A novel HCN4 variant related to familial sinus bradycardia, left ventricular noncompaction, and thoracic aortic aneurysm

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Thoracic aortic aneurysms (TAAs) may present in syndromic and isolated forms. Hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4) plays a crucial role in the generation of sinus rate and rhythm, and mutations in the HCN4 gene were first identified as a genetic cause of sinus bradycardia. In 2014, Schweizer et al. reported for the first time that HCN4 channel dysfunction, in addition to its known association with sinus node dysfunction, may be implicated in the impaired formation of ventricular structure and lead to myocardial noncompaction. Subsequently, HCN4 mutations linked to left ventricular noncompaction (LVNC) were found to occur, according to a recent meta-analysis, in 1% of LVNC cases. Defects of the mitral valve were also noted.¹

Vermeer et al.² reported HCN4 variants (including p.Tyr481His and p.Gly482Arg) in families with sinus bradycardia and LVNC that cosegregated with TAA. Another team of researchers found the HCN4 p.Gly482Arg variant in a proband with sinus bradycardia, ascending aorta dilation of 42 mm in diameter at the age of 35 years (figure 1A).⁴ Our novel variant in the HCN4 gene (p.Arg483_Val487del) (figure 1g) corresponds with the variants described by Vermeer et al.² and Hanania et al.,³ so this further confirms the existence of the HCN4 mutation hot-spot site specific for the combined phenotype of sinus bradycardia, LVNC, and TAA, as previously suggested.⁴

A developmental effect represents a potential explanation for the coexistence of bradycardia and structural cardiac alterations. In addition to an established function of HCN4 in cardiac pacing, it was identified as a primary marker for the cardiac progenitors of the first heart field in the early development of the embryonic heart, forming both the main parts of the cardiac muscle and the conduction system.⁵ A potential link with the development of TAA may also be based on findings from studies in mice, which demonstrated HCN4 expression in the endothelium of the aorta.³⁵

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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FIGURE 1  A – transthoracic echocardiography (parasternal long-axis view): thoracic ascending aorta aneurysm located in the upper part of the sinotubular junction. Ascending aorta diameters: A – aortic annulus (22.7 mm), B – sinuses of Valsalva (35.7 mm), C – sinotubular junction (33.8 mm), and D – tubular ascending aorta (46 mm). B, C – transthoracic 2-dimensional echocardiography (apical 4-chamber view): B – left ventricular noncompaction and the bilayer wall involving the midventricular and apical segments; C – color flow Doppler ultrasound showing blood flow from the ventricular cavity into deep intertrabecular spaces at end-diastole (arrow); D, E – steady-state free precession images in 4-chamber (D) and short-axis (E) views: prominent trabeculations are seen together with the thin, compacted layer of the myocardium (arrows). F – single-shot steady-state free precession coronal image demonstrating a mild dilatation of the ascending aorta.
REFERENCES


FIGURE 1  G – pedigree of the family. An asterisk indicates age at death; black filling, the coexistence of left ventricular noncompaction, thoracic aortic aneurysm, and bradycardia; pluses, p.Arg483_Val487del-positive individuals; minus, p.Arg483_Val487del-negative individuals. The black arrow indicates the proband. H – distribution of HCN4 variants related to the complex phenotype: bradycardia, noncompaction cardiomyopathy, and thoracic aortic aneurysm. S1 to S6 denote transmembrane domains, and P a pore-forming loop.

Abbreviations: PM, pacemaker