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SPECIAL REPORT

Monomorphic and Polymorphic Ventricular Arrhythmias in Heterozygous Calsequestrin-2 Mutation Carriers

Juan Jiménez-Jáimez, PhD; Mercedes Cabrera Ramos, MD; Francisco Bermúdez-Jiménez, MD, PhD; José Manuel García Pinilla, MD, PhD; Ainhoa Robles Mezcua, MD; Rosa Macías Ruiz, MD; Miguel Álvarez, MD, PhD; Luis Tercedor, MD

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disorder caused by mutations in proteins from the sarcoplasmic reticulum, leading to a cytosolic calcium overload and delayed afterdepolarizations causing polymorphic ventricular tachycardia and sudden cardiac death.[1] The 2 main disease-causing genes are ryanodine receptor 2, with an autosomal dominant inheritance pattern, and calsequestrin 2 (*CASQ2*), classically described as the autosomal recessive form of the disease.[2] Recent and isolated reports have described cohorts of *CASQ2*-CPVT heterozygous carriers as presenting with a mild CPVT phenotype.[3] However, data about the presence of ventricular arrhythmias (VAs) in this kind of patients are lacking, especially for monomorphic arrhythmias, that go against the natural history and current diagnostic criteria of this disorder. Currently, a definite diagnosis requires the presence of at least 3 ventricular ectopy morphologies.[4] Our aim is to describe the VAs spectrum, monomorphic and polymorphic, in 3 families with heterozygous mutations in *CASQ2* (calsequestrin 2) and autosomal dominant pattern.

We recruited 9 heterozygous *CASQ2* mutation carriers belonging to 3 unrelated families (Figure). We collected data about family history of arrhythmias or sudden cardiac death, basal and exercise electrocardiography, symptoms, and the incidence of sustained VA. VA observed in basal ECG, 24 hours ambulatory ECG or treadmill test were classified based on their morphology. Monomorphic VA was defined as meaning only one QRS morphology was present on all tests. Probands with homozygous or compound heterozygous were also evaluated for segregation of the phenotype. The data that support the findings of this study are available from the corresponding author upon reasonable request.

All the homozygous/compound heterozygous patients presented with syncope at young age, while heterozygous carriers were in general less symptomatic and diagnosed through cascade screening at an older age (mean age 20 and 55 years in homozygous and heterozygous carriers, respectively). Eight out of 9 heterozygous carriers presented with exercise- or emotion-induced VA, some of them with no attributable symptoms (Table and Figure). About morphology, 3 of these patients presented with monomorphic ventricular ectopy/tachycardia with inferior axis and left bundle branch block pattern, not fulfilling criteria for CPVT, so they had been previously diagnosed with idiopathic outflow tract ventricular tachycardia/ectopy. Interestingly, monomorphic ventricular ectopy increased with exercise, something that is unusual for idiopathic right ventricular outflow tract ventricular ectopy. The remaining positive heterozygous patients (n=5) showed a typical CPVT phenotype with exertional pleomorphic ectopy (Figure and Table).

Family A presented with exclusively heterozygous carriers being the proband (III.4), a 32-year-old male with palpitations who developed pleomorphic ventricular ectopy and a monomorphic right ventricular outflow tract tachycardia on an exercise test (Figure [A]). He carried the synonymous mutation p.Gly127= in *CASQ2* that segregated with the phenotype of monomorphic and polymorphic ventricular ectopy. Proband from family B (III.2) experienced a syncope under adrenergic situations at the age of 15. She exhibited a typical CPVT

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Correspondence to: Juan Jiménez-Jáimez, PhD, Unidad de Arritmias y Cardiopatías Familiares, Hospital Universitario Virgen de las Nieves, Avenida de las Fuerzas Armadas 2, 18014, Granada, Spain. Email jimenez.jaimez@gmail.com

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Nonstandard Abbreviations and Acronyms

CASQ2	calsequestrin 2
CPVT	catecholaminergic polymorphic ventricular tachycardia
VAs	ventricular arrhythmias

phenotype, requiring high doses of nadolol and flecainide. She presented compound heterozygous genetic status with biallelic presence of the mutations p.Gly127= and c.783+4A>G in *CASQ2*. Her sister and parents, heterozygous, exhibited symptomatic polymorphic (father) and monomorphic (sister) VA on exercise or 24-hour Holter ECG (Figure [B]). Finally, family C presented the known p.Arg33X *CASQ2* mutation with two homozygous

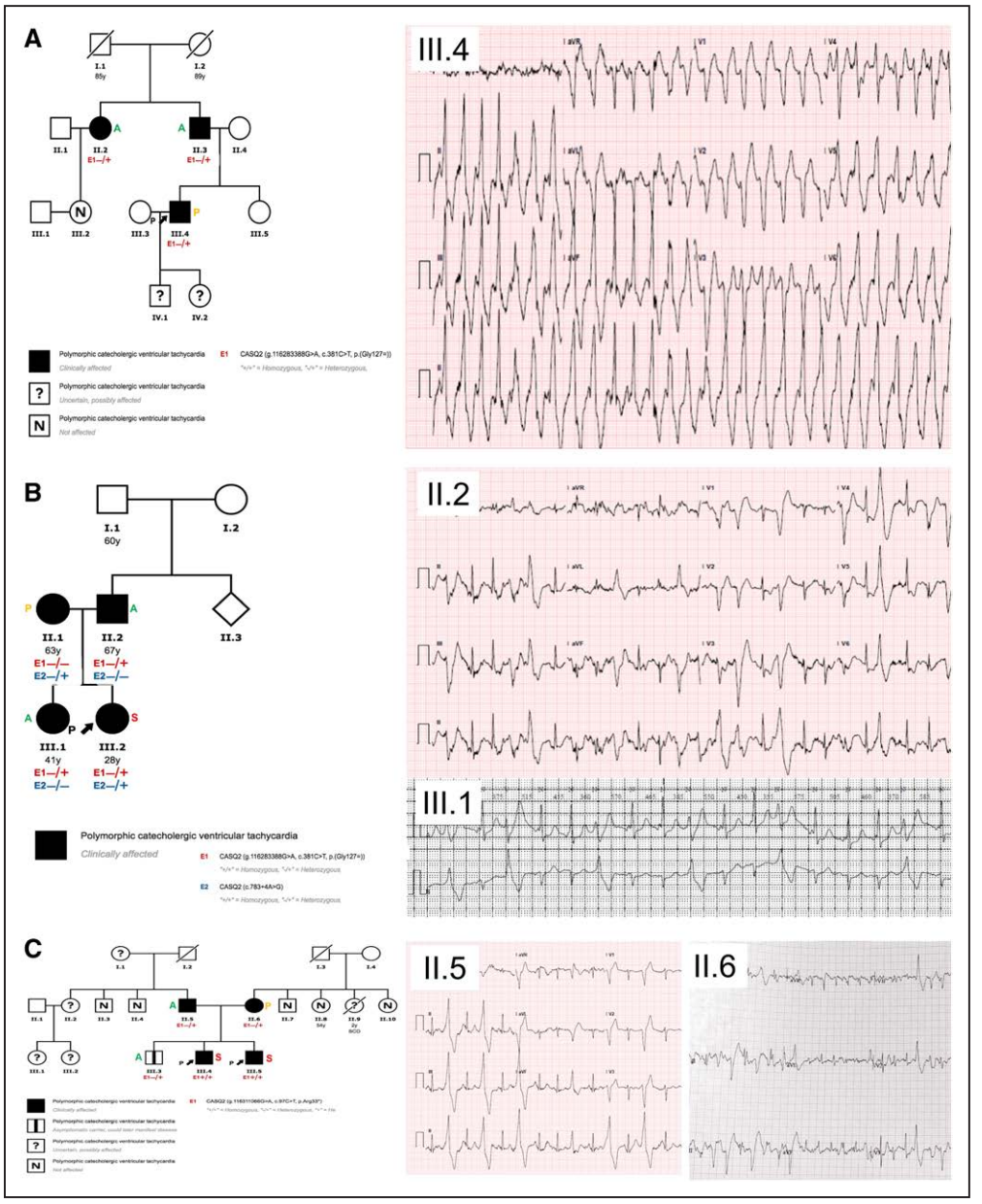

Figure. Representative pedigree and ECG traces from families and carriers.
A, Family with 3 *CASQ2* heterozygous carriers of the variant p.Gly127=. On the **right** side, exercise induced monomorphic ventricular tachycardia (VT) with inferior axis and left bundle branch block pattern in the index case, who had presented with palpitations; note fusion with isorhythmic narrow QRS complexes. **B**, Proband was carrier of compound heterozygous mutations in *CASQ2* p.Gly127= and c.783+4A>G. On the **right** side, representative ECG traces from her father and sister with polymorphic and monomorphic ventricular ectopies, respectively. **C**, Family with R33X mutation with 2 homozygous cases and 3 heterozygous cases evaluated. The father exhibited monomorphic arrhythmias on exercise (**left** side image), while the mother showed a typical catecholaminergic polymorphic ventricular tachycardia (CPVT) phenotype (**right** side image). A indicates asymptomatic; P, palpitations; and S, syncope.

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Table. Clinical and Genetical Features of CASQ2 Mutation Carriers

Family/ pedigree	Proband status	Age/sex	Main symptom	Genotype	Ventricular arrhythmias on exercise	Monomorphic RVOT ectopy?	Sustained VT	Treatment
A/II.II	–	71/F	Asymptomatic	c.381C>T p.Gly127=	+	+	–	BB
A//II.III	–	66/M	Asymptomatic	c.381C>T p.Gly127=	+	–	–	BB
A/II.IV	+	32/M	Palpitations	c.381C>T p.Gly127=	+	–	+	Flecainide
B/II.1	–	63/F	Palpitations	c.783+4A>G	+	+	–	BB
B/II.2	–	67/M	Asymptomatic	c.381C>T p.Gly127=	+	–	–	BB
B/III.1	–	41/F	Asymptomatic	c.381C>T p.Gly127=	+	–	–	BB
B/III.II	+	28/F	Syncope	c.381C>T p.Gly127= and c.783+4A>G	+	–	–	BB+flecainide
C/II.5	–	53/M	Asymptomatic	R33X	+	+	–	BB
C/II.6	–	52/F	Palpitations	R33X	+	–	–	Flecainide
C/III.3	–	18/M	Asymptomatic	R33X	–	–	–	No
C/III.4	+	10/M	Syncope	R33X	+	–	–	BB+flecainide
C/III.5	+	5/M	Syncope	R33X	+	–	–	BB+flecainide

BB indicates β-blockers; CASQ2, calsequestrin 2; F, female; M, male; RVOT, right ventricular outflow tract; and VT, ventricular tachycardia.

probands with syncope at 5 and 10 years old. The father was heterozygous showing asymptomatic exercise-induced ventricular ectopy with just one QRS morphology with inferior axis and left bundle branch block pattern. However, the heterozygous mother exhibited a typical CPVT phenotype presenting as exertional palpitations.

Our data confirm the presence of VA in an autosomal dominant fashion for *CASQ2*-CPVT, and expand the phenotype spectrum of *CASQ2* mutations carriers beyond the typical polymorphic VA. In our cohort, almost half of the patients with heterozygous *CASQ2* mutations exhibited exclusively monomorphic VA. This phenotype is more suggestive of idiopathic ventricular tachycardia rather than typical CPVT. Differentiating both entities is crucial given the potential relationship of the latter with sudden cardiac death. However, arrhythmic risk of this recently identified subtype of patients is unknown and prognosis might be dependent on the specific *CASQ2* variant, as serious events have been described before in *CASQ2* heterozygous carriers.[5] Establishing the pathogenicity of heterozygous variants in *CASQ2* according to phenotype-genotype segregation in each family is essential. Early identification of these cases is critical to prevent arrhythmic syncope or sudden cardiac death; therefore, we recommend consideration for *CASQ2* heterozygous variants in these cases and prompt genetic testing.

ARTICLE INFORMATION

Affiliations

Cardiology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain (J.J.-J., F.B.-J., R.M.R., M.A., L.T.). Cardiology Department, Hospital Universitario Iozano Blesa, Zaragoza, Spain (J.J.-J., F.B.-J., R.M.R., M.A., L.T.). Instituto de Investigación Biosanitaria (ibs.GRANADA), Universidad de Granada, Spain (M.C.R.). Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain (F.B.-J.). Cardiology Department, Hospital Universitario Virgen de la Victoria, Málaga, Spain (J.M.G.P., A.R.M.).

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