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Molecular genetics of skeletal muscle channelopathies

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Skeletal muscle channelopathies are genetic disorders associated with variants in genes encoding ion channels and related proteins expressed in skeletal muscle. Most commonly, these involve genes encoding voltage-gated ion channels (VGICs) that regulate sarcolemmal excitability, including *CLCN1* for ClC-1, *SCN4A* for the Nav1.4 α subunit, *CACNA1S* for the Cav1.1 α subunit, and *KCNJ2* for Kir2.1. Skeletal muscle channelopathies primarily manifest with two clinical symptoms: myotonia, characterized by delayed muscle relaxation, and paralysis and classified into two disease types: non-dystrophic myotonia and periodic paralysis. Recent advances in the clinical application of next-generation sequencing have improved diagnostic rate and provided epidemiological evidence of the diseases. Furthermore, atypical phenotypes have been identified, indicating that skeletal muscle channelopathies present a broad clinical spectrum. This review provides an updated overview of the clinical and genetic aspects of skeletal muscle channelopathies and discusses key issues that require further investigation.

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INTRODUCTION

Skeletal muscle channelopathies are genetic disorders caused by variants in genes encoding ion channels and associated proteins expressed in skeletal muscle [1]. These disorders primarily involve genes encoding voltage-gated ion channels (VGICs), which regulate the excitability of the sarcolemma. Examples include *CLCN1* for ClC-1, *SCN4A* for the Nav1.4 α subunit, *CACNA1S* for the Cav1.1 α subunit, and *KCNJ2* for Kir2.1. Skeletal muscle channelopathies typically present with two primary clinical symptoms: myotonia, defined as delayed relaxation following skeletal muscle contraction, and paralysis. These conditions are categorized into two types: non-dystrophic myotonia and periodic paralysis (Fig. 1). Recent advancements in the clinical application of next-generation sequencing (NGS) have improved diagnostic accuracy and contributed epidemiological evidence for these diseases. Furthermore, atypical phenotypes have been identified, revealing a broad clinical spectrum of skeletal muscle channelopathies. In this review, we present the classification of skeletal muscle channelopathies based on clinical manifestations, genetic findings, and ion channel function. Additionally, we highlight recent developments, including the identification of atypical phenotypes and novel potential causative genes discovered through NGS. Finally, we discuss current challenges that warrant resolution in the near future.

CLINICAL CLASSIFICATION OF SKELETAL MUSCLE CHANNELOPATHIES

Skeletal muscle channelopathies are classified according to their primary clinical symptoms: myotonia and paralysis. Myotonia is characteristic of non-dystrophic myotonia, whereas paralysis is associated with periodic paralysis (Fig. 1) [1]. All non-dystrophic myotonias are genetic disorders involving ion channel genes expressed in skeletal muscle, such as *CLCN1* or *SCN4A*. In contrast, periodic paralysis is further divided into two categories. Primary periodic paralysis is linked to variants in ion channel genes including *SCN4A, CACNA1S*, and *KCNJ2*. Secondary periodic paralysis encompasses conditions such as thyrotoxic periodic paralysis and sporadic periodic paralysis.

Non-dystrophic myotonia

Myotonia congenita (MC). Myotonia congenita (MC) is an inherited disorder caused by loss-of-function of the skeletal muscle chloride channel (ClC-1), encoded by the *CLCN1* gene on chromosome 7. MC is classified into two clinical phenotypes based on inheritance: Thomsen's disease in the autosomal dominant form and Becker's disease in the autosomal recessive form. Both phenotypes are characterized by myotonia and generalized muscle hypertrophy. Generally, males are more symptomatic than females. Becker's disease is typically more common and severe than Thomsen's disease. Initial symptoms often include difficulty initiating gait and falls. Additional symptoms include delayed upper eyelid descent following upward gaze, lid lag with visible sclera between the iris and upper eyelid, and frozen myotonia, in which patients are unable to change posture abruptly [2]. Symptoms typically worsen after ≥10 min of rest. Muscle tone improves with repeated contractions, a feature known as the "warm-up phenomenon." Although apparent muscle hypertrophy is prominent, magnetic resonance imaging (MRI) findings suggest it may compensate for subclinical myopathy [3]. As cardiac arrhythmia has been reported more frequently in patients with MC than in healthy controls, electrocardiograms should be routinely performed [4].

Sodium channel myotonia. Sodium channel myotonia (SCM) is an autosomal dominant disorder caused by abnormal function of the

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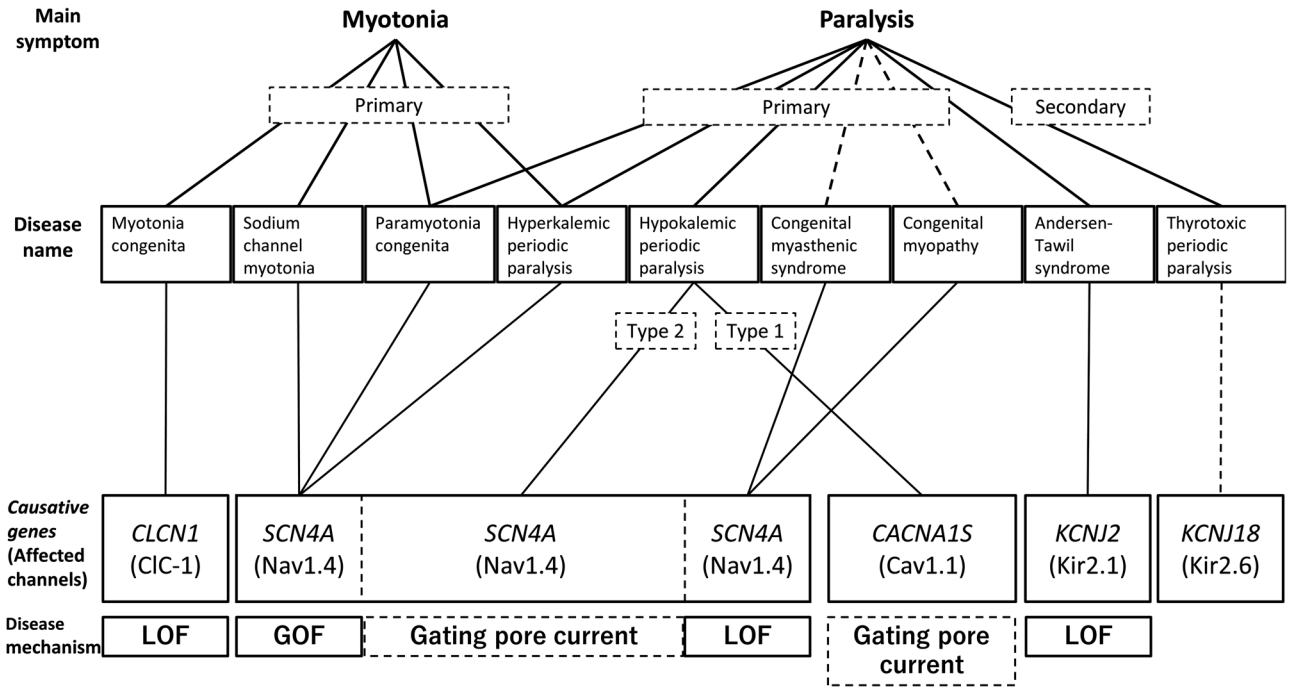

Fig. 1 Classification of skeletal muscle channelopathies. Diseases classified as skeletal muscle channelopathies are shown. LOF loss of function, GOF gain of function

skeletal muscle voltage-gated sodium channel (Nav1.4) α subunit, encoded by the *SCN4A* gene on chromosome 17. SCM was formerly referred to as potassium-aggravated myotonia (PAM), and includes clinical phenotypes such as *myotonia fluctuans*, and *myotonia permanens* [5]. Although PAM was a previously common term, it is now less frequently used because myotonic symptoms are not consistently induced by potassium intake, and potassium tolerance testing should be avoided. The primary symptom of SCM is muscle stiffness following exercise or consumption of potassium-rich foods, without paralysis or paramyotonia. If a patient with myotonia also exhibits paralysis or paramyotonia, diagnoses such as paramyotonia congenita or hyperkalemic periodic paralysis should be considered (see next paragraph).

Paramyotonia congenita. Like SCM, paramyotonia congenita (PMC) is an autosomal dominant disorder resulting from abnormal function of Nav1.4 α subunit, encoded by the *SCN4A* gene. PMC is characterized by muscle stiffness triggered by cold exposure. Muscle weakness and paralysis may also occur. Unlike the typical myotonia associated with the warm-up phenomenon in MC, myotonic symptoms in PMC worsen with repetitive movements—a hallmark known as paramyotonia, which gives the disorder its name. Recent reports have described infants with life-threatening respiratory impairment and laryngospasm associated with *SCN4A* variants linked to SCM/PMC, raising concern for a potential role in sudden infant death syndrome (SIDS) [6].

Periodic paralysis

Hyperkalemic periodic paralysis. Hyperkalemic periodic paralysis (HyperPP) is an autosomal dominant disorder caused by abnormal function of Nav1.4 α subunit, encoded by the *SCN4A* gene. HyperPP is an allelic disorder that shares the same causative gene, *SCN4A*, as SCM and PMC. In particular, HyperPP may show clinical overlap with PMC. The primary symptom of HyperPP is recurrent paralytic attacks accompanied by hyperkalemia, typically lasting only a few hours. During interictal periods, mild myotonia may occur in the eyelids and fingers. Paralysis tends to be more severe in the lower extremities, usually beginning at age ≤10 years and decreasing in frequency after middle age. Respiratory failure is extremely rare. Serum creatine kinase (CK) levels are often elevated during the interictal period. Triggers include consumption of potassium-rich foods, post-exercise rest, cold, and pregnancy. Although paralytic attacks are common into adulthood, chronic progressive myopathy may develop in midlife.

Hypokalemic periodic paralysis. Hypokalemic periodic paralysis (HypoPP) is an autosomal dominant disorder characterized by flaccid paralytic attacks with hypokalemia [7]. Unlike HyperPP, HypoPP is typically not associated with myotonia. Serum potassium levels during attacks are generally <3.0 mEq/L. Initial attacks often begin around puberty. Frequency varies widely, from a few episodes over a lifetime to nearly daily occurrences, generally decreasing after middle age. Episodes tend to last longer than those in HyperPP, from several hours to half a day, but may persist for several days. Paralysis primarily affects the lower extremities, does not involve respiratory muscles, and is less likely to cause dysphagia. Attacks often occur early in the morning or at night and may be triggered by mental stress, strenuous activity, or a high-carbohydrate diet consumed the previous day. Most patients experience only paralytic episodes and remain asymptomatic during interictal periods. Approximately 25% of patients develop a myopathy subtype marked by slowly progressive lower limb weakness. A pure myopathy subtype without paralytic episodes exists but is rare. Notably, a recent follow-up study found that myopathic changes may progress independently of paralytic episodes [8–10].

Two causative genes have been identified so far: HypoPP1 caused by the *CACNA1S* gene on chromosome 1, encoding the skeletal muscle voltage-gated calcium channel (Cav1.1) α1 subunit, and HypoPP2 caused by *SCN4A* gene coding Nav1.4 α subunit. These subtypes are clinically indistinguishable. Most cases present with typical HypoPP—recurrent paralysis with hypokalemia without myotonia. However, specific *SCN4A* variants are associated with unique phenotypes, including p.Ala204Glu variant [11], p.Ile582Val variant [12] and p.Pro1158Ser [13]. Additionally, a subtype known as normokalemic periodic paralysis (NormoPP),

characterized by normal serum potassium during attacks, is also linked to *SCN4A* variants [14].

Andersen–Tawil syndrome. Andersen–Tawil syndrome is an autosomal dominant hereditary disorder defined by a triad of periodic paralysis, arrhythmia/electrocardiographic abnormalities, and congenital microdysmorphia [15, 16]. Clinical manifestations vary: some families exhibit only arrhythmias and electrocardiogram (ECG) abnormalities without tetraplegic episodes, while others show the reverse. Unlike HypoPP, serum potassium levels during attacks are variable—commonly low, but sometimes normal or elevated. Reports from Europe and the United States describe syncope as a cardiac symptom associated with fatal ventricular arrhythmias. Also known as long QT syndrome type 7 (LQT7), the condition is better characterized by U waves, as QTc prolongation is not commonly observed. In interictal phases with normal serum potassium, ventricular arrhythmias and elevated U waves are the most common ECG findings. Congenital microdysmorphia includes hypertelorism, auricular hypoplasia, broad nasal bridge, mandibular hypoplasia, dental anomalies, and clinodactyly of the fifth finger. Psychiatric or neurodevelopmental symptoms have not been reported. Variants in the *KCNJ2* gene, encoding inwardly rectifying potassium channel 2.1 (Kir2.1), are present in approximately two-thirds of cases. A *KCNJ5* gene variant, encoding Kir3.4, has been identified in Japan, although it is thought to have low penetrance [17, 18].

Thyrotoxic periodic paralysis (TPP) and sporadic periodic paralysis (SPP). Thyrotoxic periodic paralysis (TPP) is rare in Caucasian populations but represents a more common form of periodic paralysis in East Asia and South America [19, 20]. It is a secondary hypokalemic periodic paralysis that occurs in patients with hyperthyroidism. The clinical presentation of TPP closely resembles that of primary HypoPP and occurs predominantly in males. Given the differing prevalence among populations, a genetic component has been suspected. In TPP cases from United States, Brazil, France, Hong Kong, Thailand and Singapore, a variant in the *KCNJ18* gene, which encodes the inwardly rectifying potassium channel Kir2.6, has been identified [20]. However, this variant accounts for only at most estimated 30% of cases and has not been found in Japanese patients, suggesting that other causative genes remain unidentified. Conversely, patients with typical features of HypoPP but without a clear family history are classified as having sporadic periodic paralysis (SPP). The existence of SPP raises the possibility that thyroid dysfunction may act as an exacerbating factor rather than a primary cause, and that an underlying genetic predisposition is necessary. Genome-wide association studies (GWAS) in patients with TPP have identified several disease-susceptible single nucleotide variants (SNVs) [21, 22], some of which are also associated with SPP [23, 24]. One SNV has been shown to influence the expression of Kir2.1 via lincRNA [24, 25]. These findings support the hypothesis that shared genetic susceptibility underlies both TPP and SPP. Further study of the molecular genetics of TPP and SPP remains an important area of research.

GENETICAL CLASSIFICATION OF SKELETAL MUSCLE CHANNELOPATHIES: DISEASE-ASSOCIATED VARIANTS AND THE FUNCTIONAL ALTERATION OF ION CHANNELS

Voltage-gated chloride channel diseases: MC

As stated above, MC is caused by variants in the *CLCN1* gene, which encodes CLC-1, a channel that functions as a dimer. MC presents in two phenotypes based on inheritance pattern: Thomsen's disease (autosomal dominant) and Becker's disease (autosomal recessive). Hundreds of variants have been identified in MC, which distributed throughout CLC-1. Most variants represent the loss-of-function by decreasing membrane expression efficiency and/or reducing channel conductance. Additionally, certain variants associated with the autosomal dominant form are considered dominant negative variants, interfering with normal channel function. Despite numerous functional studies of CLC-1 with the variant, the genotype–phenotype relationship, including inheritance patterns in MC, remains unclear [26].

Voltage-gated sodium channel diseases: SCM, PMC, and HyperPP

SCM, PMC, and HyperPP are allelic disorders caused by the same gene, *SCN4A*. Although variants are dispersed across the Nav1.4 α subunit, extensive functional and simulation studies on these variants have enhanced understanding of their pathological mechanisms [27]. Generally, variants associated with HyperPP tend to locate near the pore region, resulting in abnormal persistent currents. These currents induce myofiber hyperexcitability, which may cause sustained depolarization and lead to inexcitability called as "depolarization-induced paralysis". In contrast, variants associated with SCM or PMC are typically located in modules related to fast inactivation and/or activation. These functional alterations promote myofiber hyperexcitability, producing sustained action potentials clinically manifesting as myotonia. Whether functional alterations in mutant channels lead to sustained action potentials or depolarization-induced paralysis depends on the magnitude of dysfunction. Thus, a variant linked to PMC may also result in a HyperPP clinical phenotype. Although some variants are classified as "HyperPP variants" (e.g., p.Thr704Met, p.Met1592Val) or "SCM variants" (e.g., p.Gly1306Ala, known as "*myotonia fluctuans*," and p.Gly1306Glu, known as "*myotonia permanens*"), clinical phenotypes cannot typically be predicted based solely on variant location.

Hypokalemic periodic paralysis: HypoPP1 and HypoPP2

As previously described, HypoPP arises from variants in two genes: *CACNA1S* (HypoPP1) and *SCN4A* (HypoPP2), though the clinical presentation is indistinguishable between the two. The reason that mutations in different channel genes produce the same phenotype remained unclear until the discovery of an aberrant leakage current, termed "gating pore current", which marked a significant advance in this research area [28, 29]. Variants associated with HypoPP in both *CACNA1S* and *SCN4A* share a distinctive feature: most are located in the voltage-sensing domain (VSD), a critical module of voltage-gated ion channels [30, 31].

Gating pore currents are believed to pass through functional and structural gaps created by changes in the side chain of the original amino acid—typically positively charged arginine—resulting from the variant within the voltage sensor region of Cav1.1 α1 subunit or Nav1.4 α subunit [27, 32–34]. Because the VSD scaffold differs between these channels, the precise mechanisms underlying voltage dependence and ion selectivity of gating pore currents remain poorly defined. However, gating pore current is recognized as the primary channel dysfunction common to Cav1.1 α1 subunit (HypoPP1) and Nav1.4 α subunit (HypoPP2).

The mechanism how gating pore currents induce paralytic episodes remains unresolved. Ultimately, there are limitations to understanding pathogenesis solely at the single-channel protein level; insights at the cellular or organ level are essential. Studies in model mice suggest involvement of Na^+-K^+-$2Cl^-$- cotransporters (NKCC) [35, 36].

ANDERSEN–TAWIL SYNDROME

One of the primary genes associated with Andersen–Tawil syndrome (ATS) is the *KCNJ2* gene, which encodes the inwardly rectifying potassium channel Kir2.1. Kir2.1 forms a tetramer and

Table 1. Epidemiological studies of skeletal muscle channelopathies

Causative genes		*CLCN1*	*SCN4A*			*CACNA1S*	*KCNJ2*
Clinical phenotypes		**MC**	**SCM & PMC**	**HyperPP**	**HypoPP2**	**HypoPP1**	**ATS**
References	Country						
Vivekanandam et al. [8] (cases)	UK	871	244		12	127	67
Stuunernberg et al. [40] (cases)	Netherland	128	160	10	10	80	17
Brugnoni et al. [41] (cases)	Italy	24*	18*	/	/	/	/
Brugnoni et al. [42] (cases)		/	/	/	12	38	/
Sasaki et al. [43] (pedigrees)	Japan	30	36	11	12	16	/
Yuan et al. [44] (cases)		39	40	/	/	/	/
Yuan et al. [45] (cases)		/	/	14	5	9	6

"SCM & PMC" indicates the combined number of the two phenotypes. Parenthesis indicate the unit used to count the number of diseases. Data from Sasaki et al. are based on the number of pedigrees, whereas the other studies report the number of individual cases. Asterisks (*) indicate the number of cases after excluding cases with hetero compound variants

contributes to establishing the resting membrane potential. ATS-associated variants demonstrate loss-of-function, resulting in an unstable resting membrane potential. However, a wide range of clinical phenotypes is observed, even among family members with identical variants. Moreover, unlike HypoPP or HyperPP, the serum potassium level during paralytic attacks in ATS shows variations. Some variants exhibit dominant-negative effects, although the molecular mechanism remains unclear at the single-channel protein level [16]. Recently, a study using model mice has suggested that the sensitivity for the serum potassium in ATS depends on the severity of reduction of Kir currents [37].

EPIDEMIOLOGY OF SKELETAL MUSCLE CHANNELOPATHIES

Several epidemiological studies on skeletal muscle channelopathies were conducted before the 2000s; however, most relied on clinical diagnosis without genetic confirmation. Since the 2010s, studies incorporating genetic confirmation have emerged. A large cohort study from the United Kingdom (UK) was published in 2013 [38] and updated in 2023 [39]. Following the UK study, large cohorts from the Netherlands were reported [40], along with several cohorts from Italy [41, 42] and Japan [43–45]. Together, these studies cover a broad spectrum of skeletal muscle channelopathies. A summary of the literature is shown in Table 1. The largest cohort is from the UK, where updated data from 2011 were published in 2023. In UK study, the minimum disease frequency was estimated based on the total UK population in 2021. The overall minimum frequency of skeletal muscle channelopathies was 1.99 cases per 100,000 persons. By clinical phenotype, MC was 1.13 cases per 100,000 persons; SCM and PMC were 0.35 cases per 100,000 persons; PP, including HyperPP and HypoPP, was 0.41 cases per 100,000 persons [39]. This data is particularly valuable for rare diseases such as skeletal muscle channelopathies. However, due to epidemiological differences among countries, these figures may not be directly applicable elsewhere. For instance, the frequency of HypoPP2 in Japan is significantly higher than in the UK or Italy. This discrepancy likely reflects differences in genetic background among races.

ATYPICAL PHENOTYPE-GENOTYPE CASES IN SKELETAL MUSCLE CHANNELOPATHIES

Compound heterozygous variants

Compound heterozygosity of the *CLCN1* gene in congenital myotonia has been reported. Additionally, cases with variants in both *CLCN1* and *SCN4A* genes have been identified, presenting with specific periodic paralysis-like symptoms [41, 46, 47]. For patients with atypical symptoms or unusual patterns in "exercise tests", which are electro-neurophysiological examinations composed of nerve conduction studies (NCS) under specific exercise conditions [48], a comprehensive analysis of all known causative genes may be necessary.

Congenital myasthenic syndrome, congenital myopathy, and fetal hydrops due to SCN4A variants

There have been reports of congenital myasthenic syndrome caused by variants in the *SCN4A* gene. Reported examples include compound heterozygous variants such as p.Val1442Glu and p.Ser246Leu [49], as well as homozygous variants such as p.Arg1454Trp [50] and p.Arg1457His [51]. Multiple familial cases of congenital myopathy [52, 53], and more severe cases involving fetal hydrops and stillbirth [54, 55], have also been reported. These cases commonly involve compound heterozygosity or homozygosity of *SCN4A* loss-of-function variants. In many instances, the parents of affected individuals are asymptomatic despite carrying a heterozygous loss-of-function variant, suggesting that *SCN4A* is most likely to be resistant to haploinsufficiency [53, 55]. This interpretation is supported by studies using SCN4A-null model mice [56].

Potential causative genes for HypoPP beyond CACNA1S or SCN4A: The broad clinical spectrum of periodic paralysis

In addition to *CACNA1S* and *SCN4A*, other potential causative genes for HypoPP have been reported. These include the inwardly rectifying potassium channel Kir2.6 (*KCNJ18* gene) [20], mitochondrial ATP synthase subunits (*MT-ATP6* and *MT-ATP8* genes) [57], ryanodine receptor type 1 (*RyR1* gene) [58], Na^+-K^+-ATPase type 2 (*ATP1A2* gene) [59], and minichromosome maintenance 3-associated protein (*MCM3AP* gene) [60]. Some cases involve atypical periodic paralysis with central nervous system disturbances [59]. There is ongoing discussion regarding whether these conditions should be classified within the same hereditary periodic paralysis category as HypoPP1 and HypoPP2. However, they underscore the broad clinical spectrum of periodic paralysis.

Future perspective: unsolved questions and strategy for the development of novel therapeutics for skeletal muscle channelopathies

Advancements in sequencing technologies have significantly contributed to clarifying the epidemiological status of rare diseases such as skeletal muscle channelopathies. These technologies have also facilitated a deeper understanding of the clinical spectrum and led to the identification of atypical phenotypes, including congenital myasthenic syndrome, congenital myopathy, and fetal hydrops. However, numerous issues remain unresolved.

The natural history of skeletal muscle channelopathies is still largely unknown. For instance, some patients with HypoPP develop progressive myopathy in middle age, but the underlying cause remains unclear. MRI studies suggest that myopathy progression may not correlate with paralytic attacks [8–10, 61]. Conversely, although muscle atrophy is uncommon in non-dystrophic myotonia, certain cases exhibit severe atrophy [62]. Recent MRI studies have shown that subclinical myopathy may progress even in non-dystrophic myotonia in patients with apparent muscle hypertrophy, likely due to compensatory mechanisms [3, 63]. Understanding how skeletal muscle hyperexcitability contributes to myopathy is a significant scientific challenge.

Another major issue is the limited availability of therapeutic options for skeletal muscle channelopathies. The development of new treatments has been minimal thus far. In the case of myotonia, Nav channel blockers such as mexiletine have been established as effective agents to alleviate painful myotonia [64]. More recently, lamotrigine has demonstrated comparable efficacy to mexiletine [65]. Nonetheless, some patients with myotonia continue to experience pain despite high doses of mexiletine or lamotrigine. Therefore, effective pain control remains a crucial issue in the management of myotonia.

For the prevention of HypoPP attacks, acetazolamide and dichlorphenamide have been approved to reduce the frequency of episodes [7, 66, 67]. However, certain patients with HypoPP derive no benefit from acetazolamide or may experience worsened symptoms [68]. Experimental studies using HypoPP model mice have identified several potential therapeutic compounds, including bumetanide and KCNQ/Kv7 blockers, which have shown efficacy in ameliorating attacks [35, 36, 69]. Additionally, model cells and drug screening systems have been developed to identify gating pore blockers, which could serve as a fundamental treatment approach for HypoPP [70]. The development of novel therapeutics requires accurate genetic diagnosis, precise epidemiological data, robust patient registry systems, and well-designed proof-of-concept studies.

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