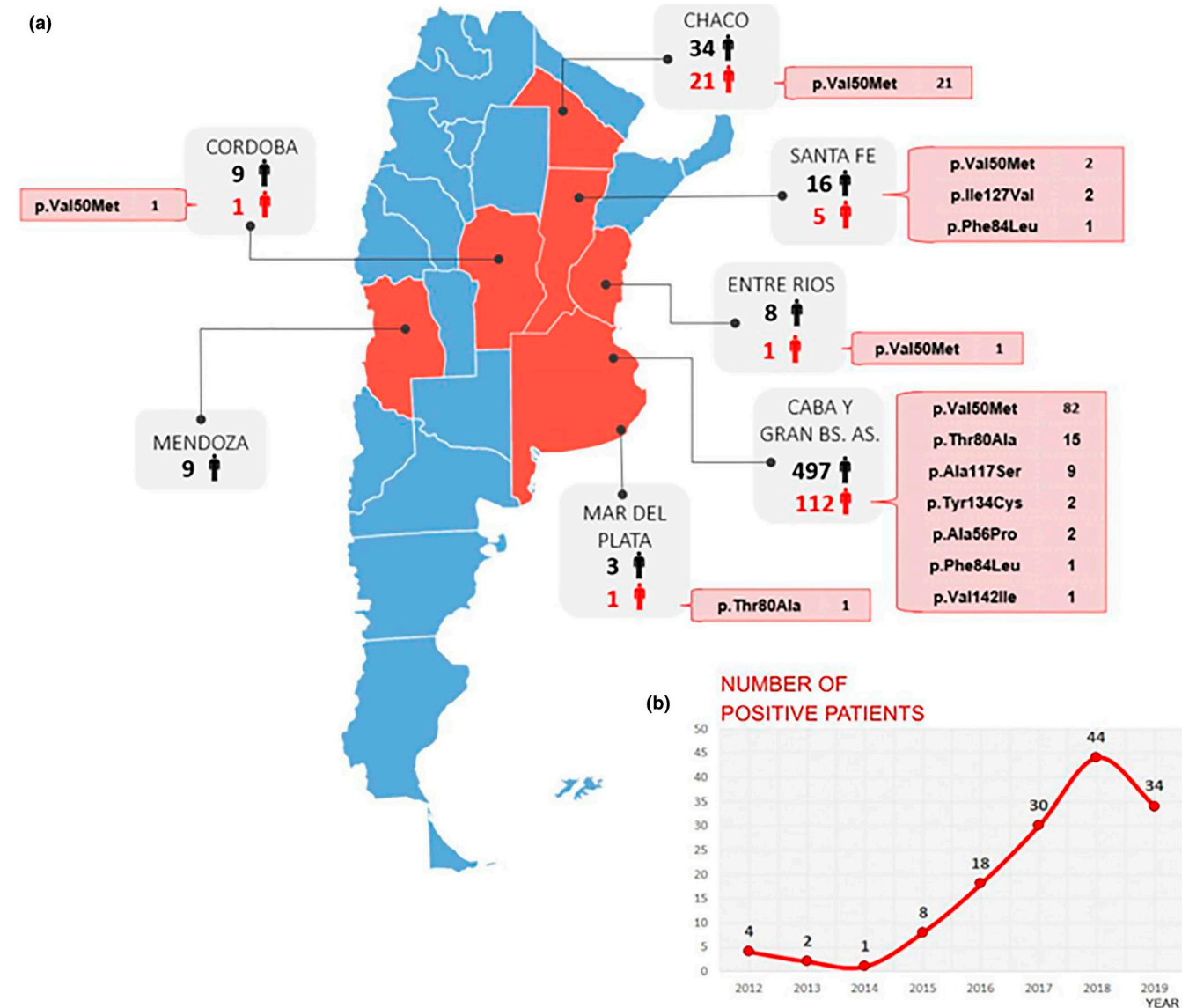


FIGURE 2 (a) Geographical distribution of 576 samples referred to HIBA laboratory for TTR gene sequencing from July 2012 to September 2019 and mutations found (black: number of samples sent to HIBA laboratory; red: number of patients positive for a TTR mutation). (b) Total number of positive patients per year. NCBI Reference Sequence NM_000371.4

TABLE 1 Description of positive patients included in the RIA of HIBA

Characteristics/ Mutation	Global <i>n</i> = 20	p.Thr80Ala <i>n</i> = 9	p.Val50Met <i>n</i> = 6	p.Ala56Pro <i>n</i> = 2	p.Phe84Leu <i>n</i> = 1	p.Tyr134Cys <i>n</i> = 1	p.Val142Ile <i>n</i> = 1
Female (%)	6 (30)	3 (33)	0	2 (100)	0	1 (100)	0
Mean age at diagnosis, years	54	54	60	27	77	64	69
Mean years of symptoms previous to diagnosis	-3	-1	-2	-5	-1	-3	-7
Family history (%)	14 (70)	8 (89)	2 (33)	2 (100)	1 (100)	1 (100)	0
Mean number of Pedigree	4	3	4	5	No data	2	—

Note: NCBI reference sequence NM_000371.4.

Our data show phenotypic heterogeneity for all mutations found in patients with ATTRv included in RIA. It should be noted that some patients who were studied at HIBA came from neighboring countries such as Peru and

Bolivia; therefore, the prevalence of mutations differs at our center versus the general prevalence in the country. The frequency and distribution of TTR mutations depend on the population analyzed (González-Duarte et al., 2018; Zhen

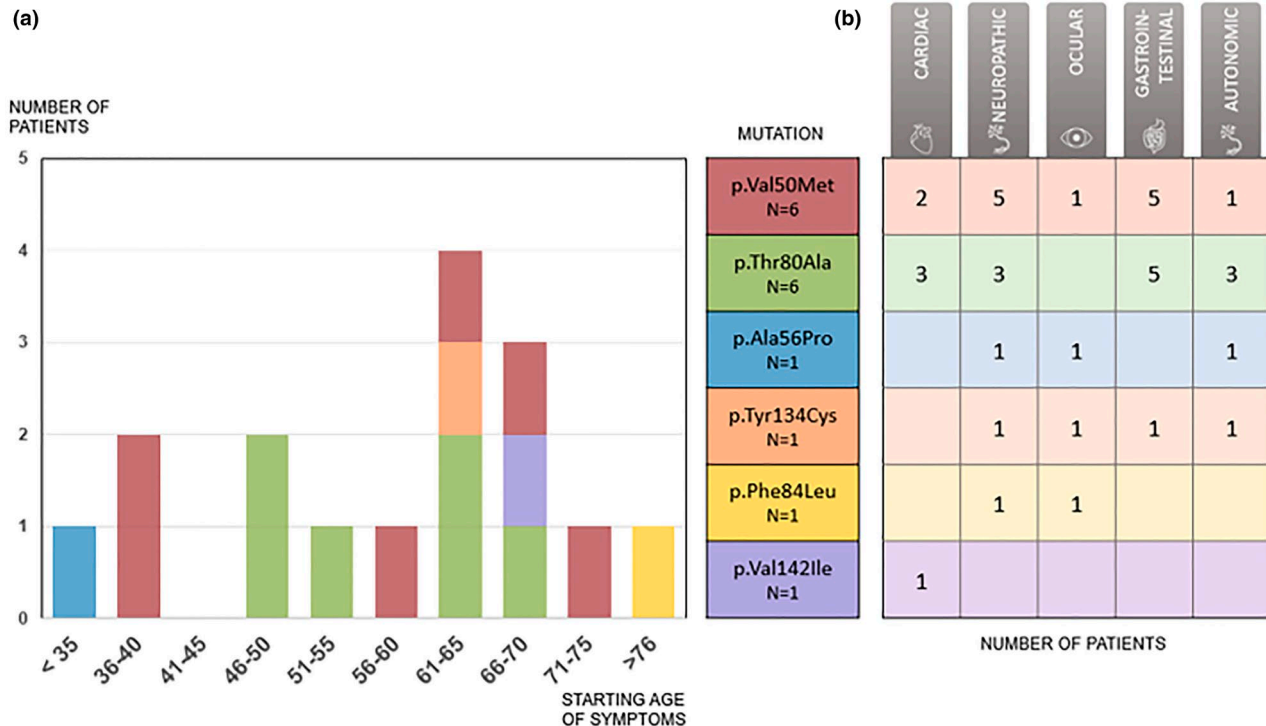


FIGURE 3 (a) Distribution of age at onset of patients included in RIA of Hospital Italiano de Buenos Aires. (b) Phenotypic presentation of symptomatic positive patients included in RIA of Hospital Italiano de Buenos Aires. NCBI Reference Sequence NM_000371.4

et al., 2015). There is extensive evidence of the multisystemic nature of ATTRv, even in patients with predominant neurological involvement (Coelho et al., 2013; Rowczenio et al., 2019; Waddington-Cruz et al., 2019). Thus, diagnosis and multidisciplinary clinical follow-up of these patients is paramount. Although the most prevalent phenotype in patients included in the RIA with p.Val50Met ATTRv was polyneuropathy, most of them showed gastrointestinal symptoms, and a third showed heart compromise. In those patients, the age of onset of symptoms was quite variable (43 vs. 68 years). Although, the number of patients with known clinical history (or clinical evaluation in our institution) is small, it is impossible to determine the prevalence of early or late phenotypes. Like global evidence, our data show that patients with ATTRv with this genotype present multisystemic involvement (Maurer et al., 2016).

These demographic report help us to characterize the different clinical manifestations and the course of the disease in non-endemic populations, enabling us to enhance and standardize diagnosis and treatment in our population. A relevant data in our report is the great genetic heterogeneity found in our country.

Studying our genetic variants and determining the genotype–phenotype correlation is essential for drafting local guidelines. Being able to understand the rate of symptom development of each mutation in our environment allow us to generate appropriate recommendations for our population. In turn, this shows the need for building collaborative

relationships in the region in an attempt to improve the treatment of the disease for our population. There is a need to carry out multicentric studies with the aim of determining ATTRv prevalence in Argentina and Latin America, the prevalence and distribution of associated mutations, and the phenotypic characteristics of the disease in our region.

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CONFLICTS OF INTEREST

We received an educational grant for the translation and publication of the article by Pfizer. The authors maintained independence from design through data collection analysis and writing the manuscript. The authors report no other conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Data curation, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora and Maria Lourdes Posadas Martinez; Formal analysis, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Funding acquisition, Maria Adela Aguirre, Elsa Nucifora,

and Maria Lourdes Posadas Martinez; Investigation, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Methodology, Maria Soledad Saez, Maria Adela Aguirre, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Project administration, Maria Adela Aguirre, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Resources, Maria Lourdes Posadas Martinez; Software, Maria Lourdes Posadas Martinez; Supervision, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Validation, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora and Maria Lourdes Posadas Martinez; Visualization, Maria Soledad Saez, Maria Adela Aguirre, Elsa Nucifora, and Maria Lourdes Posadas Martinez; Writing – original draft, Maria Soledad Saez, and Maria Lourdes Posadas Martinez; Writing – review and editing, Maria Soledad Saez, Maria Adela Aguirre, Diego Perez de Arenaza, Patricia Sorroche, Elsa Nucifora, and Maria Lourdes Posadas Martinez.

ETHICS STATEMENT

This study was conducted in accordance with the amended Declaration of Helsinki. This is an institutional research protocol ethics committee-approved study (approval number 5234).

DATA AVAILABILITY STATEMENT

The policy of data sharing is the following: to request the data base to the corresponding author, with the objective of the approved protocol, and with prior agreement between both parts.

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