Korean Circ J. 2023 May;53(5):347-349
https://doi.org/10.4070/kcj.2022.0356
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Research Letter



# A Novel Transthyretin Gene Mutation in Hereditary Transthyretin Amyloidosis: A Case Series of Met13dup Patients



**Received:** Dec 28, 2022
**Revised:** Mar 5, 2023
**Accepted:** Mar 21, 2023
**Published online:** Apr 14, 2023

**Correspondence to**
**Darae Kim, MD, PhD**
Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: daraekyrie@gmail.com



**ORCID iDs**
Kina Jeon
https://orcid.org/0000-0003-2532-9286
Darae Kim
https://orcid.org/0000-0003-3284-0904
Meesoon Park
https://orcid.org/0009-0000-0144-1148
Jin-Oh Choi
https://orcid.org/0000-0002-2441-2267
Kihyun Kim
https://orcid.org/0000-0002-5878-8895
Seok Jin Kim
https://orcid.org/0000-0002-2776-4401
Jung-Sun Kim
https://orcid.org/0000-0002-7221-2737
Eun Seok Jeon
https://orcid.org/0000-0002-9946-5611

**Kina Jeon, MD[1], Darae Kim, MD, PhD[1], Meesoon Park, BSN[1], Jin-Oh Choi, MD, PhD[1], Kihyun Kim, MD, PhD[2], Seok Jin Kim, MD, PhD[2], Jung-Sun Kim, MD, PhD[3], and Eun Seok Jeon, MD, PhD[1]**

[1]Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Division of Hemato-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Hereditary transthyretin cardiac amyloid cardiomyopathy (ATTR-CMP) is caused by the accumulation of misfolded amyloid proteins produced by transthyretin (TTR) gene mutations.[1)2)] Mutations can cause various phenotypic manifestations affecting multiple organs, including the heart and nerves. More than 140 mutations have been identified, and their distributions vary among regions.[3)4)] While Val30Met is the most common TTR mutation worldwide, Asp38Ala is the most prevalent type in South Korea. Here we describe a series of a novel TTR gene mutation, Met13dup, which manifested as a mixed phenotype of polyneuropathy and cardiomyopathy.

## CASE 1

A 68-year-old male was referred to our hospital because of recurrent syncope episodes. He had been repeatedly hospitalized because of acute heart failure within the last 3 years. Even with years of medical treatment, heart failure symptoms worsened, and N-terminal pro b-type natriuretic peptide (NT-proBNP) level was 3,179 pg/mL. He also reported progressive paresthesia and postural hypotension with gastrointestinal symptoms, such as indigestion and constipation. Electrocardiogram (ECG) showed atrial fibrillation (AF) with low voltage in the limb leads, and echocardiography revealed increased wall thicknesses of the left ventricle (LV, 15 mm), right ventricle (RV, 9.3 mm) with thickened mitral, tricuspid valves. Cardiac magnetic resonance (CMR) unveiled subendocardial late-gadolinium enhancement (LGE), suboptimal nulling, and elevation of the extracellular volume. Technetium-99m and diphosphonate (DPD) scan showed grade 3 radionuclide myocardial uptake. Cardiac biopsy confirmed ATTR-CMP, and TTR gene analysis showed Met13dup mutation. Nerve conduction study (NCS) showed terminal latency in the median nerves, suggesting carpal tunnel syndrome. A thorough investigation uncovered unknown heart diseases in his parents, and two out of three siblings had shared similar neurologic symptoms, such as paresthesia, peripheral edema, and diarrhea. Their cardiac manifestations were not evident at the time, but genetic tests revealed Met13dup mutations.

**Funding**

This research was supported by a fund (code: 2022-ER0507-00) by Research of Korea Disease Control and Prevention Agency.

**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Jeon K, Kim D, Park M, Choi JO, Kim K, Kim SJ, Kim JS, Jeon ES; Data curation: Kim D, Park M, Choi JO, Kim K, Kim SJ, Kim JS, Jeon ES; Formal analysis: Kim D, Park M, Kim K, Kim SJ, Kim JS, Jeon ES; Funding acquisition: Kim D, Park M, Choi JO, Kim K, Kim SJ, Jeon ES; Investigation: Jeon K, Kim D, Choi JO, Jeon ES; Methodology: Kim D, Jeon ES; Project administration: Kim D, Park M, Choi JO, Jeon ES; Resources: Kim D; Supervision: Kim D, Choi JO, Kim K, Kim SJ, Kim JS, Jeon ES; Validation: Kim D, Choi JO, Jeon ES; Visualization: Kim D, Jeon ES; Writing - original draft: Jeon K, Kim D; Writing - review & editing: Jeon K, Kim D.

## CASE 2

An 82-year-old female with previous history of hypertension and diabetes came to the emergency clinic with symptoms of acute heart failure. Her blood pressure had normalized even without anti-hypertensive medication. NT-proBNP was 16,590 pg/mL with troponin T level at 0.09 ng/mL. Computed tomography showed LV hypertrophy, so she was diagnosed with hypertrophic cardiomyopathy and then referred to our clinic. ECG showed AF with low voltage. Echocardiography showed increased LV wall thickness (17 mm) with spared apical strain and thickened aortic, mitral, tricuspid valves. CMR exhibited subendocardial LGE with suboptimal nulling. DPD scan showed grade 3 radionuclide myocardial uptake. Endomyocardial biopsy confirmed ATTR-CMP, and TTR gene analysis showed Met13dup mutation. She also had progressive lower leg paresthesia and indigestion, which had been present for a decade before heart failure symptoms. NCS showed signs of carpal tunnel syndrome, chronic lumbosacral radiculopathy, and severe cardiovagal, adrenergic dysfunction. By family screening, the same Met13dup mutations were in all four of her daughters. They were all in their 40s to 50s and had already started to experience neurologic symptoms without significant cardiac manifestations.

## CASE 3

An 82-year-old male with persistent AF and coronary artery disease visited a cardiology clinic because of recurrent presyncope episodes. His primary physician referred him to an arrhythmia specialist. Echocardiography showed a thickened LV wall (12 mm) and thickened valves with restrictive filling patterns. He had mild exertional dyspnea, but NT-proBNP was 1,556 pg/mL. DPD scan showed grade 3 radionuclide myocardial uptake. Endomyocardial biopsy confirmed ATTR-CMP, and TTR gene analysis revealed Met13dup mutation. NCS showed autonomic adrenergic dysfunction and severe sympathetic postganglionic sudomotor dysfunction. During family screening, his son in his early 50s had Met13dup mutation without symptoms.

## DISCUSSION

Patients with Met13dup mutation in our series experienced an earlier onset of peripheral and autonomic neuropathy and later cardiac manifestations that eventually required hospitalization due to heart failure (**Figure 1**). Met13dup is a novel mutation variant, which we have recently reported to the Transthyretin Amyloid Outcome Survey (THAOS) registry.[3)4)] It is noteworthy that this late-onset variant presented as a mixed phenotype with peripheral and autonomic neuropathy as the first manifestation. In addition, given that the average age of our patients was 77, we would like to emphasize the importance of TTR genetic testing, regardless of age. Although the average age at diagnosis of cardiac involvement was similar to that of wild-type ATTR, Met13dup mutation is distinct for the presence of significant peripheral and autonomic neuropathy, which are uncommon in patients with wild-type ATTR.[5)]


https://doi.org/10.4070/kcj.2022.0356

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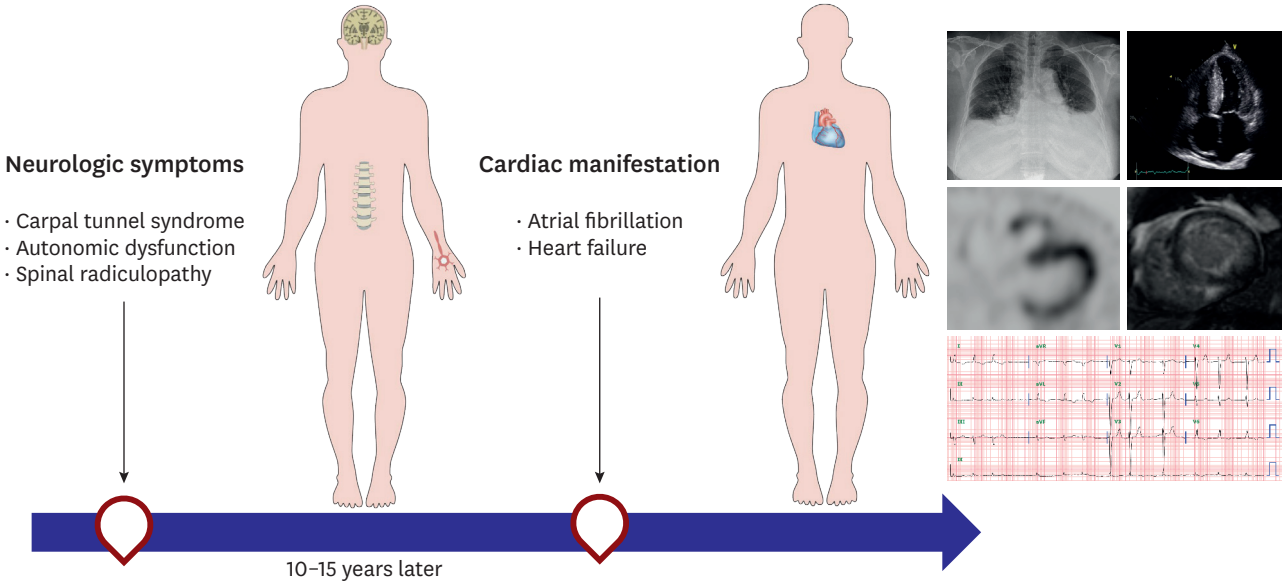


**Figure 1.** An overview of clinical presentation in Met13dup hereditary transthyretin amyloidosis patients.
(This figure includes images of case 1.)

## REFERENCES

1. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol* 2010;7:398-408.
PUBMED | CROSSREF
2. Kim D, Choi JO, Kim K, Kim SJ, Jeon ES. Untangling amyloidosis: recent advances in cardiac amyloidosis. *Int J Heart Fail* 2020;2:231-9.
PUBMED | CROSSREF
3. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol* 2016;68:161-72.
PUBMED | CROSSREF
4. Damy T, Kristen AV, Suhr OB, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). *Eur Heart J* 2019;43:391-400.
PUBMED | CROSSREF
5. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation* 2016;133:282-90.
PUBMED | CROSSREF


https://doi.org/10.4070/kcj.2022.0356