

[CASE REPORT]

First Japanese Case of Hereditary Transthyretin Amyloid Cardiomyopathy with an Ile68Leu Variant: A Case Report

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Abstract:

Transthyretin amyloid cardiomyopathy (ATTR-CM) is increasingly recognized because of improved diagnostic modalities and disease-modifying therapy. We report the first Japanese case of hereditary ATTR-CM (ATTRv-CM) caused by the Ile68Leu variant, which has been previously described in European cohorts. A man in his 40s presented with heart failure and typical imaging findings of transthyretin amyloid cardiomyopathy (ATTR-CM). Genetic testing identified the Ile68Leu variant, which was absent in East Asian population databases. This case expands the genetic spectrum of ATTRv-CM in Japan and suggests that cardiac-predominant non-Val30Met TTR variants may occur in Japanese patients, with implications for the diagnosis, family counseling, and cascade screening in the future.

Key words: hereditary transthyretin amyloid cardiomyopathy, Ile68Leu variant, genetic counseling

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Introduction

In recent years, advances in diagnostic modalities and the development of disease-modifying therapies for transthyretin amyloid cardiomyopathy (ATTR-CM) have led to an increased recognition of amyloidosis. Consequently, previously overlooked cases are now being diagnosed, leading to an increase in the number of identified patients (1-3).

Hereditary ATTR-CM (ATTRv-CM) is an autosomal dominant disorder caused by pathogenic variants in the transthyretin (*TTR*) gene, which encodes a serum transport protein synthesized in the liver. Mutant *TTR* misfolds and forms amyloid fibrils that are deposited in multiple organs, producing diverse clinical manifestations ranging from neuropathy to cardiomyopathy-predominant phenotypes (4). ATTRv-CM is distinct from wild-type ATTR-CM (ATTRwt-CM), which lacks a pathogenic variant. Although over 150 disease-causing variants of *TTR* have been reported worldwide, the Val30Met variant is more prevalent in Japan, par-

ticularly in endemic areas such as Kumamoto and Nagano prefectures. However, other variants have been reported in Japanese families (5).

We herein describe the first Japanese case of ATTRv-CM associated with *TTR* c.262A>T, commonly referred to as Ile68Leu under the legacy numbering system, which has not been previously reported in this population.

Case Report

The patient was a Japanese man in his 40s with no prior medical history and no abnormal findings on routine health examinations. The patient had not been diagnosed with carpal tunnel syndrome and had no symptoms suggestive of peripheral neuropathy, autonomic dysfunction, or ocular involvement. Two months prior to presentation, he developed a fever and cough and was diagnosed with bronchopneumonia at a local clinic. Chest radiography revealed cardiomegaly with a cardiothoracic ratio of 52% (Fig. 1A), and the patient was referred to our cardiology department for

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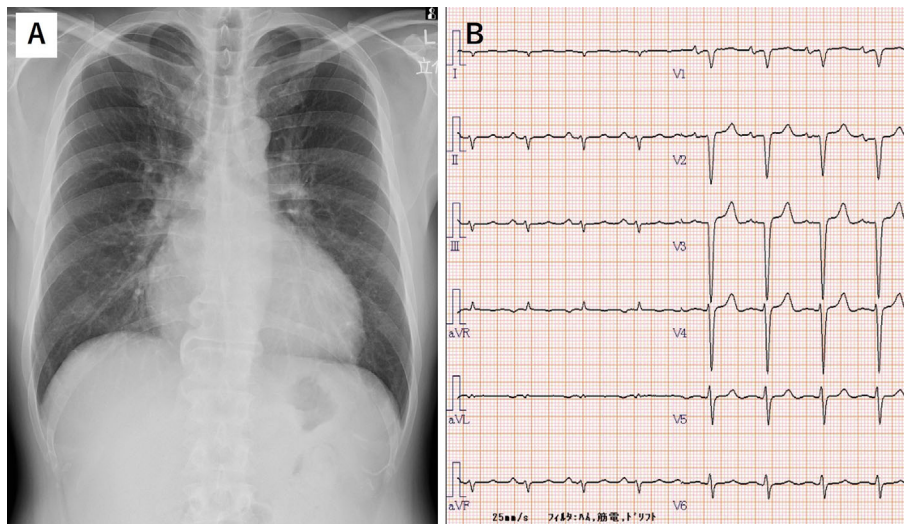


Figure 1. (A) Chest radiography reveals a cardiothoracic ratio of 52%. (B) Twelve-lead electrocardiography demonstrates a normal sinus rhythm and low voltage in the limb leads.

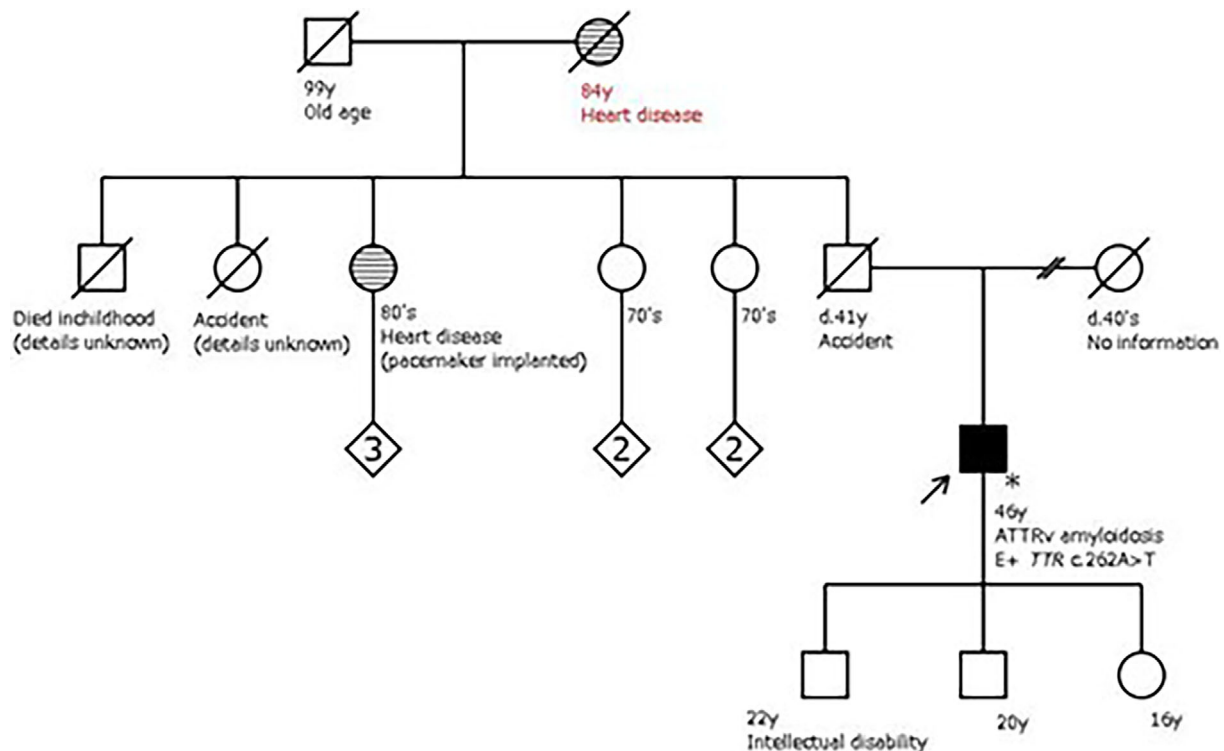


Figure 2. Pedigree of the patient and family members. Both parents died in their 40s, and details regarding the maternal family history were unknown. Based on interviews with the patient and family members, all known relatives were of Japanese descent, and there was no family history of amyloidosis.

further evaluation. At presentation, the patient was classified as New York Heart Association (NYHA) functional class II. Regarding his family history, both parents died in their 40s: his father died in an accident and his mother of an unspecified cause. No detailed medical information was available, and there was no known family history of the disease. Based on interviews with the patient and family members, all known relatives were of Japanese descent, and no non-Japanese ancestry was identified (Fig. 2). A 12-lead electro-

cardiogram demonstrated a sinus rhythm of 92 beats/min with low voltage in the limb leads and QS patterns in leads V1-V3 (Fig. 1B). Transthoracic echocardiography revealed increased left ventricular (LV) wall thickness (interventricular septum, 15 mm; posterior wall, 18 mm) (Fig. 3A and B). The LV ejection fraction was reduced to 38% with diffuse hypokinesia (Fig. 3C). Two-dimensional speckle-tracking echocardiography showed a global longitudinal strain (LS) of 7.7% with a relative apical LS ratio (average apical LS/

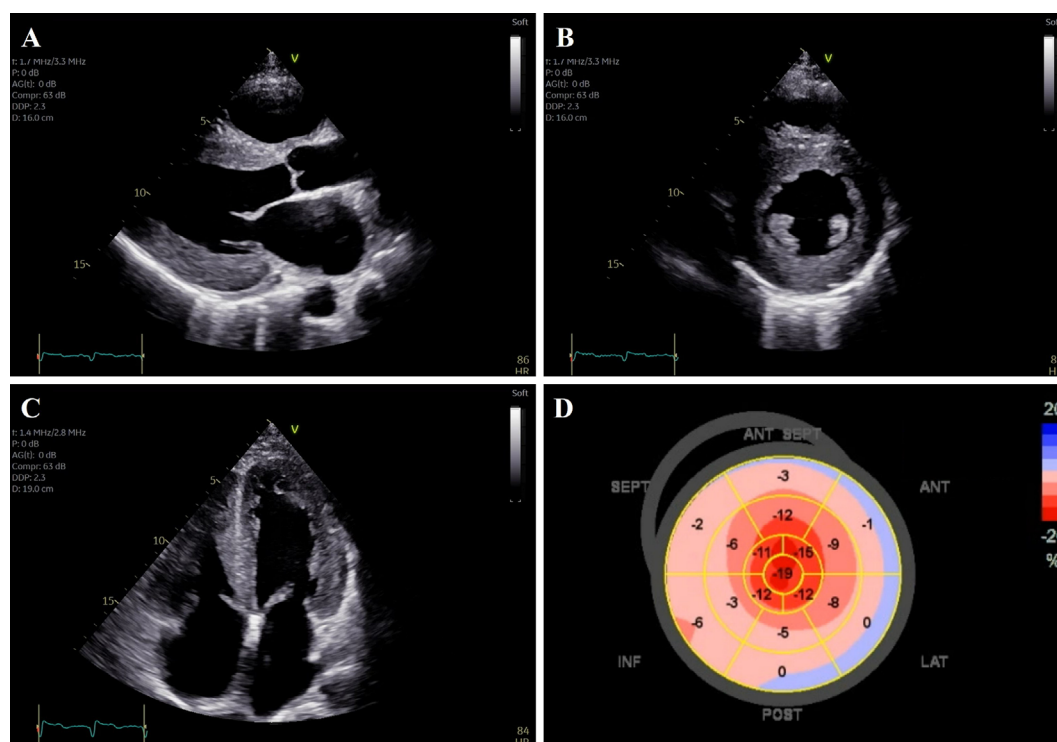


Figure 3. Transthoracic echocardiography reveals concentric left ventricular wall thickening (interventricular septum, 15 mm; posterior wall, 18 mm) in the (A) parasternal long-axis and (B) parasternal short-axis views. (C) Global wall motion is reduced, with a left ventricular ejection fraction of 38%. The apical four-chamber view is shown. (D) Two-dimensional speckle tracking demonstrates a decreased global longitudinal strain of 7.7% and an apical sparing pattern (apical longitudinal strain ratio of 3.0).

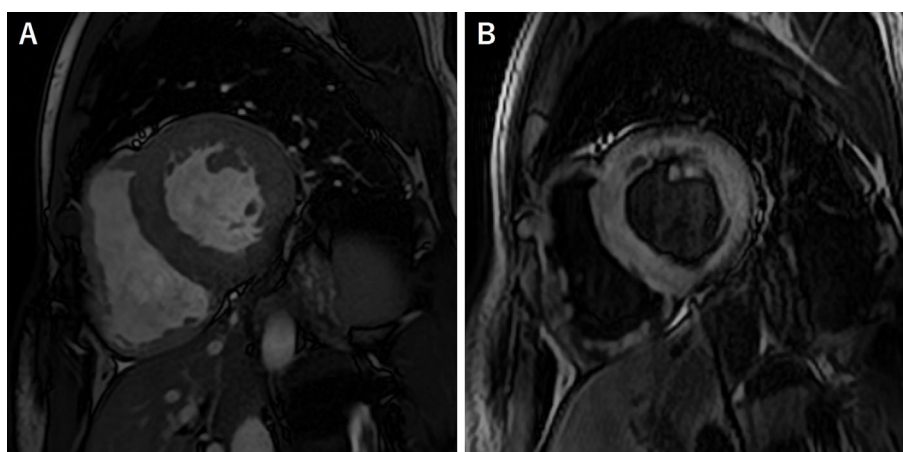


Figure 4. (A) Cine images from cardiac magnetic resonance imaging also demonstrated concentric left ventricular wall thickening, consistent with the echocardiographic findings. (B) Late gadolinium enhancement is observed in the myocardium.

average basal + mid LS) of 3.0, consistent with an apical sparing pattern (Fig. 3D). Laboratory testing revealed elevated levels of B-type natriuretic peptide (253 pg/mL) and high-sensitivity troponin I (30.7 pg/mL). The patient's renal function was preserved, with a serum creatinine level of 0.93 mg/dL, estimated glomerular filtration rate of 70.0 mL/min/1.73 m², and urinalysis showing no significant proteinuria or hematuria. Serum and urine immunofixation were

negative for monoclonal protein, and the free light chain levels were within normal limits (κ , 15.8 mg/L; λ , 16.4 mg/L; κ/λ ratio, 0.96), making AL amyloidosis unlikely. Cardiac magnetic resonance imaging revealed diffuse late gadolinium enhancement throughout the myocardium (Fig. 4A, B). Technetium-99 m pyrophosphate scintigraphy revealed an intense myocardial uptake consistent with Perugini grade 3 (Fig. 5A, B).

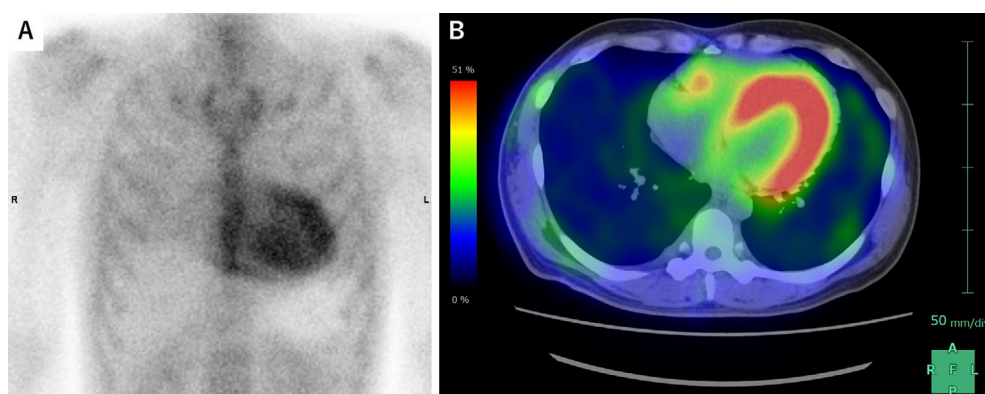


Figure 5. (A) Technetium-99m pyrophosphate scintigraphy reveals Perugini grade 3 uptakes on the anterior planar image. (B) Single-photon emission computed tomography confirms radiotracer accumulation in the myocardium.

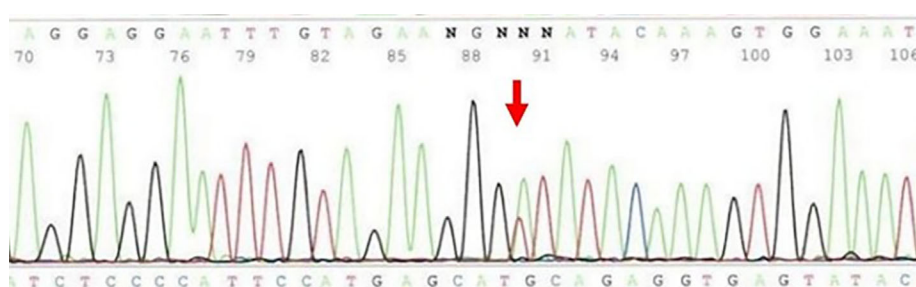


Figure 6. Sanger sequencing of the transthyretin (*TTR*) gene reveals a c.262A>T (p.Ile88Leu) variant in the proband. In the forward chromatogram, a double peak of A/T is observed at the mutation site (red arrow).

The patient had no history of long-standing hypertension, and because ATTR-CM was suspected as the cause of cardiomyopathy, genetic counseling was provided by a clinical geneticist, followed by genetic testing. Sanger sequencing of the *TTR* gene revealed a heterozygous c.262A>T variant (Fig. 1). To assess allele frequency, we searched the Genome Aggregation Database (gnomAD, v2.1.1 and v3.1.2; <https://gnomad.broadinstitute.org/>; accessed August 27, 2025). Variant pathogenicity was assessed according to the American College of Medical Genetics and Genomics guidelines. The Ile68Leu variant met the following criteria: PS4 (significantly increased prevalence in affected individuals compared with controls), PM2 (absence in population databases for East Asians), PP1 (co-segregation with disease in multiple affected family members in the published literature), PP2 (missense variant in a gene with a low rate of benign missense variation), PP4 (patient phenotype being highly specific for ATTR-CM), and PP5 (variant being reported as pathogenic in multiple publications). Based on these criteria, the variant was classified as pathogenic (6, 7). The patient was married and had three children (two sons and one daughter). The inheritance pattern, 50% transmission risk to offspring, and recommendations for cascade screening were also explained. The patient consented to inform family members about the genetic findings and avail-

ability of predictive testing.

The patient was treated with spironolactone (25 mg/day), enalapril (2.5 mg/day), and empagliflozin (10 mg/day). After discussion among multiple cardiologists, vutrisiran, a subcutaneously administered RNA interference agent that suppresses hepatic transthyretin synthesis, was initiated as a disease-modifying therapy for ATTRv-CM. Although variant-specific treatment data for Ile68Leu are limited, treatment was selected based on the patient's relatively young age, hereditary disease background, and clinically significant cardiomyopathy.

At approximately 1 year after the diagnosis, the patient remained free from heart failure hospitalization. His NYHA functional class was II, and his follow-up BNP levels changed from the baseline to 171 pg/mL. His clinical status was also stable.

Discussion

This report describes the first case of ATTRv-CM caused by the Ile68Leu variant in a Japanese patient. To date, the Ile68Leu variant has primarily been reported in Europe (particularly in Italy) and is strongly associated with the cardiac phenotype (8-10). This case expands the known genetic spectrum of ATTRv-CM in the Japanese population (5). The

absence of this variant in the East Asian gnomAD subset supports its rarity in this region (6). In Japan, the Val30Met variant is the most common and is typically associated with neuropathy-predominant phenotypes, particularly in endemic areas (5). However, multiple pathogenic TTR variants have been reported. The presence of undiagnosed cases of ATTRv-CM cannot be excluded, and the true prevalence may be higher than that currently recognized (11).

In European cohorts, the Ile68Leu variant was identified as a pathogenic cause of ATTR-CM, usually manifesting in middle-aged to older individuals with predominant cardiac involvement. A multicenter Italian study confirmed that most patients with this variant presented with heart failure and was regarded as a representative cardiac variant of ATTR-CM (8-10). We report the Ile68Leu variant in a Japanese patient, suggesting that this variant may occur in patients of different ethnicities and geographic regions. This finding highlights that, although the Japanese population is often perceived as genetically homogeneous, diverse TTR variants may be present. Our patient exhibited clinical features consistent with the cardiac-predominant phenotype previously described in European I68 L carriers (9).

With advances in diagnostic modalities and the availability of disease-modifying therapies, ATTR-CM has been increasingly recognized as an underdiagnosed cause of heart failure (3). Thus, ATTRv-CM should be considered even in patients presenting solely with cardiac symptoms without neurological involvement (12). Moreover, distinguishing between ATTRwt-CM and ATTRv-CM is challenging. Genetic testing is crucial not only for an accurate diagnosis and phenotypic characterization, but also for familial risk assessment (13). The identification of the Ile68Leu variant in a Japanese patient suggested the possible presence of additional previously unrecognized cases, and systematic genetic screening may identify further carriers (14). If future reports reveal geographic clustering, the possibility of a founder effect should be considered, underscoring the importance of increasing awareness among healthcare providers of this condition. From a therapeutic perspective, recent clinical trials have demonstrated the efficacy of TTR stabilizers, such as tafamidis and acoramidis, and RNA interference therapies, such as vutrisiran, regardless of variant type or phenotype. Early initiation is particularly recommended in cardiac-dominant presentations, as in this case (15-18). However, the treatment response of the Ile68Leu variant of ATTRv-CM to these agents remains uncertain and warrants a careful follow-up (8).

The clinical significance of this case lies not only in reiterating the established importance of genetic testing in ATTRv, but also in demonstrating a practical diagnostic implication in Japan. Because Val30Met is the best-recognized TTR variant in Japan and is often associated with neuropathy-predominant phenotypes, clinicians may be less likely to suspect ATTRv in Japanese patients who present with predominantly cardiac manifestations. Our case suggests that cardiac-predominant non-Val30Met variants, such

as Ile68Leu, should also be considered in Japanese patients, particularly when differentiating ATTRv-CM from ATTRwt-CM, which has implications for family counseling and cascade screening.

In conclusion, we described the first Japanese case of ATTRv-CM caused by the Ile68Leu variant. This case expands the genetic spectrum of ATTRv-CM in Japan and highlights the need to consider cardiac-predominant non-Val30Met TTR variants. The accumulation of additional cases and longitudinal follow-up are needed to better define the clinical characteristics, systemic manifestations, and treatment responsiveness of the Ile68Leu variant.

The authors state that they have no Conflict of Interest (COI).

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