This periodic depolarization underlies the synchronous and rhythmic contraction of the heart chambers.[284]

Pathologic variants in genes encoding for ion channel proteins are well-known causes of inherited arrhythmia disorders, such as LQTS, short QT syndrome (SQTS), BrS, CPVT, and AV block, to name a few. The involved genes include those encoding for the cardiac sodium channel, potassium channels, and calcium channels. In these disorders, pathologic variants in the affected gene result in disturbance of the function of the encoded ion channel protein, leading to abnormalities in the function of the AP. In several of these genes, pathologic variants can cause a heterogeneous array of clinical features, at times differing even within the same family. For instance, pathologic variants in the cardiac sodium channel gene *SCN5A* are responsible for LQTS type 3 (LQT3), which develops due to a gain in channel function. On the other hand, pathologic *SCN5A* variants also cause BrS, an electrocardiographically distinguishable disorder compared with LQT3, which occurs due to a loss of sodium channel function.[285] In addition to causing ventricular tachyarrhythmias, atrial fibrillation, atrial standstill, and AV block,[286] *SCN5A* is known to cause an arrhythmogenic form of DCM and an arrhythmogenic form of LVNC.[287]

The 2006 Scientific Statement on "Contemporary definitions and classification of the cardiomyopathies," endorsed by the AHA, placed "ion channel disorders" under the classification of primary genetic cardiomyopathies.[288] This decision was largely based on data regarding the role of pathologic variants in genes encoding defective ion channel proteins, governing cell membrane transit of sodium, potassium, and calcium ions leading to ion channel-related arrhythmia disorders, including LQTS, SQTS, BrS, and CPVT and the role of these disorders in the development of cardiomyopathies.[288] This classification scheme has continued to be evaluated, and the list of overlapping cardiomyopathy–arrhythmia phenotypes has grown over time, with primary and secondary causes of ion channel dysfunction seen in many cardiomyopathies. Pathogenic variations in the *SCN5A* gene, resulting in electrical and structural cardiac remodeling, (ie, arrhythmogenic DCM), was first described in 2003 by Groenewegen et al in a large family with atrial standstill, a rare form of atrial cardiomyopathy.[289] At the same time, it was shown that the clinical spectrum of rare *SCN5A* pathologic genetic variants could be expanded to ARVC and DCM, accompanied by arrhythmias and conduction disorders.[131,290] In 2008, new evidence showed that pathologic variants in the SCN5A gene might represent a risk factor for rhythm disturbances in LVNC.[291] These disorders are inherited as autosomal dominant traits. The frequency of *SCN5A*-mediated cases in patients with ACMs is approximately 2%;[292] however, when pathologic variants in the *SCN5A* and *LMNA* genes are taken together, they account for up to 5%–10% when considering only patients with DCM with progressive cardiac conduction defects and supraventricular and/or ventricular arrhythmias. Both RV and LV dilation and dysfunction can occur, as can broad and heterogeneous electrical abnormalities, including atrial standstill, progressive AV block, atrial fibrillation, sick sinus syndrome, VT, torsades de pointes, and VF, resulting in arrhythmic sudden death in some cases.

SCN5A may also play a role in ACM without having pathogenic gene variants. In ARVC, it is clear that when pathologic variants in genes encoding the cardiac desmosome are identified, $Na_v1.5$, which has been shown to coprecipitate with the desmosomal protein *PKP2*, can be disrupted and dysfunctional. The loss of *PKP2* expression has been shown to alter the amplitude and kinetics of the sodium current (I_{Na}).[293] In addition, pathologic variants in *PKP2* have been associated with a sodium channelopathy phenotype, whereas decreased immunoreactive $Na_v1.5$ protein has been detected in the majority of human ARVC heart samples.[294] These observations indicate a close functional association between $Na_v1.5$ and mechanical junction proteins, which is further supported by the finding that $Na_v1.5$ coprecipitates with the AJ protein N-cadherin[295] and demonstrating the presence of "adhesion/excitability" nodes formed by aggregates of $Na_v1.5$ and N-cadherin.[296] Leo-Macias et al described the presence of these adhesion/excitability nodes in cardiac myocytes and demonstrated that (1) the AJ protein N-cadherin serves as an attractor for $Na_v1.5$ clusters, (2) the $Na_v1.5$ in these clusters are major determinants of the cardiac sodium current, and (3) clustering of $Na_v1.5$ facilitates its regulation by molecular partners.[296] Te Riele et al further demonstrated that $Na_v1.5$ is in a functional complex with cell adhesion molecules and that a primary $Na_v1.5$ defect can affect N-cadherin biology, resulting in reduced size and density of N-cadherin clusters at the ID.[295]

The finding that $Na_v1.5$ coprecipitates with the AJ protein N-cadherin demonstrates the link to the junction/ID/desmosome and supports the hypothesis that sodium channel dysfunction can occur via disruption of binding partners being mutated (ie, supporting the PKP2 and arrhythmia scenario). Therapy for this disorder has not been well studied and is not standardized. Pacemakers and ICDs have been used for some individuals with varying outcomes. Pharmacological therapies have been disappointing, and no specific pharmacotherapy has thus far been recommended for these patients.

4.3. Cytoskeletal defects

The cytoskeleton is the cell's basic scaffold in which other subcellular components are spatially arranged so as to communicate efficiently between the cell's internal and external environments. In striated muscle cells, the cytoskeleton consists of myofibrillar and extramyofibrillar portions. The myofibrillar cytoskeleton is composed of thin and thick myofilaments and titin filaments, providing the foundation for myocyte contraction and relaxation. The extramyofibrillar cytoskeleton consists of microfilaments, microtubules, and IFs.

IFs serve as a scaffold connecting the sarcomere to other organelles (such as mitochondria or the nucleus) to maintain