- If the SA node is damaged (e.g., *sick sinus syndrome*), other fibers or even the AV node can take over pacemaker function, albeit at a much slower intrinsic rate (causing bradycardia).
- If the atrial myocytes become "irritable" and depolarize independently and sporadically (as occurs with atrial dilation), the signals are variably transmitted through the AV node leading to the random "irregularly irregular" heart rate of *atrial fibrillation*.
- If the AV node is dysfunctional, varying degrees of *heart block* occur, ranging from simple prolongation of the P-R interval on the electrocardiogram (ECG; *first degree heart block*), to intermittent transmission of the signal *(second degree heart block),* to complete failure *(third degree heart block).*

As already discussed, coordinated cardiac contraction depends on the orderly transmission of electrical currents from myocyte to myocyte via gap junctions. Thus, abnormalities in the structure or spatial distribution of gap junctions, which are seen in a variety of disorders (e.g., IHD and dilated cardiomyopathies), can cause arrhythmias. Ischemia, myocyte hypertrophy, and inflammation (e.g., myocarditis or sarcoidosis) also promote increased "irritability" that leads to spontaneous aberrant myocyte depolarization; because of the electrical interconnection of myocytes, such random events can cause inappropriate firing of adjacent cells and create abnormal electrical circuits (so-called reentry circuits) that lead to *ventricular tachycardia*, which may progress to fatal ventricular fibrillation. Likewise, deposition of nonconducting material (e.g., amyloid), and even small areas of fibrosis, can disrupt myocyte-to-myocyte signaling, again sowing the seeds for development of reentry circuits that can give rise to potentially fatal arrythmias.

Heritable conditions associated with arrhythmias are important to recognize, since they may alert physicians to the need for intervention to prevent sudden cardiac death (discussed later) in the proband and their family members. Some of these disorders are associated with recognizable anatomic abnormalities (e.g., congenital anomalies, hypertrophic cardiomyopathy, mitral valve prolapse). However, other heritable disorders precipitate arrythmias and sudden death in the absence of structural cardiac pathology (so-called primary electrical disorders). These syndromes can only be diagnosed by genetic testing, which is performed in those with a positive family history or an unexplained nonlethal arrhythmia.

The primary electrical abnormalities of the heart that predispose to arrhythmias are listed in Table 12-6. The most important of these are the so-called *channelopathies*, which are caused by mutations in genes that are required for normal ion channel function. These disorders (mostly with autosomal dominant inheritance) either involve genes that encode the structural components of ion channels (including Na^+, K^+, and Ca^+ channels), or accessory proteins that are essential for normal channel function. Ion channels are responsible for conducting the electrical currents that mediate contraction of the heart, and it is thus not surprising that defects in these channels may provoke arrythmias. The prototype is the *long QT syndrome*, characterized by prolongation of the QT segment in ECGs and susceptibility to malignant ventricular arrhythmias. Ion channels are needed for the normal function of many tissues, and certain channelopathies are also associated with skeletal muscle disorders and diabetes. Nevertheless, the most common channelopathies are isolated disorders of the heart, and their most feared consequence is sudden cardiac death (discussed below).

Table 12-6 Selected Examples of Causal Genes in Inherited Arrhythmogenic Diseases*

Disorder	Gene	Function
Long QT syndrome†	*KCNQ1*	K^+ channel (LOF)
	KCNH2	K^+ channel (LOF)
	SCN5A	Na^+ channel (GOF)
	CAV3	Caveolin, Na^+ current (GOF)
Short QT syndrome†	*KCNQ1*	K^+ channel (GOF)
	KCNH2	K^+ channel (GOF)
Brugada syndrome†	*SCN5A*	Na^+ channel (LOF)
	CACNB2b	Ca^{++} channel (LOF)
	SCN1b	Na^+ channel (LOF)*
CPVT syndrome†	*RYR2*	Diastolic Ca^{++} release (GOF)
	CASQ2	Diastolic Ca^{++} release (LOF)

*Different mutations can cause the same general syndrome and mutations in some genes can cause multiple different phenotypes; thus, loss of function (LOF) mutations may cause long QT intervals, whereas gain of function (GOF) mutations result in short repolarization intervals.
†**Long QT syndrome** manifests as arrhythmias associated with excessive prolongation of the cardiac repolarization; patients often present with stress-induced syncope or sudden cardiac death (SCD), and some forms are associated with swimming. **Short QT syndrome** patients have arrhythmias associated with abbreviated repolarization intervals; they can present with palpitations, syncope, and SCD. **Brugada syndrome** manifests as ECG abnormalities (ST segment elevations and right bundle branch block) in the absence of structural heart disease; patients classically present with syncope or SCD during rest or sleep, or after large meals. **CPVT** does not have characteristic ECG changes; patients often present in childhood with life-threatening arrhythmias due to adrenergic stimulation (stress-related).
LOF, Loss of function mutations; GOF, gain of function mutations; CPVT, catecholaminergic polymorphic ventricular tachycardia.
Modified from Cerrone M , Priori SG: Genetics of sudden death: focus on inherited channelopathies. Eur Heart J, 2011:32, 2109-2118.

Sudden Cardiac Death (SCD)

SCD is most commonly defined as unexpected death from cardiac causes either without symptoms, or within 1 to 24 hours of symptom onset (different authors use different criteria); this happens in some 300,000 to 400,000 individuals each year in the United States alone. Coronary artery disease is the leading cause of SCD, responsible for 80% to 90% of cases; unfortunately, SCD is often the first manifestation of IHD. Interestingly, there is typically only chronic severe atherosclerotic disease; acute plaque disruption is found in only 10% to 20% of cases. Healed remote MIs are present in about 40%.

With younger victims, other nonatherosclerotic causes are more common etiologies for SCD:

- Hereditary or acquired abnormalities of the cardiac conduction system
- Congenital coronary arterial abnormalities
- Mitral valve prolapse
- Myocarditis or sarcoidosis
- Dilated or hypertrophic cardiomyopathy
- Pulmonary hypertension
- Myocardial hypertrophy. Increased cardiac mass is an independent risk factor for SCD; thus, some young individuals who die suddenly—including athletes—have