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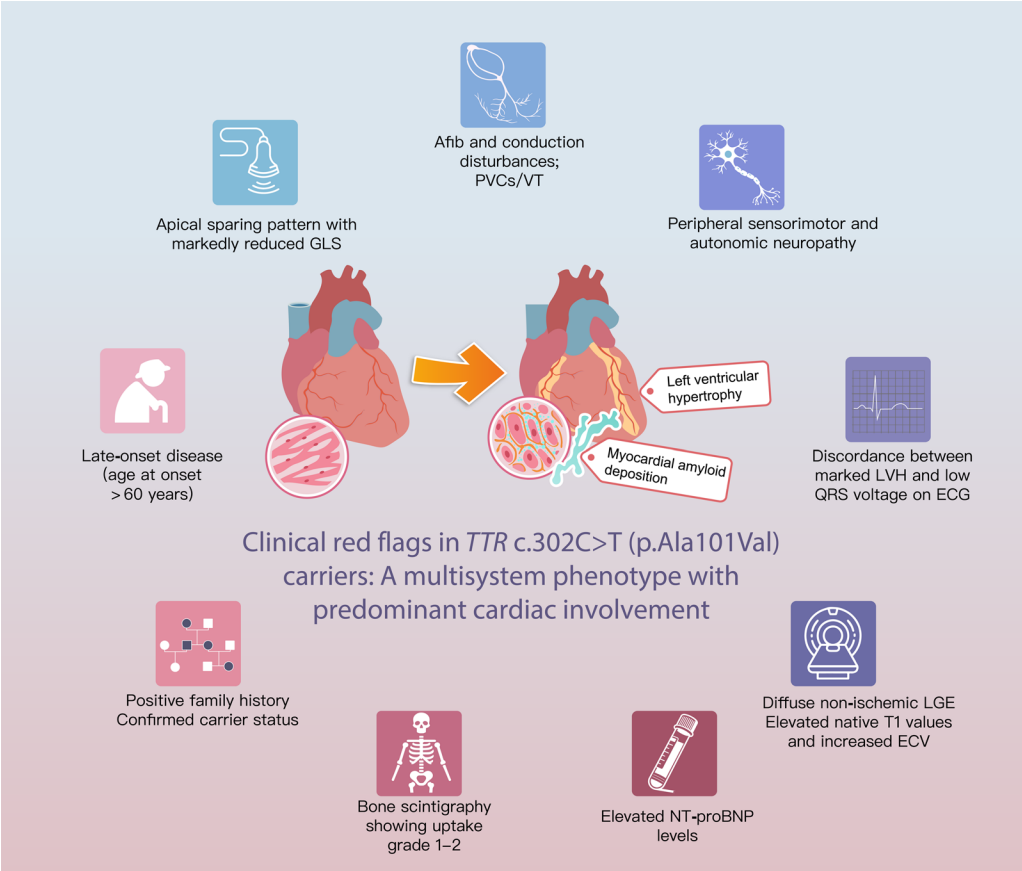
CARDIAC RESEARCH

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Clinical phenotypes linked to the p.Ala101Val mutation in the *transthyretin* gene in Belarusian patients with transthyretin amyloidosis

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Graphical abstract



Hereditary transthyretin amyloidosis (ATTRv) is a rare autosomal dominant multisystem disorder caused by pathogenic variants in the transthyretin (*TTR*) gene. Disease pathogenesis is driven by gain-of-function missense mutations that destabilize the *TTR* tetramer, resulting in monomer dissociation, protein misfolding, and amyloid fibril formation. Amyloid deposits accumulate predominantly in peripheral nerves and myocardium, leading to progressive polyneuropathy and/or cardiomyopathy.[1]

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To date, more than 130 pathogenic *TTR* variants have been described, with marked phenotypic heterogeneity influenced by mutation type as well as geographic and ethnic background.[2] One of the most extensively studied variants is p.Val50Met, which causes early-onset sensorimotor and autonomic neuropathy in endemic regions such as Portugal and Japan, while presenting with later onset and mixed cardiac-neurological phenotypes in other populations.[3] The p.Val122Ile variant, present in approximately 3% to 4% of individuals of African ancestry, predominantly leads to late-onset cardiomyopathy.[4] Other clinically relevant variants include p.Thr60Ala, frequently observed in Ireland and the United Kingdom and associated with combined neuropathic and cardiac involvement, as well as p.Ile68Leu and p.Leu111Met, which are linked to early-onset cardiomyopathy in Italian and Danish populations.

The rare *TTR* variant c.302C>T (p.Ala101Val) has been reported mainly in patients with cardiac ATTRv. We analyzed clinical data from five unrelated Belarusian probands treated for hereditary amyloidosis at the Republican Scientific and Practical Center "Cardiology" between 2024 and 2025 (Table S1, Supplemental Digital Content, https://links.lww.com/CARES/A14). Genetic testing performed at the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus identified the pathogenic variant c.302C>T (p.Ala101Val) in the *TTR* gene by Sanger sequencing (Figure S1, Supplemental Digital Content, https://links.lww.com/CARES/A14). Multiple sequence alignment demonstrated moderate evolutionary conservation of the A81 residue (A101 in human *TTR*), supported by a PhyloP score of 1.64 (Figure S2, Supplemental Digital Content, https://links.lww.com/CARES/A14). ATTRv was confirmed by exclusion of light-chain amyloidosis and by positive bone scintigraphy with technetium-99m-labeled tracers. Histopathological confirmation was available in four patients. Pedigree analysis (Figure S3, Supplemental Digital Content, https://links.lww.com/CARES/A14) demonstrated autosomal dominant inheritance with vertical transmission across successive generations. All probands were heterozygous for the variant. Multiple heterozygous carriers were identified among first- and second-degree relatives, including asymptomatic individuals, indicating incomplete and likely age-dependent penetrance. The study was approved by the institutional ethics committee, and all participants provided written informed consent.

All patients presented with late disease onset, ranging from 64 to 74 years (patient No.1 [ID 989c; Figures S4 and S5, Supplemental Digital Content, https://links.lww.com/CARES/A14], male, 69 years; patient No. 2 [ID 1009c; Figures S6–S8, Supplemental Digital Content, https://links.lww.com/CARES/A14], male, 68 years; patient No. 3 [ID 1017c; Figures S9 and S10, Supplemental Digital Content, https://links.lww.com/CARES/A14], male, 69 years; patient No. 4 [ID 929c; Figures S11 and S12, Supplemental Digital Content, https://links.lww.com/CARES/A14], male, 64 years; patient No. 5 [ID 1022c; Figures S13 and S14, Supplemental Digital Content, https://links.lww.com/CARES/A14], female, 74 years). Four probands exhibited a predominant cardiac phenotype with amyloid cardiomyopathy, while 1 patient (No. 5, female, 74 years) manifested primarily with arrhythmic events in the absence of overt cardiomyopathy. Two patients (Nos. 1 and 4) developed advanced biventricular heart failure with severe ventricular dysfunction, extensive myocardial infiltration on cardiac magnetic resonance imaging, diffuse transmural late gadolinium enhancement, and markedly increased native T1 and extracellular volume (Table S1 and Figure S5, Supplemental Digital Content, https://links.lww.com/CARES/A14). Bone scintigraphy demonstrated grade 2 myocardial tracer uptake. Despite repeated pleural drainage for persistent effusions, both patients died within 1 year of diagnosis because of progressive heart failure. Two additional patients (Nos. 2 and 3) demonstrated concentric left ventricular hypertrophy, biatrial dilation, and systolic dysfunction. Strain echocardiography revealed the characteristic apical sparing pattern (Figure S7, Supplemental Digital Content, https://links.lww.com/CARES/A14), and cardiac magnetic resonance imaging confirmed diffuse myocardial involvement with elevated T1 mapping and extracellular volume (Figure S8, Supplemental Digital Content, https://links.lww.com/CARES/A14). Holter monitoring recorded persistent atrial fibrillation, frequent ventricular ectopy, and episodes of nonsustained ventricular tachycardia.

One patient (No. 2) developed advanced conduction disease requiring pacemaker implantation, subsequently upgraded to cardiac resynchronization therapy due to high right ventricular pacing burden and reduced left ventricular ejection fraction. In both cases, bone scintigraphy showed low-grade myocardial uptake (grade 1).

The patient No. 5 presented with recurrent syncope due to supraventricular and ventricular arrhythmias confirmed by electrophysiological testing. Despite preserved systolic function, imaging demonstrated concentric hypertrophy and subendocardial and subepicardial amyloid infiltration on cardiac magnetic resonance imaging (Figure S12, Supplemental Digital Content, https://links.lww.com/CARES/A14). Bone scintigraphy again revealed only grade 1 uptake.

Neurological evaluation identified sensorimotor and/or autonomic neuropathy in all patients, with carpal tunnel syndrome present in two cases (Table S1, Supplemental Digital Content, https://links.lww.com/CARES/A14).

The p.Ala101Val variant was first described in the United Kingdom in 2007 and subsequently reported in Polish, Russian, Singaporean, and Chinese cohorts.[5,6] Across these studies, disease onset was typically late, ranging from 58 to 81 years, with predominant cardiac involvement (Table S2, Supplemental Digital Content, https://links.lww.com/CARES/A14).

Žebrauskienė et al.[7] recently reported four Lithuanian patients with this variant, including 1

homozygote who developed early and severe neuropathic disease, while the remaining cases exhibited classical features of amyloid cardiomyopathy with low-voltage electrocardiogram and elevated cardiac biomarkers (Table S2, Supplemental Digital Content, https://links.lww.com/CARES/A14). A further homozygous case was described in the Polish population with disease onset at 55 years.[8] Biochemical and biophysical analyses of the p.Ala101Val *TTR* protein have confirmed its pathogenicity and demonstrated intermediate tetramer stability compared with wild-type *TTR* and highly unstable early-onset variants, consistent with delayed amyloid formation and late clinical presentation.[9] Although *TTR* stabilizers such as tafamidis, diflunisal, and AG10 partially inhibited fibril formation *in vitro*, none completely suppressed amyloidogenesis.[9] Disease-modifying therapy was not available to the Belarusian patients. An important observation in our cohort was the relatively low myocardial tracer uptake on bone scintigraphy in several patients (grades 1–2), a phenomenon also reported in Polish patients with the same variant.[8] Reduced scintigraphic sensitivity has been described for other *TTR* variants, including p.Val50Met, p.Phe84Leu, and p.Ser97Tyr,[10] and may relate to amyloid fibril composition. Fibrils composed predominantly of full-length *TTR* (type B) demonstrate minimal tracer uptake, whereas mixed fragment-containing fibrils (type A) show strong myocardial accumulation.[10] Although late-onset disease is more commonly associated with type A fibrils, overlap exists between fibril type and age of onset. These findings underscore the importance of genetic testing in patients with strong clinical suspicion of ATTR cardiomyopathy and inconclusive scintigraphy.

In conclusion, we report five unrelated Belarusian patients carrying the pathogenic *TTR* variant c.302C>T (p.Ala101Val), which appears to confer a late-onset ATTRv phenotype dominated by amyloid cardiomyopathy, frequent arrhythmias, neurological involvement, and reduced sensitivity of bone scintigraphy. The clinical presentation closely mirrors that reported in other populations, reinforcing the pathogenic significance of this rare variant and highlighting the need for genotype-informed diagnostic strategies in ATTR cardiomyopathy.

Comprehensive clinical, imaging, and genetic data are available in Tables S1–S2 and Figures S1–S14, Supplemental Digital Content, https://links.lww.com/CARES/A14).

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None.

Ethical statements

This study was approved by the Institutional Review Board of the State Institution Republican Scientific and Practical Centre "Cardiology" (Approval No. 14, December 14, 2024). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. This study was conducted in accordance with the Declaration of Helsinki.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions

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Supervision: Svetlana M. Komissarova, Nadiia M. Rineiska, Natallia N. Chakova. All authors reviewed and approved the final manuscript.

AI statement

No generative artificial intelligence or artificial intelligence–assisted technologies were used in the preparation, writing, analysis, or editing of this manuscript. The authors take full responsibility for the accuracy, integrity, and originality of the work.

References

[1] Griffin JM, Rosenblum H, Maurer MS. Pathophysiology and therapeutic approaches to cardiac amyloidosis. Circ Res. 2021;128:1554–75.

[2] Rowczenio D, Quarta CC, Fontana M, et al. Analysis of the *TTR* gene in the investigation of amyloidosis: a 25-year single UK center experience. Hum Mutat. 2019;40:90–6.

[3] Tozza S, Severi D, Spina E, et al. The neuropathy in hereditary transthyretin amyloidosis: a narrative review. J Peripher Nerv Syst. 2021;26:155–9.

[4] Parcha V, Malla G, Irvin MR, et al. Association of transthyretin Val122Ile variant with incident heart failure among black individuals. JAMA. 2022;327:1368–78.
[5] Gawor M, Holcman K, Franaszczyk M, et al. Spectrum of transthyretin gene mutations and clinical characteristics of Polish patients with cardiac transthyretin amyloidosis. Cardiol J. 2022;29:985–93.
[6] Nasonova SN, Gaintsev EA, Zhirov IV, et al. Is it possible for immunoglobulin light chain amyloidosis and transthyretin amyloidosis to be concomitant? A case report. Russ J Cardiol. 2026;30:6628.
[7] Žebrauskienė D, Sadauskienė E, Masiulienė R, et al. Rare c.302C>T *TTR* variant associated with transthyretin amyloidosis. Medicina (Kaunas). 2024;60:237.
[8] Gawor-Prokopczyk M, Lipowska M, Truszkowska G, et al. Rare transthyretin gene variants (p.Ala45Thr, p.Val91Ala, p.Phe53Cys, p.Ala101Val, p.Glu109Lys, and p.Phe53Leu): diagnostic pitfalls and clinical characteristics of Polish patients with transthyretin cardiac amyloidosis. Pol Arch Intern Med. 2024;134:16877.
[9] Sha Q, Zhang Y, Wang M, et al. Biochemical and biophysical properties of a rare TTRA81V mutation causing mild transthyretin amyloid cardiomyopathy. ESC Heart Fail. 2024;11:112–25.
[10] Saro R, Pavan D, Porcari A, Sinagra G, Mojoli M. Lights and shadows of clinical applications of cardiac scintigraphy with bone tracers in suspected amyloidosis. J Clin Med. 2023;12:7605.