



## Autosomal Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia

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**Key words:** tachycardia, genetics, sudden death, catecholamine, syncope

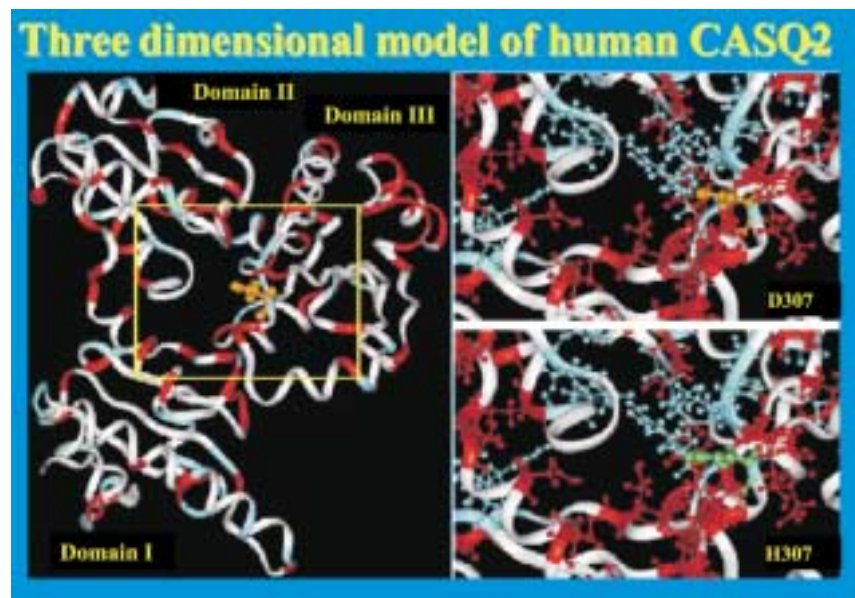
IMAJ 2002;4:1095–1096

Catecholamine-induced polymorphic ventricular tachycardia is a rare disease that occurs in subjects without obvious organic heart disease; it is characterized by episodes of syncope, seizures or sudden death in response to physiologic or emotional stress. The disease, first described as a case report in 1975 [1], was defined as a clinical entity by Leenhardt et al. in 1995 [2]. They described 21 children with no organic heart disease and normal baseline electrocardiogram (except for sinus bradycardia) who were referred for stress- or emotion-induced syncope. The average age of symptom onset was about 8 years, and PVT could be induced by exercise, isoproterenol infusion or other forms of adrenergic stimulation in all patients. In about 30% of cases there was a family history of similar symptoms, suggestive of genetically mediated disease, but no further information was available.

In 1999, Swan et al. from Finland [3] described two unrelated families with typical catecholamine-induced PVT segregating in an autosomal dominant mode. However, symptoms in these two families began at a later age (mean  $21 \pm 10$  years), and ventricular arrhythmias had a distinctive pattern of bi-directional VT, somewhat different from that described by Leenhardt et al., which was more chaotic in appearance. Using linkage analysis, Swan and co-workers [3] mapped the disease-causing gene to the long arm of chromosome 1 at 1q42-43. A year later, Priori et al. [4] and Laitinen et al. [5] identified several missense mutations in the ryanodine receptor 2 gene (RYR2) in seven families harboring the disease. The ryanodine receptor is a sarcoplasmic reticulum channel, responsible for the release of  $Ca^{+2}$  ions from the SR in response to  $Ca^{+2}$

ingress to the cytoplasm through the sarcolemmal Ca channels ("calcium-induced calcium release").

Our group identified several families of a Bedouin tribe in the north of Israel, afflicted by catecholamine-induced PVT [6]. Parents in these families are always consanguineously related (first, second and third-degree cousins) and asymptomatic. Families where one of the parents does not belong to the tribe are never afflicted by the disease. Nine children in the afflicted families died suddenly during the last decade, and an additional 12 children have had recurrent



**Figure 1.** A three-dimensional model of human calsequestrin 2 protein. **Left side:** Ribbon drawing of human CASQ2 three-dimensional homology model. The D307 amino acid is shown in orange. The model was calculated using "homology" and "discovery" modules of Biosym/MSI. The protein termini were omitted from the modeling calculation, leaving a G22-to-L366 amino acid core. The default parameters were used to generate a loop (E345 to P353). Energy minimization was performed using steepest-descent (100 iterations) and conjugate-gradient (1,000 iterations) algorithms. **Right side:** A closer look at the mutant position domain. The basic and acidic amino acids are shown, in blue and red respectively, as "balls and sticks." The top model is of the wild-type protein (D307), and the bottom model is of the mutant protein (H307). The substitute position is shown in orange (for D307) and green (for H307). The histidine in the mutant form appears to disrupt a band of negative amino acids and could thus upset the protein's charge balance.

PVT = polymorphic ventricular tachycardia  
SR = sarcoplasmic reticulum

syncope and seizures, always following exercise or excitement. Syncopal episodes began at a mean age of 63 years (range 3–12). One 7 year old asymptomatic child was diagnosed during an exercise test.

Patients were of either gender (nine females, four males) and each had an unrevealing physical examination. ECG was normal, including the QT and QTc intervals, except for resting sinus bradycardia ( $63 \pm 13$  beats/minute), and echocardiogram did not disclose any pathology. All patients had PVT induced by exercise or isoproterenol infusion at a mean heart rate of  $110 \pm 10$  beats/min. Patients were treated with beta-blockers with complete resolution of symptoms in 11 and decreased incidence of symptoms in 2 patients with questionable compliance. Parents and siblings (n=28) were asymptomatic and had normal ECGs and no arrhythmias on exercise or isoproterenol infusion. The data were consistent with an autosomal recessive form of catecholamine-induced PVT.

A genome-wide search using polymorphic markers on DNA samples from the Bedouin families mapped the disease locus to a 16 Mb interval on the short arm of chromosome 1 (1p13-21). A maximal Lod score of 8.24 was obtained with the marker DIS189 at  $\theta=0.00$  [6]. Recombination and haplotype analysis with two additional markers refined the linkage interval to an 8 Mb interval [7].

Different candidate genes residing in this interval were sequenced and found to be normal in the patients. The recent implication of RYR2 in the dominant form of catecholamine-induced PVT has focused our attention on the calsequestrin 2 gene (CASQ2) located in the linkage interval. Sequencing the CASQ2 gene revealed a missense mutation resulting in an aspartic acid to histidine change at position 307 of the protein [7]. Calsequestrin is a cardiac SR protein capable of binding a large number of  $\text{Ca}^{+2}$  cations, and serves as the major  $\text{Ca}^{+2}$  reservoir within the SR of cardiac myocytes. It contains a large number of anionic amino acid residues, mostly Asp and Glu [8], constituting part of a protein complex required for normal operation of intracellular  $\text{Ca}^{+2}$  release [9].

The mutation found in these families causes exchange of a negatively charged aspartic acid to a positively charged histidine. A three-dimensional model of human calsequestrin 2 protein suggests that the histidine in the mutant form disrupts the electric balance of the protein, resulting in less efficient  $\text{Ca}^{+2}$  binding [Figure 1].

The mechanism responsible for PVT in these patients is not known. Disruption of the SR  $\text{Ca}^{+2}$  release process may result in intracellular  $\text{Ca}^{+2}$  overload triggering early and/or late after depolarizations [8]. After-depolarizations have been implicated in the genesis of different arrhythmias, including PVT [9], and are known to be influenced by catecholamines [10]. However, a definite link between the mutation and the clinical manifestations in this tribe awaits further investigation.

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ECG = electrocardiogram

## Capsule

### **Helicobacter and hydrogen in the gut**

A major cause of gastritis, peptic ulcers and certain cancers is the bacterium *Helicobacter pylori*. Olson and Maier show that the colonization success of this common pathogen is boosted by hydrogen gas produced by other intestinal occupants. Molecular hydrogen in the mucous lining of the stomach stimulates the

pathogen to produce more of a constitutive enzyme, hydrogenase, required to harvest the energy through a series of heme-containing electron carriers.

*Science* 2002;298:1788

