CACNA1C Timothy syndrome

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The CACNA1C gene encodes the pore-forming subunit of the Ca

V

1.2 L-type Ca

2+

channel, a critical component of membrane physiology in multiple tissues, including the heart, brain, and immune system. As such, mutations altering the function of these channels have the potential to impact a wide array of cellular functions. The first mutations identified within CACNA1C were shown to cause a severe, multisystem disorder known as Timothy syndrome (TS), which is characterized by neurodevelopmental deficits, long-QT syndrome, life-threatening cardiac arrhythmias, craniofacial abnormalities, and immune deficits. Since this initial description, the number and variety of disease-associated mutations identified in CACNA1C have grown tremendously, expanding the range of phenotypes observed in affected patients. CACNA1C channelopathies are now known to encompass multisystem phenotypes as described in TS, as well as more selective phenotypes where patients may exhibit predominantly cardiac or neurological symptoms. Here, we review the impact of genetic mutations on Ca

V

1.2 function and the resultant physiological consequences.