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The novel *TRPM4* c.448G>T variant is associated with familial conduction disorders, cardiomyopathy, and sudden cardiac death

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Dilated cardiomyopathy (DCM) is a common cause of heart failure, which may be associated with electrical conduction disturbances and life-threatening arrhythmias. Its etiology is reported to be genetic in up to 65% of cases. Transient receptor melastatin 4 channel (*TRPM4*) is a Ca^{2+}-activated transmembrane non-selective cation channel. *TRPM4* contributes to the depolarization of excitable cells in the myocardium by changing the frequency and duration of action potentials by influencing the Ca^{2+} influx [1]. Genetic variants in *TRPM4* have been linked to inheritable conduction diseases (congenital atrioventricular node block and right bundle branch block) and Brugada syndrome, suggesting that this ion-channel may play a role in electrical propagation [2]. Furthermore, an association with systemic arterial hypertension and left ventricular hypertrophy has been described in animal models [3, 4]. A recent study has also reported a *TRPM4* variant to be associated with DCM [5].

We herein describe a family with a novel, likely pathogenic, heterozygous variant (class IV) in the *TRPM4* gene presenting with conduction disorders, DCM, and sudden cardiac death (SCD).

A 40-year-old Caucasian male was admitted to our department due to progressive malaise and exertional dyspnea. He was diagnosed to have congestive heart failure (New York Heart Association [NYHA] III). Twelve-lead electrocardiogram (ECG) showed a complete left bundle branch block (LBBB) (Fig. 1, upper left panel), and transthoracic echocardiography revealed a severely dilated left ventricular (LV) end-diastolic volume index of 110 mL/m^2, normal LV wall thickness (7 mm), and severely reduced LV ejection fraction (17%). Cardiac magnetic-resonance (CMR) imaging excluded ischemic heart disease but revealed septal edema (T2-weighted imaging showing hyperintensity; Fig. 1, upper middle panel). Serum high-sensitivity troponin assays and C-reactive protein levels were normal. Cardiac 18-FDG PET-CT scanning excluded active myocarditis and cardiac sarcoidosis. Further work-up was unremarkable, and the diagnosis of DCM was established.

The patient had a past medical history of Hodgkin's lymphoma, for which he received 6 cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine 7 months prior. Cumulative dose of doxorubicin was 600 mg (300 mg/m^2). A 12-lead ECG prior to initiation of chemotherapy had already shown a complete LBBB, but the patient reported no signs of congestive heart failure.

The family history was remarkable. The daughter of a first-degree male cousin had suffered SCD at the age of 7 years. Autopsy findings revealed

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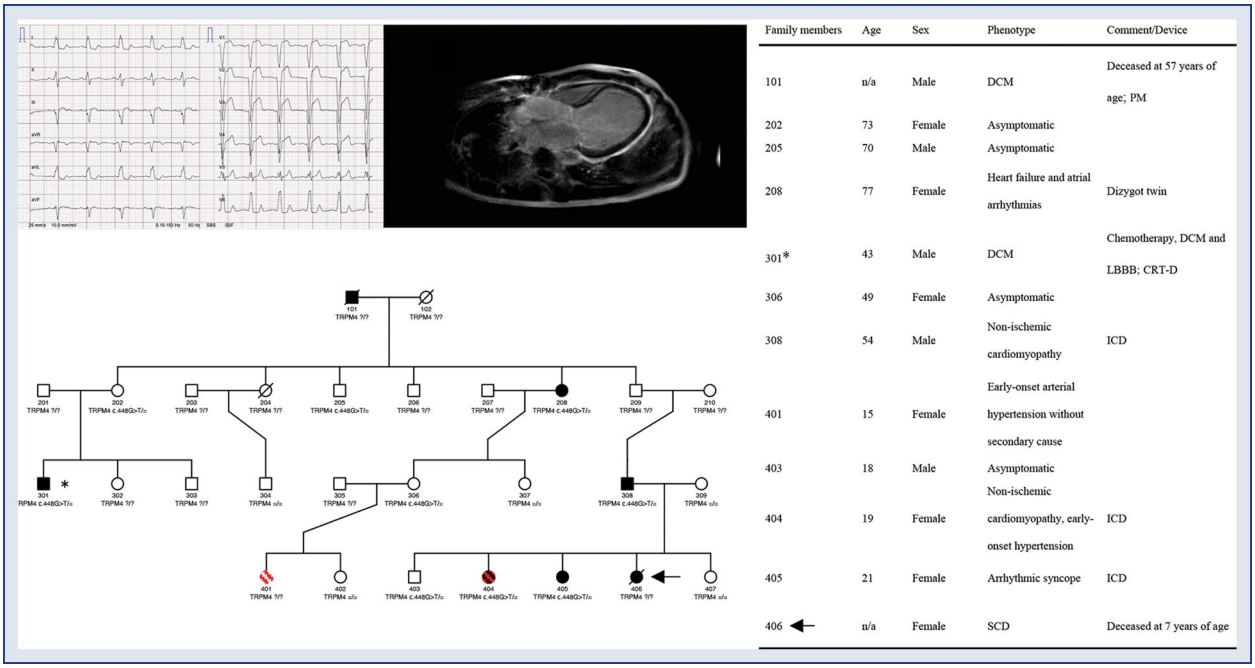

Family members	Age	Sex	Phenotype	Comment/Device
101	n/a	Male	DCM	Deceased at 57 years of age; PM
202	73	Female	Asymptomatic	
205	70	Male	Asymptomatic	
208	77	Female	Heart failure and atrial arrhythmias	Dizygot twin
301*	43	Male	DCM	Chemotherapy, DCM and LBBB; CRT-D
306	49	Female	Asymptomatic	
308	54	Male	Non-ischemic cardiomyopathy	ICD
401	15	Female	Early-onset arterial hypertension without secondary cause	
403	18	Male	Asymptomatic	
404	19	Female	Non-ischemic cardiomyopathy, early-onset hypertension	ICD
405	21	Female	Arrhythmic syncope	ICD
406 ←	n/a	Female	SCD	Deceased at 7 years of age

Figure 1. Top left panel showing electrocardiogram of presented patient with a left bundle-branch block (LBBB). Top central panel showing a cardiac magnetic resonance imaging and a four-chamber view with a dilated left ventricle. Bottom left panel showing the family tree of the presented patients. Asterisk marks the presented patient; arrow marks the index patient. Black filled circles and boxes present patients with a cardiac phenotype; red diagonal lines in circles present patients with early-onset hypertension. Genotype is shown below the respective circles and boxes. Equal sign indicating wild type. Right panel showing description of genotypically positive family members; DCM — dilated cardiomyopathy; CRT-D — cardiac resynchronization therapy plus defibrillator; ICD — implantable cardioverter-defibrillator; PM — pacemaker; SCD — sudden cardiac death.

the presence of DCM. Molecular autopsy was refused by her parents. Genetic testing was performed in her sister at the age of 17 years following a syncopal episode and suspected hypertrophic cardiomyopathy. Next-generation sequencing, which covered a cardiomyopathy panel of 31 genes using the HiSeq2500 Illumina system (ACTC1, ACTN2, ANKRD1, CALR3, CAV3, CSRP3, FHL1, GLA, JPH2, LAMP2, LDB3, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEXN, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL, and TRPM4), revealed a novel heterozygous variant in the *TRPM4* gene (c.448G>T; p.Gly150* — transcript: NM_017636.3), classified as likely pathogenic (class IV) according to the 2015 American College of Medical Genetics Criteria [6]. Although most of the variants in the *TRPM4* gene lead to channel gain of function, there are some loss of function missense variants reported that are associated with cardiovascular disease [7, 8]. This nonsense mutation leads to a premature stop codon, but the variant affects the last nucleotide in exon 4 and is predicted to cause the loss of the neighboring splice donor site (SpliceAI score 0.878) [9]. Both aberrant splicing and the stop mutation likely lead to nonsense-mediated mRNA-decay. Cascade screening revealed several relatives with conduction disease, atrial arrhythmias, or SCD in this family (Fig. 1, lower left and right panels), and this *TRPM4* variant co-segregated with the phenotype in this family, suggesting a Mendelian autosomal-dominant inheritance with variable penetrance. Based on these criteria, the pathogenicity of this variant is likely. Of note, a variable phenotypic expression and incomplete penetrance is a well-known entity in inherited cardiomyopathies, which likely explains the findings in this family.

The same heterozygous variant in *TRPM4* was confirmed in our patient by genetic cascade screening. We must consider that chemotherapy for lymphoma may have contributed to the DCM phenotype in this patient. Doxorubicin therapy may frequently lead to toxic cardiomyopathy in a dose-dependent manner. Nevertheless, this patient had a preexisting LBBB, suggesting the

presence of a prior heart condition. Unfortunately, cardiac imaging had not been performed prior to initiation of chemotherapy.

It is possible that cardiotoxic chemotherapy could act as a second hit in our patient, who has a genetic predisposition for DCM. Garcia-Pavia et al. [10] investigated a patient cohort with a history of chemotherapy-induced cardiomyopathy. After genotyping 213 patients who underwent chemotherapy predominantly with anthracyclines, they found a significantly higher rate of titin (*TTN*) truncating variants in patients with cardiomyopathy as compared to those without cardiomyopathy. This finding may suggest a genetic predisposition to develop chemotherapy-induced cardiomyopathy.

A limitation to our finding is the lack of functional studies that would support the pathogenicity of the described variant.

In conclusion, we describe a novel, likely pathogenic, heterozygous variant in the *TRPM4* gene affecting a family over 4 generations being associated with a phenotype of conduction disease, atrial arrhythmias, DCM, and SCD.

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