RYR2 and CASQ2 Mutations in Patients Suffering From Catecholaminergic Polymorphic Ventricular Tachycardia

To the Editor:

Catecholamine-induced polymorphic ventricular tachycardia (CPVT) is characterized by episodes of syncope, seizures, or sudden death in response to physical activity or emotional stress. The two modes of inheritance that have been described are autosomal dominant\(^1\) and autosomal recessive.\(^2\) Mutations in the ryanodine receptor 2 gene (RYR2), which encodes a cardiac sarcoplasmic reticulum Ca\(^{2+}\) release channel, were shown to cause the autosomal dominant form of the disease.\(^3\)

Recently, Priori et al\(^4\) reported on clinical and molecular characterization of 30 probands with catecholaminergic polymorphic ventricular tachycardia and their 118 family members. A mutation screening of the RYR2 gene identified mutations in only 14 of 30 probands and in 9 family members.

Our group has recently described a missense mutation in a highly conserved region of the calsequestrin 2 gene (CASQ2) as the potential cause of the autosomal recessive form of CPVT.\(^5\) The CASQ2 protein serves as the major Ca\(^{2+}\) reservoir within the sarcoplasmic reticulum of cardiac myocytes and is part of a protein complex that contains the ryanodine receptor. The mutation converts a negatively charged aspartic acid into a positively charged histidine in a highly negatively charged domain and is likely to exert its deleterious effect by disrupting Ca\(^{2+}\) binding.

It is possible that at least some of the nongenotyped CPVT probands described by Priori et al\(^4\) may carry mutations in the CASQ2 gene. Lack of family history in part of the probands’ affected families may suggest a recessive inheritance, increasing the likelihood that some of them harbor mutations in a common gene.

We suggest that a full genetic evaluation of CPVT patients should include mutation screening for both known genes, RYR2 and CASQ2.

Hadas Lahat, PhD
Elon Pras, MD
Genetic Institute
Sheba Medical Center
Tel Aviv University
Tel Hashomer, Israel
epras@post.tau.ac.il

Michael Eldar, MD
Heart Institute
Sheba Medical Center
Tel Aviv University
Tel Hashomer, Israel
meldar@post.tau.ac.il

Response

We agree with Drs Lahat and Eldar that homozygous CASQ2 mutations may be the cause of catecholaminergic polymorphic ventricular tachycardia (CPVT) in our patients.\(^1\) We have screened the coding region of the CASQ2 gene in all of the probands and failed to identify a CASQ2 homozygous mutation in any of them. This observation suggests that CASQ2-related CPVT, so far described only in the consanguineous kindred reported by Lahat et al,\(^2\) may be an uncommon variant of CPVT.

We also agree that in patients with CPVT, genetic analysis should include assessment of the RYR2 and CASQ2 genes.

Silvia G. Priori, MD, PhD
Raffaella Bolise, MD
Mirella Mennini, PhD
Barbara Colombi, BS
Carlo Napolitano, MD, PhD
Molecular Cardiology
IRCCS Fondazione Salvatore MAUGERI
University of Pavia
Via Ferrata 8
27100 Pavia, Italy
spriori@fsm.it

Fernando Coltorti, MD
Maurizio Gasparini, MD
Cardiac Electrophysiology Unit
Istituto Clinico Humanitas
Rozzano, Italy

Roberto Keegan, MD
Servicio de Cardiología (R.K.) HIGA
Dr. José Penna
Bahía Blanca, Argentina

Fernando E. S. Cruz Filho, MD
Instituto de Cardiología Laranjeiras
Ministry of Health of Brazil (F.E.S.C.F.)
Rio de Janeiro, Brazil

Fabrizio Drago, MD
Pediatric Cardiology
Ospedale Bambin Gesù
Roma, Italy

Gabriele Viganti, MD
Ospedale Niguarda
Milano, Italy

Abraham Benatar, MD
Pediatric Cardiology (A.B.)
Academic Hospital VUB
Brussels, Belgium

Luciano De Simone, MD
Pediatric Cardiology
Ospedale Meyer
Firenze, Italy

Angelica DeLogu, MD
Pediatric Cardiology
Ospedale Gemelli
Roma, Italy

Ryr2 and CASQ2 Mutations in Patients Suffering From Catecholaminergic Polymorphic Ventricular Tachycardia
Hadas Lahat, Elon Pras and Michael Eldar

Circulation. 2003;107:e29
doi: 10.1161/01.CIR.0000050555.40735.ED
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/3/e29

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/