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## **CALCIUM CHANNEL DYSFUNCTION CAUSES MULTISYSTEM DISORDER**

### **Information for the public:**

Thu Sep 30, 2004 05:46 PM ET

A mutation in the tiny channels that control calcium levels in a cell appears to be responsible for Timothy syndrome -- a rare disorder characterized by irregular heartbeats and autism, new research suggests.

The mutation results in continuous inward flow of calcium, suggesting that it may be possible to treat the syndrome with certain heart drugs that block calcium channels, lead author Dr. Igor Splawski, from Harvard Medical School in Boston, and colleagues note in the scientific journal *Cell*.

The team has been working with children with Timothy syndrome since 1989, Splawski told Reuters Health. Of 17 cases he has seen, 10 died at an average age of 2.5 years. With treatment for the irregular heartbeats though, some of the children have survived, and one is still alive at age 20.

Researchers at Children's Hospital Boston, the Howard Hughes Institute and the University of Utah said the syndrome included genetic heart defects, webbed hands and feet, immune system deficiency and autism, according to an article released by the journal *Cell*.

Among affected patients who have survived past infancy, the researchers also observed impairments in language skills, movement, and thinking ability. Autism and related disorders is also common among patients with the syndrome.

Genetic analysis performed on 13 of the children revealed a calcium channel mutation in every case. Given the syndrome's link with autism, Splawski said it is possible that calcium problems may also be found in children with the usual type of autism.

However, Splawski said it's unlikely that such children would have the same mutation seen with Timothy syndrome, since they do not have the other symptoms associated with the disorder.

"But it is possible that other mutations in the same gene or similar genes may be associated with" the usual type of autism, he added.

The syndrome comprises such a broad array of problems because the defect covers a very fundamental type of calcium channel. Study author Mark Keating likened the calcium channel to a screen door.

"After you go through the screen door, it automatically closes," he said. "This mutation dismantles the automatic closing mechanism, so the door just stays open."

Calcium is one of the most important molecules in the body, and its influx affects heart muscle, gastrointestinal tissues, lungs, smooth muscle and the brain, especially in areas known to be associated autism.

The disease is named Timothy syndrome, after one of the paper's authors.

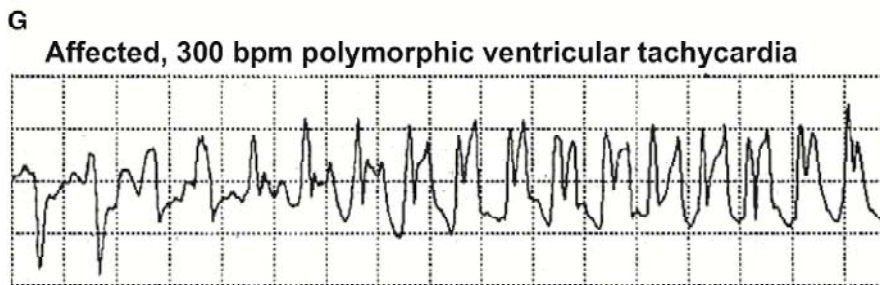
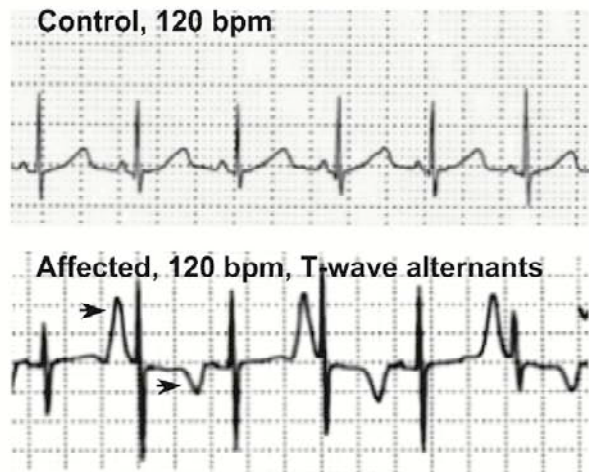
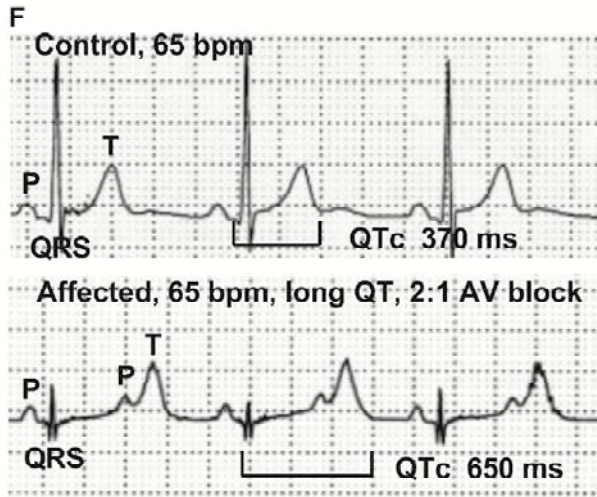
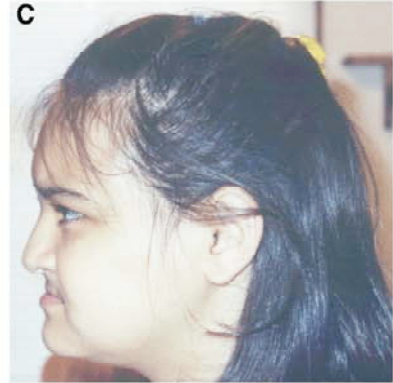
**Information for the scientific community:****Introduction**

“Ja, Kalzium, das ist alles!” So stated Nobel laureate Otto Loewi in 1959, and it is now clear that  $\text{Ca}^{2+}$  is the ultimate signaling molecule for organisms ranging from prokaryotes to humans. In higher organisms,  $\text{Ca}^{2+}$  mediates processes as diverse as synaptic transmission, muscle contraction, insulin secretion, fertilization, and gene expression (Berridge et al., 2003; Brini and Carafoli, 2000; Ren et al., 2001). Because  $\text{Ca}^{2+}$  cannot be metabolized, cells have evolved complex mechanisms for regulating intracellular  $\text{Ca}^{2+}$  levels, which are 10,000-fold lower than extracellular levels. Many proteins have been adapted to bind and transport  $\text{Ca}^{2+}$ , in some cases to reduce  $\text{Ca}^{2+}$  levels and in others to trigger second-messenger pathways. Excitable cells contain voltage-dependent calcium channels that can dramatically increase cytosolic  $\text{Ca}^{2+}$ . In heart and brain, the L-type calcium channel  $\text{CaV}1.2$  (*CACNA1C*, *\_1C*, *\_11.2*) mediates this process (Catterall, 2000; Mikami et al., 1989; Schultz et al., 1993). By contrast with physiology, the role of  $\text{Ca}^{2+}$  signaling in development is poorly understood.

The importance and ubiquity of  $\text{Ca}^{2+}$  as an intracellular signaling molecule suggest that altered channel function could give rise to widespread cellular and organ defects. Previously characterized calcium channel disorders, however, have been marked by dysfunction of a distinct organ system, particularly the membrane excitability of neurons and skeletal muscle. For example, calcium channel syndromes like hypokalemic periodic paralysis and malignant hyperthermia affect skeletal muscle (Monnier et al., 1997; Ptacek et al., 1994), episodic ataxia affects the cerebellum (Ophoff et al., 1996), familial hemiplegic migraine affects vascular smooth muscle (Ophoff et al., 1996), and stationary night blindness affects retina (Bech-Hansen et al., 1998; Strom et al., 1998). None of these disorders has illustrated the full extent of  $\text{Ca}^{2+}$  signaling in human development and physiology.

Cardiac arrhythmias cause sudden loss of consciousness and sudden death in approximately 1 million Europeans and North Americans every year (Priori et al., 2002; Zheng et al., 2001). Over the last decade, we and others have identified arrhythmia susceptibility genes by studying familial syndromes (Antzelevitch, 2003; Keating and Sanguinetti, 2001). These genes include *SCN5A*, *KVLQT1*, and *HERG*, which encode important cardiac sodium and potassium channels. In the vast majority of arrhythmia syndromes, individuals appear normal except for subtle electrocardiographic abnormalities.

Here, we describe the phenotypic characterization of Timothy syndrome (TS), an arrhythmia disorder associated with dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism. We show that this disorder results from a recurrent, de novo missense mutation in the  $\text{CaV}1.2$  L-type calcium channel gene. The  $\text{CaV}1.2$  gene is expressed in multiple tissues. We demonstrate through functional expression in heterologous systems that the disease-associated mutation causes abnormal  $\text{Ca}^{2+}$  current. This gain-of-function mechanism is mediated through failed channel inactivation, suggesting that calcium channel blockers may be useful for treating this and related disorders.



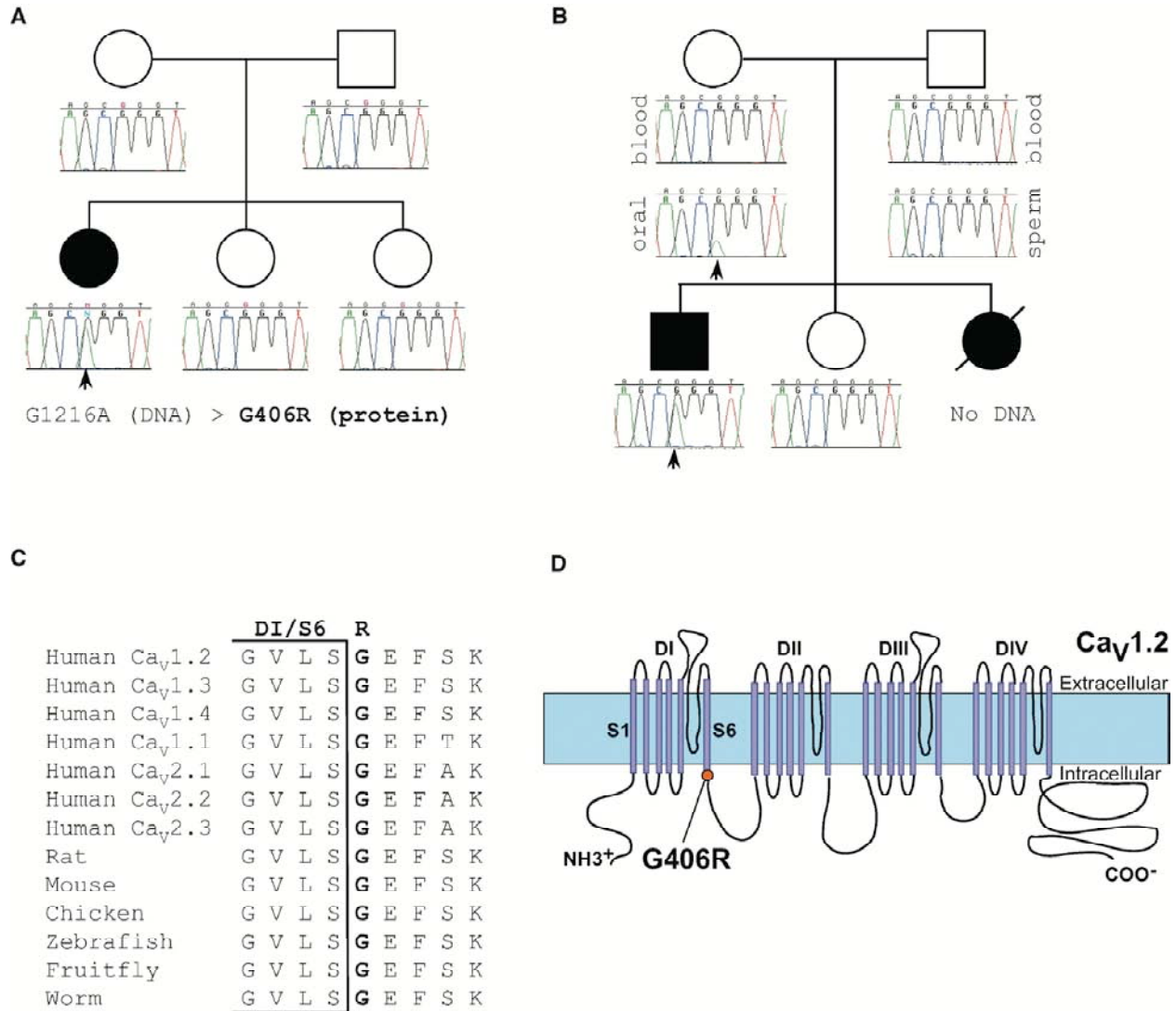


Figure 2. Identical De Novo Cav1.2 Missense Mutation Causes Timothy Syndrome

(A) TS pedigree showing sporadic occurrence of the disease phenotype and de novo G1216A missense mutation. This mutation leads to the substitution of glycine 406 with arginine (G406R). Circles and squares indicate females and males, respectively. Filled and empty symbols denote affected and unaffected individuals. Sequence tracings were derived from blood DNA samples unless otherwise indicated.

(B) TS family with two affected children. A small mutant peak (green, arrow) in the mother's sequence from oral mucosa DNA is apparent. This peak is not seen in the sequence of her blood DNA, indicating mosaicism. Germline mosaicism explains the presence of two affected children in this family. The individual with a slash is deceased.

(C) Amino acid sequence alignment showing conservation of glycine 406 from multiple species. Bracket indicates the end of the sixth transmembrane segment of domain I (DI/S6).

(D) Predicted topology of CaV1.2, showing the location of the mutation.