

Ion Channel Gene Mutations Causing Skeletal Muscle Disorders: Pathomechanisms and Opportunities for Therapy

Lorenzo Maggi ^{1,*}, Silvia Bonanno ¹, Concetta Altamura ² and Jean-François Desaphy ²

¹ Neuroimmunology and Neuromuscular Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy; silvia.bonanno@istituto-besta.it

² Department of Biomedical Sciences and Human Oncology, School of Medicine, University of Bari Aldo Moro, 70124 Bari, Italy; concetta.altamura@uniba.it (C.A.); jeanfrancois.desaphy@uniba.it (J.-F.D.)

* Correspondence: lorenzo.maggi@istituto-besta.it

Abstract: Skeletal muscle ion channelopathies (SMICs) are a large heterogeneous group of rare genetic disorders caused by mutations in genes encoding ion channel subunits in the skeletal muscle mainly characterized by myotonia or periodic paralysis, potentially resulting in long-term disabilities. However, with the development of new molecular technologies, new genes and new phenotypes, including progressive myopathies, have been recently discovered, markedly increasing the complexity in the field. In this regard, new advances in SMICs show a less conventional role of ion channels in muscle cell division, proliferation, differentiation, and survival. Hence, SMICs represent an expanding and exciting field. Here, we review current knowledge of SMICs, with a description of their clinical phenotypes, cellular and molecular pathomechanisms, and available treatments.

Keywords: ion channels; myotonia; periodic paralysis; myopathies; SCN4A; CACNA1S; CLCN1; KCNJ2

Citation: Maggi, L.; Bonanno, S.; Altamura, C.; Desaphy, J.-F. Ion Channel Gene Mutations Causing Skeletal Muscle Disorders: Pathomechanisms and Opportunities for Therapy. *Cells* **2021**, *10*, 1521. <https://doi.org/10.3390/cells10061521>

Academic Editor:
Alexander E. Kalyuzhny

Received: 4 May 2021
Accepted: 10 June 2021
Published: 16 June 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Primary ion channelopathies are rare diseases caused by mutations in genes encoding ion channel subunits. The first ion channelopathy was identified in hyperkalemic periodic paralysis (hyperPP), a genetic disease affecting exclusively skeletal muscles and caused by mutations in the *SCN4A* gene encoding the alpha subunit of voltage-gated sodium channel Nav1.4, which expression is limited to the skeletal muscle fibers [1]. The discovery of *CFTR* gene mutations linked to cystic fibrosis was contemporaneous, but the chloride channel activity of the CFTR protein was not known yet. Thus, skeletal muscle ion channelopathies (SMICs) have been a paradigm for the discovery of ion channelopathies affecting all organs. Considering the importance of ion channels in modulating membrane electrical activity, the diseases related to ion channel mutations were characterized by disturbance of muscle fiber excitability, such as the non-dystrophic myotonias (NDM) presenting with muscle stiffness (myotonia) due to membrane over-excitability and the periodic paralysis (PP) showing episodes of paralysis due to sarcolemma inexcitability.

Yet, with the development of more advanced technologies, including next-generation and whole-exome sequencing, it appears more and more evident that ion channel mutations may cause further muscle phenotypes, including progressive myopathies, altering muscle structure, thereby highlighting a significant role of ion channels in muscle cell division, proliferation, differentiation, and survival.

Hence, SMICs represent a large heterogeneous group of rare genetic disorders resulting in long-term disabilities with a relevant burden to the patients, families and National Health Care Services. SMICs usually present in childhood, but late-onset cases have been reported. SMICs diagnosis requires a high clinical suspicion, being mainly based on

the detailed clinical history and neurological examination, followed by molecular confirmation.

Here, we review current knowledge of SMICs, with a description of clinical phenotype, cellular and molecular pathomechanisms, and available therapies. We also included the description of two neuronal ion channelopathies (*TRPV4* and *KCNA1* genes), which may have pronounced effects on skeletal muscles. Ion channel gene mutations and related clinical muscular phenotypes are summarized in Table 1.

Table 1. Ion channels gene mutations and related clinical muscular phenotypes.

Protein	Gene	Inheritance	Clinical Phenotype	Phenotype MIM	Age at Onset	Muscle Biopsy	Specific Features	Treatment
SODIUM CHANNEL SUBUNITS								
Nav1.4	SCN4A	AD	Sodium channel myotonia (SCM; includes potassium-aggravated myotonia, myotonia fluctuans, myotonia permanens, ACZ-responsive myotonia, and SNEL)	608390	Highly variable (neonatal–early childhood–adulthood)	non-specific myopathic pattern	Predominance in cranial muscles, precipitated by cold, presence of warm-up, muscle weakness absent or mild with late-onset Myotonia and episodic muscle weakness precipitated by cold,	Mexiletine, lamotrigine, carbamazepine, ACZ, flecainide, and propafenone
		AD	Paramyotonia congenita (PMC)	168300	First decade	non-specific myopathic pattern	paradoxical myotonia, predominant in cranial muscles, possible fixed muscle weakness in late disease stages.	As for SCM
		AD	Hyperkalemic periodic paralysis (hyperPP)	170500	First decade	Vacuolar and tubular aggregate myopathy	Episodic flaccid muscle weakness lasting up to 2 h accompanied by hyperkalemia > 4.5 mEq/L. Associated with myotonia.	ACZ, diclorophenamide
		AD	Hypokalemic periodic paralysis type 2 (hypoPP2)	613345	Childhood–third decade	Vacuolar and tubular aggregate myopathy	Episodic flaccid muscle weakness lasting up to 24 h accompanied by hypokalemia < 3.5 mEq/L. Decremental response of the CMAP on RNS.	ACZ, K ⁺ sparing diuretics (spironolactone, triamterene)
		AR	Congenital myasthenic syndrome type 16 (CMS16)	614198	Neonatal or early infancy	non-specific myopathic pattern	Predominant involvement of bulbar and respiratory muscles.	Pyridostigmine and ACZ may be beneficial
		AR	Congenital myopathy	n.a.	Neonatal or early infancy	No evident nemaline rods or structural abnormalities	Predominant axial and pelvic muscle weakness, delayed motor milestones,	ACZ

							improvement in strength over time	
CALCIUM CHANNEL SUBUNITS								
Cav1.1	CACNA1S	AD	Hypokalemic periodic paralysis type 1 (hypoPP1)	170400	Childhood–second decade	Vacuolar myopathy (non-rimmed)	Episodic flaccid muscle weakness lasting up to 24 h accompanied by hypokalemia < 3.5 mEq/L. Fixed myopathy often developing in late disease stages.	ACZ, diclorphenamide
		AD	Malignant hyperthermia susceptibility type 5 (MHS5)	601887	When exposed to volatile anesthetics or succinylcholine	No structural abnormalities	MHS	Dantrolene (antidote)
		AR	Congenital myopathy	n.a.	Neonatal or early infancy	Centronuclear or core myopathy	Hypotonia, delayed motor milestones, facial involvement (ophthalmoplegia), progressive muscle weakness (mainly axial).	ACZ
Stac3	STAC3	AR	Bailey-Bloch congenital myopathy/Native American Myopathy (NAM)	255995	Neonatal or early infancy	non-specific myopathic pattern	Dysmorphic facial features and facial weakness (ptosis) susceptibility to MHS; multiple joint contractures	n.a.
Orai 1	ORAI1	AD	Tubular aggregate myopathy (TAM2)	615883	Childhood	tubular aggregates in type II fibers, predominance of type I fibers (1 patient)	Slowly progressive	n.a
		AR	CRAC channelopathies	612782	<1 year	myopathic pattern; no evident nemaline rods or structural abnormalities.	Congenital non-progressive myopathy; immunodeficiency as the main feature.	n.a.
Stim 1	STIM1	AD	Stormorken syndrome (STRMK), York platelet syndrome	185070	Childhood–early adult	tubular aggregates in	Thrombocytopenia, anemia, asplenia, congenital miosis,	n.a.

						type II fibers, predominance of type I fibers	and ichthyosis, asymptomatic to slowly progressive proximal muscle weakness	
		AD	Non-syndromic tubular aggregate myopathy (TAM1)	160565	Childhood	tubular aggregates mainly in type II fibers; predominance type I fibers	Slowly progressive, elevated CPK	n.a.
		AR	CRAC channelopathies	612783	<1 year	n.a.	Congenital non-progressive myopathy; immunodeficiency as the main feature.	n.a.
	Ryr1	AD	Malignant hyperthermia susceptibility type 1 (MHS1)	145600	When exposed to volatile anesthetics or depolarizing muscle relaxants	Central core, multiminicore myopathy	MHS	Dantrolene (antidote)
		AD/AR	Central core disease	117000	First decade, rarely in adulthood	Central cores in type 1 fibers, predominance of type 1 fibers	Floppy infant; non-progressive/slowly progressive myopathy; joint contractures	n.a.
		AR	Multiminicore myopathy with external ophthalmoplegia	255320	Neonatal or early infancy	Dystrophic signs and minicores	Hypotonia, delayed motor milestones, dysmorphic facial features and facial weakness, and progressive muscle weakness	n.a.
	Ryr3	RYR3	Nemaline myopathy (NEM3)	161800	1 case, infantile	Perinuclear and subsarcolemmal nemaline bodies, wide variation in fiber size with type 1 fiber predominance and atrophy,	Dysmorphic face; normal CPK; myopathic EMG. Slowly progressive proximal limb weakness	n.a.

TRPV4	TRPV4	AD (reduced penetrance)	scapuloperoneal spinal muscular atrophy (SPSMA)	181405	Neonatal or early infancy	increased internal nuclei Grouped type 1 and 2 fiber atrophy	Non-progressive or slowly progressive scapular and peroneal muscle weakness and atrophy, and peripheral motor neuropathy	n.a.
		AD (reduced penetrance)	congenital distal spinal muscular atrophy (CDSMA)	600175	Neonatal or early infancy	neurogenic muscle damage	Variable from lower-limb muscle weakness to severe neurogenic weakness and arthrogryposis	n.a.
		AD	Hereditary motor and sensory neuropathy (HMSN2C)	606071	Variable (infancy, childhood, adulthood)	Neurogenic muscle damage and atrophy	Axonal polyneuropathy, diaphragmatic and vocal cord paresis, and distal muscle weakness	n.a.
Cav3.2	CACNA1H	AR	Congenital amyotrophy		1 case, neonatal	n.a.	Severe amyotrophy at birth	n.a.
POTASSIUM CHANNEL SUBUNITS								
Kir2.1	KCNJ2	AD	Andersen–Tawil syndrome type 1 (ATS1, LQT7)	170390	Variable onset of periodic paralysis (early childhood–adulthood)	non-specific myopathic pattern (few cases)	Potassium-sensitive periodic paralysis, cardiac arrhythmia, and facial and skeletal malformations. Prolonged QT (plus other arrhythmias). Episodic flaccid paralysis lasting up to 24h and more, usually accompanied by hypokalemia.	ACZ, dichlorphenamide, β -blockers, If hypokaliemic, K ⁺ supplementation or K ⁺ sparing diuretics. If hyperkaliemic, be careful with K ⁺ wasting diuretics for cardiac risk.
Kir3.4	KCNJ5	AD	Andersen–Tawil syndrome type 2 (ATS2, LQT13)	613785	Variable onset of periodic paralysis as for ATS1	n.a.	Same triad of symptoms of ATS1	As for ATS1
Kir2.6	KCNJ18	AD	Susceptibility to thyrotoxic periodic paralysis type 2 (TTPP2)	613239	Early adulthood	Variable, vacuolation, mitochondrial changes, glycogen granules accumulation.	Episodic flaccid paralysis during thyrotoxicosis and hypokalemia. More frequent in Asian males.	Treatment of hyperthyroidism

Sur2	ABCC9	AR	Intellectual disability myopathy syndrome (IDMS)	n.a.	Variable onset of muscle symptoms (childhood-adulthood)	(1 patient) non-specific changes (mitochondrial aggregation, fiber caliber variation)	Hypotonia, muscle weakness and fatigability, dysmorphic features, intellectual disability and developmental delay, and cardiac systolic dysfunction	n.a.
Kv1.1	KCNA1	AD	Episodic ataxia/myokymia syndrome (EA1)	160120	Childhood	non-specific, denervation findings	Muscle symptoms (preponderant in a few patients): constant myokymia and acute episodes of muscle contractions (face and limbs), stiffness, cramps, weakness, and episodic cerebellar ataxia, seizures, and hypomagnesemia.	ACZ antiepileptic drugs
CHLORIDE CHANNEL SUBUNITS								
ClC-1	CLCN1	AD	Myotonia congenita, Thomsen's disease	160800	First decade	No structural abnormalities	Myotonia with the warm-up phenomenon, cold sensitivity, predominant in limb muscles.	Mexiletine lamotrigine, carbamazepine, ACZ
		AR	Recessive generalized myotonia, Becker's disease	255700	First decade	No structural abnormalities	More severe than Thomsen's disease; transient weakness and "Herculean" appearance	As for Thomsen's disease
NICOTINIC RECEPTOR								
AChR	CHRNE	AR	Congenital myasthenic syndrome (CMS4C) associated with AChR deficiency	608931	Variable, infancy-adulthood	non-specific	Variable, from arthrogryposis multiplex congenital and fetal akinesia, ocular, bulbar and respiratory symptoms, delayed motor milestones, to mild adult muscle weakness.	Pyridostigmine, 3,4 diaminopyridine, salbutamol/albuterol, and ephedrine

CHRNA1	AD/AR (rare) Slow-channel CMS (CMS4A)		605809	Infancy–young adult non-specific		Slowly progressive with possible exacerbations. Decremental CMAP in response to RNS-EMG. Neonatal hypotonia; ocular, bulbar, respiratory muscle involvement, with predominant weakness of cervical, wrist, finger, and finger extensor muscles. Double CMAP on single nerve stimuli ENG. Neonatal hypotonia, recurrent respiratory crises.	Quinidine, fluoxetine, Worsening with pyridostigmine
	AR	Fast-channel CMS (CMS4B)	616324	Infancy	non-specific	Ocular, neck, and limb progressive muscle weakness and fatigability. Decremental CMAP in response to RNS-EMG. Ocular, bulbar, and respiratory muscle involvement, with predominant weakness of cervical, wrist, finger, and finger extensor muscles. Double CMAP on single nerve stimuli ENG. Neonatal hypotonia; ocular, bulbar (dysarthria), neck, recurrent respiratory crises, and limb progressive muscle weakness and fatigability. Decremental CMAP in response to RNS-EMG.	Pyridostigmine, 3,4 diaminopyridine
	AD	Slow-channel CMS (CMS1A)	601462	Infancy–young adult non-specific		Neonatal hypotonia; ocular, bulbar (dysarthria), neck, recurrent respiratory crises, and limb progressive muscle weakness and fatigability. Decremental CMAP in response to RNS-EMG.	Quinidine, fluoxetine, Worsening with pyridostigmine
	AD (rare)/AR Fast-channel CMS (CMS1B)		608930	Infancy	non-specific	Neonatal hypotonia; respiratory and limb	Pyridostigmine, 3,4 diaminopyridine
	CHRNA1	CMS2C associated with AChR deficiency	616314	Birth	non-specific		

CHRND	AD	Slow-channel CMS2A	616313	Infancy–young adult non-specific		progressive muscle weakness. Decremental CMAP in response to RNS-EMG Ocular, bulbar, respiratory muscle involvement, with predominant weakness of cervical, wrist, finger, and finger extensor muscles. Double CMAP on single nerve stimuli ENG. Ocular, bulbar, respiratory muscle involvement, with predominant weakness of cervical, wrist, finger, and finger extensor muscles. Double CMAP on single nerve stimuli ENG.	Quinidine, fluoxetine, Worsening with pyridostigmine
	AD	Slow-channel CMS3A	616321	Infancy—young adult	non-specific	Neonatal hypotonia; ocular, episodic respiratory insufficiency, bulbar (swallowing), and proximal limb muscle weakness. Decremental CMAP in response to RNS-EMG.	Quinidine, fluoxetine, Worsening with pyridostigmine
	AR	CMS3C associated with AChR deficiency	616323	Birth	non-specific	Neonatal hypotonia; ocular, neck, respiratory, muscle weakness and fatigability. Decremental CMAP in response to RNS-EMG.	Pyridostigmine
	AR	Fast-channel CMS3B	616322	Infancy	non-specific		Pyridostigmine, 3,4-diaminopyridine

References are given in the text. Abbreviations: ACZ: Acetazolamide; CMAP: Compound Muscle Action Potential; CPK: creatine phosphate kinase; n.a.: not available; RNS-EMG: Repetitive nerve stimulation electromyography.

2. Skeletal Muscle Sodium Channelopathies

Voltage-gated sodium channels are responsible for the upstroke of action potentials and modulate firing frequency in excitable cells. From the first week of life, the main sodium channel expressed in skeletal muscles is Nav1.4, which alpha-subunit is encoded by *SCN4A*. The spectrum of *SCN4A*-related myopathy spans from the complete loss of the channel (null mutations) to a gain of function (missense mutations) through various degrees of altered function, resulting in highly heterogeneous clinical presentation, mainly characterized by myotonia or PP, which represents a continuum in the clinical spectrum (Figure 1). In particular, the most frequent phenotype is paramyotonia congenita (PMC), followed by sodium channel myotonia (SCM), while PP is less frequent [2–4].

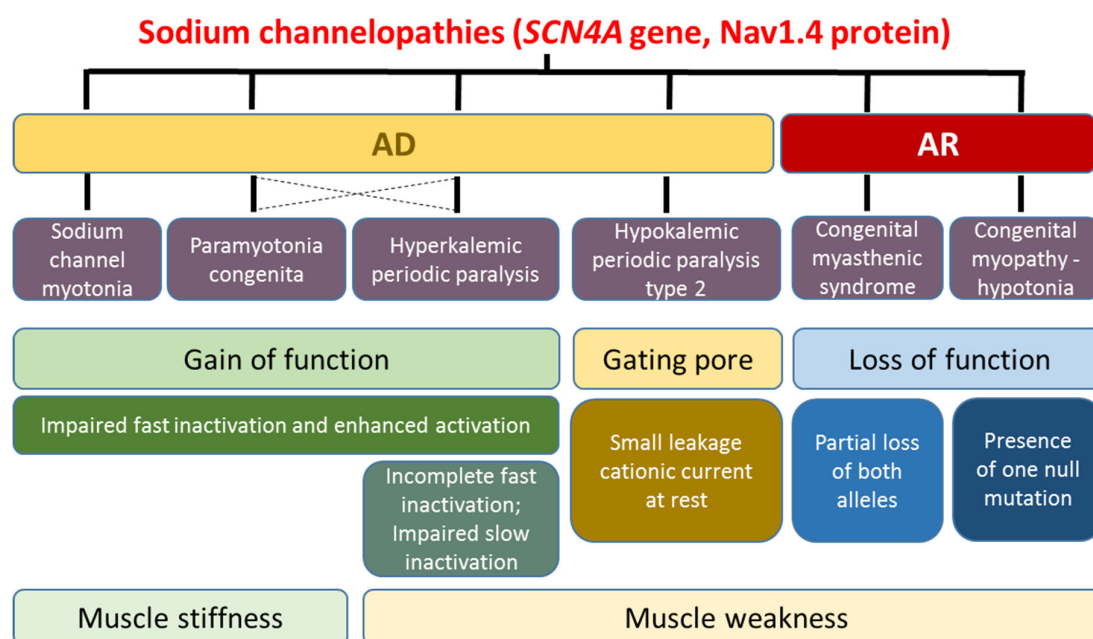


Figure 1. A schematic representation of skeletal muscle sodium channelopathies, reporting the mode of inheritance (AD: autosomal dominant; AR: autosomal recessive), disease name, mutation effects on sodium channel function, and main symptoms.

2.1. Hyperkalemic Periodic Paralysis, Paramyotonia Congenita, and Sodium Channel Myotonia

The *SCN4A* mutations were first identified in patients suffering from the autosomal dominant hyperPP [1,5,6]. HyperPP is characterized by episodes of flaccid paralysis, leading to muscle weakness, generally associated with ictal hyperkalemia (>4.5 mEq/L). The paralytic attack can last for up to 2 h. Loading of K^+ can provoke or worsen an attack; other triggers include rest after exercise, fasting, and cold exposure. Emotional stress and pregnancy can increase the likelihood of attacks. The first attack is generally experienced during the first decade of life. Permanent weakness may progressively take place after the fourth decade. Myotonia is experienced by many hyperPP patients [4,7].

PMC is allelic to hyperPP, being caused by autosomal dominant *SCN4A* missense mutations [8]. PMC is mainly characterized by paradoxical myotonia that typically worsens with exercise and shows no warm-up phenomenon, which is usually detected in myotonia congenita (MC). In addition, episodes of flaccid paralysis can represent a relevant feature in patients with PMC [4,9]. Triggers of myotonia are similar to those reported in hyperPP. Thus, PMC and hyperPP are considered as a continuum manifesting as pure PMC, pure hyperPP, or intermediary PMC plus hyperPP. Other *SCN4A* mutations are

responsible for SCM, which can be distinguished from PMC by the lack of both paradoxical myotonia and episodes of flaccid paralysis [10]. In addition, PMC differs from SCM for earlier onset, higher cold-sensitivity, and more frequent involvement of hand and cranial muscles [4,9,11]. Symptoms in SCM are quite variable in severity and may show specific features; thus, various subgroups have been described, such as myotonia fluctuans (moderate), myotonia permanens (severe), acetazolamide-responsive myotonia, potassium-aggravated myotonia, and painful myotonia. In addition, myotonia permanens can be associated with harmful neonatal symptoms, such as severe neonatal episodic laryngospasm (SNEL) [12].

It needs to be noted that some mutations can lead to different phenotypes, even in the same kindred. Again, this argues for a continuum of these disorders and suggests the importance of disease-modifying genes. As more mutations are identified, many variable phenotypes are emerging, such as myotonia with normokalemic/hypokalemic PP, PP associated with myotonia instead of paradoxical myotonia, or the presence of myopathic traits [13–18].

Up to date, about seventy missense *SCN4A* mutations were found to be linked to these diseases, half of which were functionally characterized. Patch-clamp and computational experiments have clearly demonstrated that myotonia is due to a gain of function of the mutated Nav1.4 channel, mainly through the defects of inactivation and enhancement of activation [19]. Thus, the mutated channel activates more quickly or inactivates more slowly or incompletely, as compared to the wild-type channel. Recovery from inactivation can be accelerated. The voltage dependence of activation and inactivation can also be shifted toward potentials favoring channel activity [19]. These effects may be temperature-dependent, in accord with the cold sensitivity of the patients. The resulting increased influx of sodium ions renders the muscle fibers more excitable and inclined to generate high-frequency firing of action potentials that persists after the end of motoneuron stimulation. Such after-discharges cause a delay in relaxation and muscle stiffness. Spontaneous firing can also occur in the absence of a nervous stimulus, which can induce muscle spasms, fasciculation, and cramps. Continuous activity can induce muscle hypertrophy.

The voltage-gated sodium channels can enter two inactivated states: the fast one normally occurring on a millisecond time scale and the slow one occurring on a second time scale. The mutations that produce a persistent inward sodium current due to incomplete fast inactivation and impair Nav1.4 slow inactivation are more inclined to induce PP than myotonia [20,21]. In these conditions, the persistent depolarization of sarcolemma may, in turn, inactivate the wild-type sodium channels, rendering the cell inexcitable with flaccid paralysis.

Treatment of myotonia relies on the use of frequency-dependent sodium channel blockers that reduce excessive action potential firing in the overexcited muscle fibers. The cardiac antiarrhythmic, mexiletine, has been granted as an orphan drug for myotonic syndromes after the success of randomized clinical trials (RCT) and is widely recognized as the first drug of choice in myotonia [22,23]. However, up to 30% of myotonic patients have an unsatisfactory response to mexiletine because of a suboptimal response or side effects [24,25]. The antiepileptic drug lamotrigine was beneficial in an RCT, and it is now considered the second choice in several countries [26,27]. Moreover, the antiarrhythmic flecainide and propafenone were proved useful in mexiletine-refractory patients carrying specific *SCN4A* mutations, suggesting the possibility of defining a mutation-driven pharmacological strategy [28–31]. It is feasible to introduce the marketed sodium channel blockers for repurposing myotonia [32–35] or developing new derivatives with increased efficacy [36,37].

Intuitively, the use of sodium channel blockers would not be recommended in hyperPP because they might worsen the fiber inexcitability. Intravenous insulin/glucose or inhaled salbutamol can be used to abort a paralytic attack because they induce the hyperpolarization of muscle membrane through stimulation of Na⁺-K⁺ pump. Prophylaxis

of recurrent attacks is based on the use of carbonic anhydrase inhibitors (CAI), acetazolamide (ACZ) or dichlorphenamide, and/or thiazide diuretics to maintain the low blood level of potassium. The CAI can enhance the activity of Ca^{2+} -activated K^+ (BK) channels and ClC-1 chloride channels in muscle membranes [38,39]. The benefits of dichlorphenamide in hyperPP were confirmed in an RCT [40]. Recommendations and guidelines on diagnosis and treatment of NDM and PP were previously detailed by Stunnenberg et al. and Statland et al., respectively [41,42].

2.2. Hypokalemic Periodic Paralysis Type 2

Hypokalemic PP type 2 (hypoPP2) is a distinct syndrome caused by the missense *SCN4A* mutations [43,44]. It is characterized by episodes of focal (limb) or more frequently generalized flaccid paralysis, with a longer duration than hyperPP, lasting more than 2 h up to days, with concomitant hypokalemia (<3.5 mEq/L), and absence of myotonia [4,7,41]. The attack triggers include carbohydrate or alcohol ingestion and rest after vigorous exercise. The disease onset is variable, occurring in between the first and third decade of life. The frequency and severity of attacks generally decrease after the third decade, but permanent weakness and progressive myopathy may develop in the proximal muscles of the lower limbs.

Ten *SCN4A* mutations have been linked to hypoPP2, which accounts for about 20% of all hypoPP cases. Indeed, around 60% of hypoPP cases are caused by *CACNA1S* mutations (hypoPP type 1, hypoPP1) [2,3]. All the hypoPP are inherited with an autosomal dominant trait. Interestingly, most *SCN4A* and *CACNA1S* hypoPP mutations share a similar molecular defect [45]. These mutations are all sited in the voltage-sensing S4 segments of the channel, neutralizing a positive charge through the substitution of an arginine residue [45]. Functional studies suggested that the mutations induce various degrees of loss of function, but it appeared that the most likely pathomechanism consists in the creation of an aberrant pore beside the normal ion conduction pathway [45]. This so-called gating pore permits small leakage of cationic currents at rest, favoring membrane depolarization in hypokalemia that, in turn, inactivates sodium channels and renders the fiber inexcitable.

Oral or intravenous potassium loading is the only way to abort a paralytic attack in hypoPP. For prophylaxis, the use of ACZ or dichlorphenamide is the preferred strategy. Their mechanism of action in hypoPP is not well defined but might involve systemic acidosis and BK channel activation. The K^+ -sparing diuretics, such as eplerenone or spironolactone, can be used in addition or alternative to CAI. Evidence has been provided that suggests a relationship between genotype and response to CAI, with hypoPP2 often less responsive than hypoPP1 and arginine-to-histidine mutations more responsive than other mutations, highlighting again the importance of genotyping for better addressing therapy [46].

2.3. Congenital Myasthenia and Congenital Myopathy Related to *SCN4A*

Very rare *SCN4A* mutations producing a loss of function of Nav1.4 channels have been associated with congenital disorders. They include congenital myasthenic syndrome (CMS) with brief and abrupt attacks of muscle weakness since birth, which may eventually lead to respiratory arrest; other mutations induce neonatal hypotonia and congenital myopathy; finally, some mutations may produce severe fetal hypokinesia leading to death in utero or soon after birth [47,48]. These mutations are inherited in an autosomal recessive mode. The presence of two mutations producing a partial loss of Nav1.4 function leads to congenital myasthenia. A heterozygous null mutation in the *SCN4A* gene is associated with neonatal hypotonia and congenital myopathy; the concomitance of two null mutations induces neonatal death [19,33]. ACZ has provided some benefits in some patients, but its mechanism of action is still unknown [49,50].

3. Calcium Channel-Related Myopathies

Calcium ions play a central role in regulating muscle function. In the short term, calcium ions released by the sarcoplasmic reticulum (SR) in response to electrical excitation of the cell membrane trigger muscle fiber contraction. In the long term, calcium ions modulate gene expression, contributing to muscle plasticity, which is the ability of muscle fibers to adapt their mass and metabolism to functional needs. Thus, calcium ion-permeable channels and associated proteins are critical for the maintenance of the contraction apparatus of muscle. Deleterious mutations in these proteins cause diseases characterized by alteration of excitability, excitation–contraction coupling, and skeletal muscle structure (Figure 2).

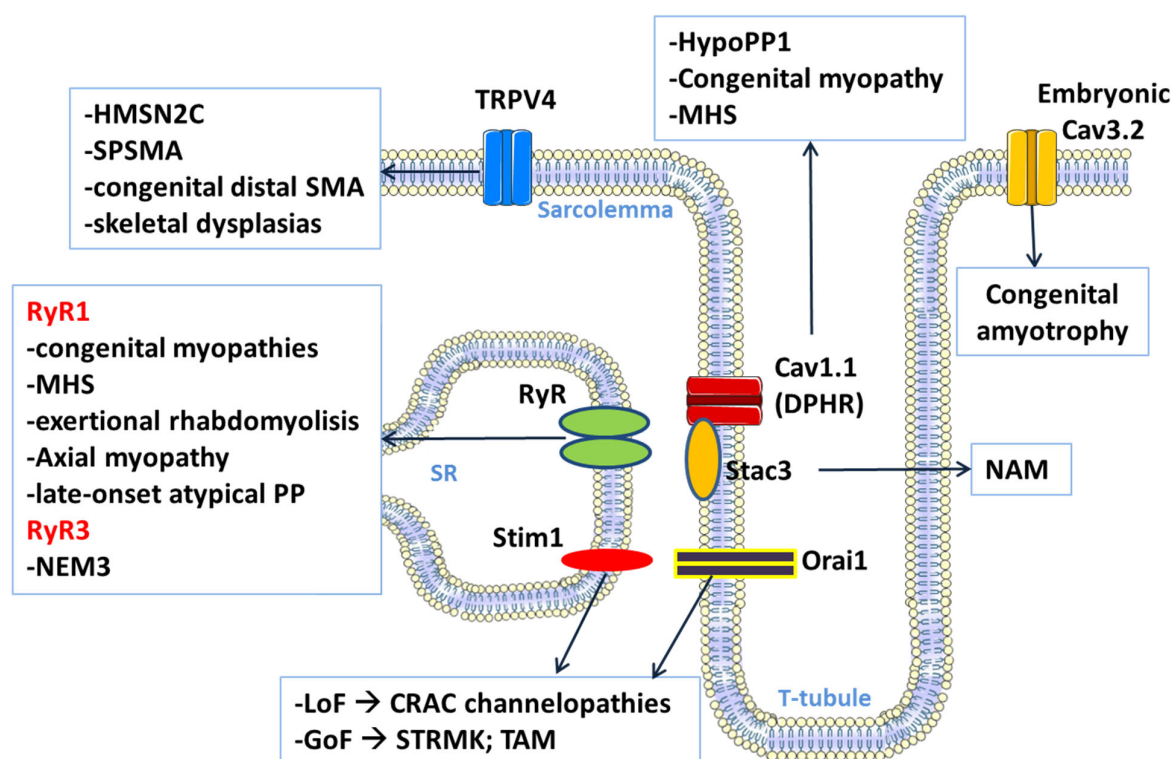


Figure 2. A schematic representation of the calcium ion-permeable channels involved in skeletal muscle myopathies. The TRPV4 channel is highly expressed even in motor neurons, and mutations cause a number of peripheral neuropathies with implications for skeletal muscles. The contribution of muscular TRPV4 channels to these diseases is unknown. The Cav3.2 channel is expressed mainly in embryonic cells, which contributes to myoblast differentiation and fusion during muscle development. (CRAC: Calcium-release activated calcium; DHPR: Dihydropyridine receptor; GoF: gain of function; HMSN2C: Hereditary motor and sensory neuropathy type 2C; HypoPP1: Hypokalemic periodic paralysis type 1; LoF: loss of function; MHS: Malignant hyperthermia susceptibility; NAM: Native American myopathy; NEM3: Nemaline myopathy type 3; SMA: Spinal muscular atrophy; SPSMA: Scapuloperoneal spinal muscular atrophy; SR: sarcoplasmic reticulum; STRMK: Stormorken syndrome; TAM: Tubular aggregate myopathy).

3.1. CACNA1S-Related Disorders

The *CACNA1S* gene codes for the Cav1.1 channel, the pore-forming subunit of the dihydropyridine receptor (DHPR), a voltage-gated L-type Ca^{2+} channel located on the T-tubule, which activates the type 1 ryanodine receptor (Ryr1) calcium channel sited in the SR, during excitation–contraction coupling.

Different phenotypes were reported in patients with mutations in *CACNA1S*, such as hypoPP1, congenital myopathy, and malignant hyperthermia susceptibility (MHS).

3.1.1. Hypokalemic Periodic Paralysis Type 1

The main phenotype caused by autosomal dominant mutations in *CACNA1S* is hypoPP1 [51]. The frequency of attacks is highly variable, from daily to once in a lifetime. The age of onset is usually earlier, and the duration of paralytic episodes longer in hypoPP1 than hypoPP2 [7]. Muscle strength is normal between attacks; however, permanent muscle weakness, regardless of the episodes of paralysis, is frequently observed in later disease stages of hypoPP1, while it is not reported in hypoPP2. In this regard, a recent paper on a large cohort of hypoPP1 patients showed that at least one-third developed permanent weakness with ageing [52].

Carbohydrate load and rest after a strenuous exercise are the most common triggers for hypoPP, although attacks may occur spontaneously. Muscle biopsy in hypoPP1 may show non-rimmed vacuoles, whereas, in hypoPP2, vacuoles occur as frequently as tubular aggregates [7]. However, hypoPP diagnosis is essentially based on medical history and then confirmed by molecular analysis. ACZ is the most common treatment choice for hypoPP, in particular for type 1 [46]. Recently, two randomized, double-blind, placebo-controlled trials showed a reduction of attack frequency with dichlorphenamide [40].

Missense mutations causing hypoPP affect highly conserved arginine residues of the S4 voltage-sensing domains of the CaV1.1, resulting in aberrant gating pore currents leading to paradoxical depolarization of the membrane in low potassium conditions and inexcitability [45,53,54].

Two mutations, p.R528H and p.R1239H, occur in nearly 80% of patients with hypoPP1 in England and The Netherlands [2,3].

3.1.2. Calcium Channel-Related Congenital Myopathy

Autosomal dominant or recessive mutations in *CACNA1S* have been detected through exome sequencing in seven families manifesting a congenital myopathy [55]. Patients presented with antenatal/congenital or early-onset generalized, predominantly axial muscle weakness. Ophthalmoplegia was detected in about one-third of the patients. Notably, one patient also developed PP. Histological analysis showed features resembling core and centronuclear myopathies. Taken together, all these features were suggestive of congenital myopathies. Notably, congenital myopathies were mostly considered as disorders of excitation–contraction coupling and impaired calcium handling [56]. There is no genotype–phenotype correlation in those patients with CaV1.1 mutation-induced congenital myopathy. Both dominant and recessive mutations caused a decrease in DHPR function in skeletal muscle, with a decrease in protein level and a relevant impairment of Ca²⁺ release induced by the sarcolemma depolarization in cultured myotubes. A further case of congenital myopathy with ophthalmoplegia has been reported by Hunter and collaborators [57]; two additional severe cases with fetal akinesia leading to premature termination of pregnancy at 26 weeks of gestation or death after 10 days of were reported by Ravenscroft and collaborators [58]. Three Turkish siblings carrying homozygous *CACNA1S* mutation presented a congenital myopathy with additional features, including cognitive delay, pes equinovarus deformity, and neurogenic changes at muscle biopsy [59].

3.2. STAC3-Related Disorder

EC coupling in skeletal muscles operates through the triad junctions, where the voltage sensor Cav1.1, through its β_{1a} subunit, physically interacts with the Ryr1 calcium release channel. Recently, the STAC3 (SH3 and cysteine-rich domain 3) protein consisting of three scaffold proteins was found to be another key component of the skeletal muscle EC coupling [60]. *STAC3* is specifically expressed in skeletal muscles, where it binds to Cav1.1 in the triads, and its inactivation generates skeletal muscle paralysis within the framework of conserved muscle differentiation and NMJ formation, indicating that the

mechanism is altered downstream muscle excitation [61,62]. Recently, a homozygous missense mutation, p.W284S of human Stac3 (c.1046G>C), was identified in a cohort of five families (5 individuals affected and 13 unaffected) presenting a rare autosomal recessive congenital myopathy [62]. The disease was initially described in 21 Lumbee Native Americans, thus called “NAM,” Native American Myopathy, also known as Bailey-Bloch congenital myopathy (MYPBB) [63–65]. The symptoms of NAM usually occur at birth or in the first years of life with facial involvement (ptosis, downturned corners of the mouth, cleft palate), bone and joint deformities (arthrogryposis, scoliosis, and short stature), MHS, congenital weakness, and delayed motor milestones. Premature death occurs by the age of 18 in 6%–30% of the cases [62,66]. Recently, the homozygous p.W284S mutation was found in 2 siblings from Qatar, and the compound heterozygous for the p.W284S and a 4-bp deletion was described in other two siblings from Puerto Rico [67], all of the patients exhibiting the NAM phenotype. In addition, 18 patients of African, Middle Eastern, and South American ancestry presenting symptoms ranging from severe prenatal/neonatal onset to slowly progressive congenital myopathy (6 months–22 years old) were found homozygous or compound heterozygous for the p.W84S mutation. Thus, the p.W284S mutation is not restricted to the Native American population [68]. The first NAM-affected patient of Turkish origin carries two heterozygous variants (c.862A>T; p.K288* and c.432+4A>T), close to but not into the p.W284S region of the STAC3 gene [69]. The STAC3 SH3-1 domain is highly conserved throughout species and is the site of all the NAM causative Stac3 variants to date [66,70]. This domain interacts with the II-III loop Cav1.1 and is crucial for EC coupling. Several in vitro and in vivo studies demonstrated that Stac3 operates as a chaperone for CaV1.1 and modulates the L-type calcium currents [60]. Lastly, it has been speculated that Stac3 directly binds to Ryr1, which possibly constitutes the long-sought physical link between CaV1.1 and Ryr1 [71]. Yet, further evidence is needed to demonstrate the existence of this binding site and its therapeutic implications in CaV1.1/ Ryr1/STAC3 channelopathies.

3.3. *STIM1 and ORAI1-Related Disorders*

Store-operated Ca^{2+} entry (SOCE) is the process by which calcium depletion in the endoplasmic or sarcoplasmic reticulum stimulates extracellular Ca^{2+} influx through the plasma membrane [72]. This calcium current is mediated by the calcium release-activated calcium modulator 1 (ORAI1) and the stromal interaction molecule type 1 (STIM1), which constitute the Ca^{2+} release-activated Ca^{2+} (CRAC) channels [73,74]. ORAI1 is a four alpha-helical transmembrane protein forming the pore unit in the sarcolemma; its activation is mediated by the direct interaction with STIM1, a single-span transmembrane protein situated on the SR membrane where it senses Ca^{2+} depletion [75,76]. Regulation and function of the CRAC channel have been largely investigated, highlighting their relevance in fundamental cellular processes such as gene transcription, cellular metabolism, vesicle trafficking, muscle contraction, and myoblasts development [77–79]. Due to their crucial role in calcium signaling, mutations in *STIM1* and *ORAI1* are associated with abnormal SOCE and multi-systemic clinical phenotypes, ranging from immune system dysregulation to hematological defects and, notably, different forms of muscle involvement depending on the loss- or gain-of-function mutations of the genes.

Loss-of-function mutations in *ORAI1* and *STIM1* result in suppressed protein expression, thus abolishing SOCE. They are very rare, all inherited in an autosomal recessive manner, and constitute the “CRAC channelopathies” that present with a homogeneous syndromic phenotype characterized by neonatal immunodeficiency with recurrent severe infections due to defective lymphocyte activation, ectodermal dysplasia (altered tooth enamel, anhidrosis), autoimmune neutropenia and thrombocytopenia, encephalopathy and seizures, along with congenital non-progressive muscular hypotonia. The myopathy in patients with *ORAI1* and *STIM1* loss-of-function mutations is characterized by delayed motor milestones, proximal lower limb weakness, nasal speech, generalized hypotonia with atrophy of type 2 fibers, and reduced fatigue resistance [74]. Missense mutations in

ORAI1 impair but not abolish *ORAI1* protein expression [80,81]; however, they cause a severe clinical CRAC channelopathy spectrum. In contrast, missense mutations in the C-terminus of *STIM1*, which may allow a minimal residual SOCE, present with a later onset and a milder phenotype [82,83].

Contrarily to loss-of-function mutations, different gain-of-function (GoF) mutations in *ORAI1* and *STIM1* result in the activation and increased SOCE. They are inherited in an autosomal dominant manner, constituting rare clinical phenotypes with a wide disease spectrum. The complex Stormorken syndrome (STRMK) is characterized by bleeding diathesis, thrombocytopenia, congenital miosis, ichthyosis, asplenia, tubular aggregate myopathy (TAM), small stature with syndromic facial features, and cognitive impairment [84,85]. However, GoF mutation in *ORAI1* and *STIM1* might also result in the York platelet syndrome [86], showing thrombocytopenia, bleeding diathesis, and muscle weakness until isolated TAM [87]. TAM is a progressive muscle disorder characterized by subsarcolemmal basophilic inclusions, stained red on modified Gomori trichrome, positive to NADH and negative for SDH reactions [88]. It remains unclear how tubular aggregates (TA) form, but it has been suggested that constitutive Ca^{2+} loading may result in misfolding and aggregation of SR proteins [89], especially in type II atrophic fibers [90]. Tubular aggregates are not specific for TAM, as they may also appear in congenital myasthenic syndrome caused by *DPAGT1* and *GFPT1* mutations [91,92], in hypoPP [93]. *STIM1* is the major gene responsible for TAM (TAM type 1). *STIM1*-EF hands at the N-terminus coordinate Ca^{2+} -binding and maintain *STIM1* in an inactive conformation. At least eight mutations in the EF hands have been reported in the His109 and Phe108 residues, a potential TAM mutation hotspot [94–97]. TAM phenotype is clinical heterogeneous ranging from slowly progressive proximal muscle weakness predominantly affecting the lower limbs, with adult onset (>35 year), to myalgia only. Serum creatine kinase is usually elevated, and patients may develop eye movement disabilities and joint contractures during disease progression [74,94,98]. Notably, the same *STIM1* mutations can also be responsible both for the STRMK [89,90,99] and the York syndrome [86], emphasizing how all these conditions represent a continuum. Slowly progressive TAM with elevated creatine phosphokinase (CPK) levels might be related even to GoF mutations in *ORAI1* (TAM type 2) transmembrane domains, which are sometimes accompanied by miosis constituting an STRMK-like syndrome [89,100–102].

A few CRAC channel modulators are currently in a clinical trial, mainly for psoriasis treatment [103]; the continuous advancement in the comprehension of the *STIM1*–*ORAI1* interaction and molecular regulation is expected to underscore new potential therapeutic targets to modulate SOCE and restore aberrant Ca^{2+} homeostasis.

3.4. *RYR1*-Related Disorders

The *RYR1* gene is located on chromosome 19q13.1 and encodes RyR1, the principal sarcoplasmic reticulum calcium release channel playing a fundamental role in the EC coupling process [104].

RYR1-related myopathies represent the most common form of congenital myopathy [105]. Phenotypes associated with *Ryr1* gene mutations include a wide range of diseases with some overlaps, hence representing a continuum in the clinical spectrum [106–112]. Hence, a relevant issue in *Ryr1* gene analysis is the definition of pathogenicity of novel variants, in particular considering the great clinical variability associated with *RYR1* mutations. In this regard, the correlation of genetic findings together with clinical, histological, and muscle imaging data may be helpful. All these diseases show impaired intracellular calcium homeostasis through different pathomechanisms, such as leaky RyR1 channels, reduced RyR1 expression, impaired RyR1 interdomain interactions, increased sensitivity to modulators/activators, or impaired excitation–contraction coupling [113]. The impaired calcium homeostasis may cause secondary cellular dysfunction with increased oxidative stress, abnormal post-translational modifications, mitochondrial dysfunction, and altered protein–protein and protein–ligand interactions [113].

3.4.1. RYR1-Related Congenital Myopathies

Autosomal dominant mutations in *RYR1* have been associated with the core myopathies (CM), the most frequent congenital myopathy subtype. Most of the mutations are missense, with a few small deletions and duplications [114–120]. Core myopathies include central core disease (CCD) and multiminicore myopathy, characterized by the presentation of cores and minicores, respectively, in the muscle fibers and defined as distinct areas of myofibrillar disruption lacking mitochondria. Patients with dominant core myopathy typically present at birth or first years of life with muscle hypotonia, proximal weakness, mild cranial involvement, and orthopedic complications, as contractures, congenital hip dislocation and scoliosis [121,122].

More recently, recessive mutations in *RYR1* have been described in patients with CCD or centronuclear myopathy, another congenital myopathy subtype [106,121,123,124].

Mutations in *RYR1* were associated with the specific subtypes of congenital myopathy, such as congenital fiber-type disproportion and rod-core myopathy [123,125]. The frequency of recessive mutations was similar to that of dominant ones [106]. Dominant mutations are usually associated with milder phenotypes, whereas patients with recessive inheritance show earlier onset, more pronounced weakness and motor function disabilities. Bulbar and extraocular muscle involvement was almost exclusively reported in the recessive cases [106].

Although there are three hotspot regions (*N*-terminal residues 1–614, central residues 2163–2458, and *C*-terminal pore/transmembrane residues 4136–4973), autosomal dominant *RYR1* mutations in CCD and MHS may cover the entire gene [106,117,126]. In recessive *RYR1*-related myopathies, mutations are widespread across the entire *RYR1* gene, usually identified as a combination of a null mutation and a missense mutation or two missense mutations, with the variable clinical severity [106,123,127,128].

Recently, an additional congenital myopathy phenotype has been described, which is characterized by irregular areas of myofibrillar disorganization with a reddish-purple granular material deposition with uneven oxidative stain and devoid of ATPase activity; this novel histological entity has been named dusty core myopathy (DCM) and is clinically indistinguishable from the aforementioned recessive core myopathy cases [111]. The authors of [111] suggested that DCM represents the most common CM associated with recessive *RYR1* mutations.

Fetal akinesia syndrome represents the most severe phenotype associated with *RYR1* mutations; it has been reported in patients carrying autosomal dominant or recessive *RYR1* mutations and with histological diagnosis of CCD [129].

3.4.2. Malignant Hyperthermia Susceptibility

MHS is characterized by muscle hypermetabolism that is triggered by anesthetic agents, particularly volatile gases (e.g., sevoflurane, desflurane) and depolarizing muscle relaxants (succinylcholine), which cause muscle rigidity and hyperthermia [130]. The incidence of MHS is estimated to be as high as one in 2000 Western Europeans, one event in every 50,000 anesthesia uses in adults, and one event in every 10,000 anesthesia uses in children. MHS represents a medical emergency and is lethal in about 70% of cases if not treated in time with supportive care measures and dantrolene, which antagonizes the excessive intracellular release of calcium by the Ryr1. Autosomal dominant mutations in *RYR1* represent by far the most frequent cause of MHS, followed by mutations in *CACNA1S*, accounting for about one-fourth of cases [131]; in addition, a few cases have been reported in association with mutations in the *STAC3* gene [132].

The in vitro contracture test on muscle biopsy tissue is the definitive diagnostic test for MHS. It cannot be routinely performed because it requires specific skills and is not possible in an emergency. In addition, false-positive diagnoses have been reported, and an underlying myopathy may produce a positive contraction test [133]. Genetic testing is

also challenging, as about half of the MHS patients have no detected mutations in *RYR1*, *CACN1A5*, or *STAC3*.

The King Denborough syndrome, which is characterized by MHS combined with a dysmorphic syndrome, was found to be associated with *RYR1* mutations [134].

3.4.3. Exertional Rhabdomyolysis

Recently, mutations in *RYR1* were found in one-third of unexplained rhabdomyolysis and/or exertional myalgia [107]. Patients usually presented between 3 and 45 years of age with rhabdomyolysis and/or exertional myalgia ($n = 12$), whereas isolated exertional myalgia was much less frequent. The most frequent triggers for rhabdomyolysis were exercise and heat [107]. Muscle strength was normal, and muscle biopsies revealed non-specific changes in most of the cases. *RYR1* mutations/variants detected in these cases have been previously reported in MHS or were localized to known MHS mutational hotspots, although only one out of the 24 reported patients had the MHS history [107].

3.4.4. Other RyR1-Related Phenotypes

Predominant axial myopathy had been reported in 12 *RYR1*-mutated patients, presenting between the third and eighth decade of life and suggesting *RYR1* as a possible cause of idiopathic camptocormia or bent spine syndrome [108,135]. Serum creatine kinase levels were normal or moderately elevated, and muscle imaging revealed the involvement of the lower paravertebral muscles and the posterior thigh. Muscle biopsy findings were described as discrete, with cores rarely reported. As for exertional rhabdomyolysis, *RYR1* sequencing revealed heterozygous missense variants previously associated with MHS trait or localizing to known MHS mutational hotspots.

Dominant or recessive *RYR1* mutations have been detected in four patients with late-onset atypical PP, both with and without congenital myopathy [112,136]. Myalgia and cramps were prominent features in all the patients. In this regard, the direct interaction between the Cav1.1 channel and RyR1 in the context of the excitation–contraction coupling makes the overlapping phenotypes when one of them is mutated, manifested by episodes of paralysis or congenital myopathy. Of note, marked impairment of the normal Cav1.1–RyR1 interaction was observed in *RYR1*-related PP and recessive type myopathies [110,136].

3.5. *RYR3-Related Myopathy with Nemaline Bodies*

The RyR3 isoform expression and its active role in mammalian muscle contractility after post-natal age are unclear [137,138]. To date, there is only one report describing the mutation in the RyR3 gene in a 22-year-old woman affected by nemaline myopathy (NEM3) [139]. The patient showed dysmorphic facial features (high-arched palate, facial weakness, and micrognathia), proximal weakness of lower limbs starting at the age of five, and normal CPK but the myopathic pattern in electromyography. Skeletal muscle biopsy revealed predominant atrophic type 1 fibers, increased internal nuclei, and abundant nemaline bodies. She presented compound heterozygous missense mutations in *RYR3*, which are classified as variants of uncertain significance, as the role of RyR3 in muscle pathology is yet to be clarified [139].

3.6. *TRPV4 Channel Related Myopathies*

Among the transient receptor potential (TRP) cation channels, the vanilloid subtype TRPV4 is one of the most abundantly expressed in skeletal muscle [140]. In mouse muscles, it was found in a fraction of muscle fibers located at the sarcolemma and myonuclei. The TRPV4 protein is ubiquitously expressed and forms calcium-permeable channels opened by cell swelling, mechanical stimuli, and a variety of endogenous lipids. Physiologically, it may contribute to mechanosensitive ion channels, and its activation may at-

tenuate fatigue by allowing Ca^{2+} influx [141,142]. Mutations in *TRPV4* can induce a number of peripheral neuropathies with implications for skeletal muscles, such as hereditary motor and sensory neuropathy type 2C mainly presenting in the pediatric age (HMSN2C), scapuloperoneal spinal muscular atrophy (SPSMA), and congenital distal SMA [143–146]. The genotype-phenotype relationship appears quite complicated. First, a number of asymptomatic carriers have been observed in several affected kindred, suggesting a reduced penetrance of some mutations. Second, *TRPV4* mutations can also cause skeletal dysplasias [147,148]. Surprisingly, a mutation previously found in a patient affected by autosomal dominant brachyolmia was detected in a patient suffering from HMSN2 [146,147]. Thus, it is now widely acknowledged that *TRPV4* channelopathies can present with great phenotypic variability and overlapping features [149–154]. Interestingly, many of the mutations reported so far affect highly-conserved arginine residues located in the N-terminal ankyrin repeat domain (ARD), which is involved in oligomerization, intracellular trafficking, and interaction with other proteins [146,155]. Mutations located in other parts of the protein have been reported. The *TRPV4* mutations linked to skeletal dysplasia were shown to cause a gain of function of the channel [147,148]. Regarding neuropathy-causing mutations, various molecular defects have been proposed, including the gain of function, loss of function, and formation of intracellular aggregates with reduced plasma membrane expression. Very recently, *in vivo* experiments in *Drosophila* and primary mouse neurons showed that the expression of a *TRPV4* mutant causes neuronal dysfunction and axonal degeneration [156]. These effects were due to increased intracellular Ca^{2+} concentration, activation of a Ca^{2+} /calmodulin-dependent protein kinase II, and impairment of axonal mitochondrial transport. Importantly, these effects were inhibited by *TRPV4* blockers, which may suggest a promising therapeutic strategy. Noteworthy, little is known about the contribution of skeletal muscle *TRPV4* channels to the diseases.

Besides peripheral neuropathies, a very recent study elegantly showed that skeletal muscle *TRPV4* channels are involved in mechanically induced myotonia because the latter is inhibited by *TRPV4* inhibitors or missing in muscles of *TRPV4*^{-/-} mice [157]. The authors proposed that mechanical stimulation of muscle fibers induces the opening of *TRPV4* channels, leading to sarcolemma depolarization that is normally dampened by *ClC-1* chloride currents. In myotonic muscles, the defective *ClC-1* chloride channel cannot counteract the *TRPV4*-induced depolarization that, in turn, triggers hyperexcitability [157].

All these studies suggest that *TRPV4* blockers may provide promising therapies. Such drugs are currently in development and have proven to be safe and well-tolerated in humans [158].

3.7. Congenital Amyotrophy Related to *CACNA1H* (T-Type Channel)

Very recently, a female baby presenting with severe amyotrophy at birth was reported [159]. Whole exome sequencing revealed the presence of two compound heterozygous mutations in the *CACNA1H* gene, which encodes a T-type voltage-gated calcium channel (Cav3.2). This channel is expressed in central and peripheral nervous systems, including motor neurons, neuroendocrine glands, smooth muscles, heart and kidney. Mutations in this gene have been clearly linked to primary hyperaldosteronism, while polymorphisms may increase susceptibility to childhood absence epilepsy and idiopathic generalized epilepsy. In these diseases, the pathomechanism is likely explained by a gain of function in the Cav3.2 channel. Conversely, functional study of mutations causing congenital amyotrophy suggested a loss of function. Since the channel may be involved in myoblast differentiation and fusion during embryogenesis, it is possible that loss of function impaired normal muscle development.

phosphatidylinositol-4,5-bisphosphate (PIP₂), which is a known activator of Kir2.1 channels. Accordingly, several ATS mutations were shown to reduce PIP₂ sensitivity [170–173]. However, other ATS mutations are distributed throughout the entire Kir2.1 protein, suggesting additional mechanisms. Indeed, some mutations were shown to impair intracellular trafficking [171,174]. Most of the ATS mutations exert a dominant negative effect on the wild-type channel subunit [169]. In addition, a mutation was shown to produce haploinsufficiency due to impaired synthesis or increased degradation [175].

Thus, the impairment of Kir2.1 channels logically accounts for the skeletal muscle and heart symptoms. In bones, experiments suggested that Kir2.1 is critical for osteoblastogenesis and bone morphogenetic protein signaling [176–178]. However, there is no clear correlation between the molecular defect and phenotypic variability, suggesting that other genes may influence the disease. One possible explanation resides in the capacity of Kir channels to form heteromultimeric channels [179,180]. Thus, the expression of the symptoms might depend on the expression balance between the various Kir subunits with respect to Kir2.1. Another possibility might be the occurrence of polymorphisms in other ion channel genes, including *KCNQ1*, *KCNH2* and *SCN5A*, which may influence the cardiac phenotype [181,182].

Noteworthy, gain-of-function mutations in *KCNJ2* have been linked to short QT syndrome [183,184].

Mutations of the *KCNJ5*-encoding Kir3.4 channel are found in about 15% of ATS cases (ATS type 2; LQT13) [162]. As for *KCNJ2*, *KCNJ5* mutations may have incomplete penetrance, and the expression of symptoms is variable [168,185,186]. This channel is responsible for the I_{K(ACH)} current in cardiomyocytes. A *KCNJ5* mutation was shown to reduce I_{K(ACH)} currents and to exert dominant negative effects on wild-type Kir3.4 and wild-type Kir2.1 channels [185,186].

The treatment of ATS may be challenging because of the need to address two distinct phenotypes—periodic paralysis and cardiac arrhythmias [161]. There is a risk that drugs beneficial to one organ may negatively affect the other. For cardiac arrhythmias, treatment includes the use of β -blockers such as propranolol. There are anecdotic observations of the positive effects of calcium or sodium channel blockers. In patients not responding to pharmacological treatment, the use of a pacemaker or an implantable defibrillator may be required. For PP, the treatment usually follows the guidelines for hypoPP or hyperPP, including the inhibitors of carbonic anhydrases such as ACZ and dichlorphenamide to reduce the frequency of attacks. However, muscle weakness exacerbation with ACZ has been reported in an ATS individual [187]. In the case of hypokalemic attacks, potassium supplementation may abort a paralytic attack while simultaneously shortening the QT interval. Potassium-sparing diuretics, such as spironolactone or triamterene, may be used in association with CAI or alone. In case of hyperkalemic attacks, the use of potassium-wasting diuretics, such as hydrochlorothiazide, should be considered very carefully due to the risk of a cardiac adverse effect of drug-induced hypokalemia.

4.2. Hypokalemic Periodic Paralysis

The *KCNE3* gene encodes MirP2, an auxiliary subunit of K channels. The missense p.R83H mutation in *KCNE3* was found in two pedigrees affected by periodic paralysis [188]. The same mutation was found in one of 14 patients affected by thyrotoxic periodic paralysis (TPP) [189]. However, the direct link between p.R83H and periodic paralysis was challenged by genetic studies performed on larger groups, showing a frequency similar in controls and patients as well as lacking segregation of the mutation with PP [190–193]. Thus, more studies are needed to verify whether *KCNE3* mutations cause hypoPP, constitute susceptibility polymorphisms, or are simply not related to hypoPP. Intriguingly, we found a reduced *KCNE3* mRNA level in muscle biopsies of two patients affected by recessive myotonia congenita (Becker's disease), but an increase in one patient with dominant myotonia congenita (Thomsen's disease), compared to control individuals [194,195].

4.3. Thyrotoxic Periodic Paralysis

TPP linked to hyperthyroidism is the most common cause of hypokalemic flaccid muscle weakness in adult Asian and Hispanic males [196]. Of note, TPP is often indistinguishable from hypoPP; thus, an assessment of thyroid function should be always performed in patients with hypoPP. Besides, sporadic periodic paralysis (SPP) is characterized by normal thyroid function and lack of *CACNA1S*, *SCN4A*, or *KCNJ2* mutation. Nevertheless, TTP and SPP are closely related since they appear to share a number of susceptibility genes [197–200]. Mutations in the *KCNJ18* gene have been reported in a few cases with TPP [201–204]. The *KCNJ18* gene encodes the skeletal muscle inward-rectifier K channel Kir2.6, the expression of which is enhanced by thyroid hormone (T_3) through a promoter response element. Several *KCNJ18* variants were shown to reduce Kir2.6 currents by affecting single-channel conductance, open probability, or cell surface expression. Some of these effects were T_3 -dependent, including altered modulation by PIP2 and PKC, which are activated during thyrotoxicosis. In addition, some Kir2.6 mutants exert a dominant negative effect not only on wild-type Kir2.6 but also on Kir2.1 channels, where the mutation is responsible for ATS1 [202]. It was proposed that wild-type Kir2.6 channels are activated by T_3 in healthy muscle to maintain the resting membrane potential, thereby balancing the T_3 -induced weakness. Consequently, the loss-of-function mutations in *KCNJ18* may increase the susceptibility of muscle to thyrotoxicosis-induced weakness. Interestingly, other susceptibility genes were identified in both TTP and SPP on chromosome 17q close to the *KCNJ2* gene, suggesting a possible influence on Kir2.1 channel expression [205–207,197]. In addition, a variant of the *ABCC8* gene encoding SUR1, the sulfonylurea receptor type 1 associated with ATP-sensitive inward-rectifier K channels (K_{ATP}), was proposed as another susceptibility gene for TPP [208]. Thus, it appears that the pathomechanism of TPP and SPP may be similar to that found in ATS. Nonetheless, many questions are still open, and more studies are needed to confirm the genotype–phenotype relationship [204,209,210].

4.4. Intellectual Disability Myopathy Syndrome

Recently, a new disease named intellectual disability myopathy syndrome (IDMS) was described in two pedigrees from Norway [211]. The disease is multisystemic, inducing intellectual disability, partial hearing loss, developmental delay, anxiety, sleep disorder, hyperreflexia, cerebral MRI anomalies, skeletal dysmorphism, cardiac systolic dysfunction, and myopathy. The muscle symptoms include generalized hypotonia in childhood and weakness and fatigability in adults. A muscle biopsy performed in one patient showed variations in fiber diameter and the presence of mitochondria aggregates. A splice-site mutation was identified in the *ABCC9* gene that codes for SUR2, the sulfonylurea receptor type 2. From genetic databases, it appeared that, in the heterozygous state, the variant frequency was higher in the Finnish population compared to other Europeans and was absent outside Europe. All the patients were homozygous for the variant, in accord with the recessive inheritance. The SUR2 variant induced a complete loss of functional K_{ATP} channels in cells co-expressing Kir6.2. In agreement with the inheritance trait, the mutant does not exert any dominant negative effect on WT SUR2. In mice, the insertion of a premature stop codon in *ABCC9*, which induced a loss of function of SUR2, jeopardized the physical performance due to increased fatigability in patients. Differences in muscle symptoms associated with SUR1 (TPP) and SUR2 variants are quite surprising since both subunits bind to Kir6.2 to form K_{ATP} channels. However, the relative abundance of SUR1 and SUR2 is probably muscle-type-specific, as shown in mice [212], and their contribution to mitochondrial K_{ATP} channels is not established yet [213]. Another important difference between ATS and IDMS regards the inheritance mode of SUR1 and SUR2 mutations. Thus, as for most of the muscle ion channelopathies, recessive mutations are more threatening than dominant ones.

4.5. Episodic Ataxia/Myokymia

The episodic ataxias are a heterogeneous group of autosomal dominant diseases characterized by recurring attacks of cerebellar ataxia. Episodic ataxia type 1 (EA1) is caused by mutations in the *KCNA1* gene encoding the voltage-dependent potassium Kv1.1 channel [214,215]. EA1 shows a broad phenotypic spectrum, including cerebellar ataxia, muscle spasticity, dyskinesia, seizures, epileptic encephalopathy, hyperthermia, and hypomagnesemia [216,217]. Muscle symptoms include constant myokymia and acute episodes of uncontrolled muscle contractions of the face and limbs, stiffness, cramps, and weakness, as well as malignant hyperthermia susceptibility in one kindred. In a few patients, muscle symptoms are largely preponderant. Functional studies of *KCNA1* mutations in heterologous systems of expression indicate a loss of function of the Kv1.1 channel through altered gating, expression, or modulation. Studies of a knock-in mouse EA1 model provided mechanistic insights for the disease [218]. Loss of function in Kv1.1 increases the excitability of basket cells to release GABA that, in turn, inhibits Purkinje cells in the cerebellum, thereby inducing ataxia [218,219]. Mutations linked to ataxia are spanned over the entire protein. However, the loss of function of juxtaparanodal Kv1.1 channels increases the motor nerve excitability, which promotes myokymia [220]. Interestingly, mutations causing preeminent muscle symptoms with little or no ataxia are clustered in the transmembrane S2 and S3 helices and the S2–S3 intracellular linker [221–223,195]. Since Kv1.1 channels are expressed in many central neurons, loss-of-function mutations may induce excessive brain excitability leading to epilepsy. Mutations affecting the channel pore region appear especially inclined to induce seizures. Those mutations in the conserved Pro-Val-Pro motif in the sixth transmembrane segment are linked to epileptic encephalopathy, i.e., recurrent seizures and intellectual disability [224,225]. The selective deletion of *KCNA1* in neurons causes epilepsy, premature death, and cardiorespiratory dysregulation in mice [226]. The variability of symptoms associated with *KCNA1* mutations suggests that mutations may manifest their effects in a cell type-dependent manner. Such effects might depend on the specific biophysical defect or on specific interactions with other proteins, such as other Kv subunits. In addition, environmental factors and gene modifiers may account for the different symptoms observed in patients carrying the same mutation [195,217]. Such a great variability in symptoms makes *KCNA1*-related diseases difficult to diagnose. For instance, next-generation sequencing recently revealed an already known *KCNA1* mutation (p.N255D) in a patient diagnosed with myotonia, presenting with hand and facial stiffness without ataxia [227].

Pharmacological therapy of *KCNA1*-related diseases is symptomatic only [216,228,229]. The carbonic anhydrase inhibitor ACZ provided some relief in a number of patients. However, limiting side effects can develop in the long term (kidney stones, excessive sweating, paresthesia, muscle stiffness and fatigability, gastrointestinal disorders, concentration and memory difficulties). In addition, non-responders have been frequently observed. The mechanism of action of ACZ in EA1 and other ion channelopathies is still unclear. Whether Kv1.1 channels are sensitive to the change in pH value is unknown. Antiepileptic drugs, including sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, phenytoin, valproic acid), phenobarbital, benzodiazepine (clonazepam, clobazam), vigabatrin, and gabapentin, have been used with some benefit to relieve ataxia and seizures. In some patients, these drugs may be ineffective or may worsen symptoms. However, there is no drug-class effect, as a patient refractory to one or more antiepileptic drugs may have benefited from another. No information is available regarding the effects of these drugs on wild-type or mutated Kv1.1 channels. In addition, information is lacking regarding the effects of treatment on muscle symptoms.

5. Chloride Channel-Related Muscle Disorders

The chloride channel family includes a variety of proteins involved in many different cellular functions, which include maintenance of ion homeostasis, trans-epithelial fluid transport, modulation of intracellular compartment pH value, cell volume regulation, and the regulation of cell excitability [230]. In skeletal muscle fibers, the high level of sarcolemma chloride conductance (g_{Cl}) is crucial for the stabilization of the resting membrane potential and the repolarization of action potentials [231].

The g_{Cl} in skeletal muscle is mediated by the voltage-gated *ClC-1* chloride channels. It was the first mammalian voltage-gated chloride-channel identified belonging to the family of *CLC* proteins [232].

With a mass of ~120 kDa, *ClC-1* is the largest protein of this family, composed of two identical subunits, each forming a gated pore. Each subunit consists of 18 α -helices, 17 of which are embedded in the plasma membrane, and 2 tandem cystathionine- β -synthase (CBS) domains located in the intracellular C-terminal region [233,234].

Loss-of-function mutations in the *CLCN1* gene abolish or reduce *ClC-1* plasma membrane currents, leading to myotonia congenita (MC), the most frequent hereditary skeletal muscle channelopathy in humans [2,235,236]. MC can be inherited either as an autosomal dominant (Thomsen's disease) or an autosomal recessive (Becker's disease) trait; Becker's disease is associated with a more severe phenotype. MC patients present with muscle stiffness and delayed muscle relaxation after a voluntary movement, a clinical sign called myotonia. Myotonia in MC is worse at rest and instead improves with exercise, the so-called warm-up phenomenon [42]. Other symptoms include muscle hypertrophy, more frequent in Becker's disease and conferring a "hercules" habitus to the patient, and cold sensitivity of myotonia, although less frequent than in patients carrying *SCN4A* mutations. Myotonia in MC is more frequently observed in the limbs, while cranial myotonia is much more suggestive of SCM or PMC [4,11,237]. Painful myotonia is more frequent in SCM than in MC [11,237]. Furthermore, patients with Becker's disease may experience transient weakness at the onset of voluntary contraction that may rarely lead to falls [238].

More than 250 *CLCN1* mutations have been found to be associated with MC. They scattered over the entire sequence of the channel protein, but a few regions with high-frequency mutations have been described in exons 4, 5, and 8 [2,239–241]. With the exception of a few nonsense mutations leading to truncated *ClC-1* proteins, all dominant mutations are missense mutations. Recessive mutations include deletions, insertions, splice-site, missense, or nonsense errors. In addition, a combination of whole exon deletions or duplications and point mutations in *CLCN1* accounted for 6% of patients with MC [242].

In vitro functional studies of *ClC-1* mutations have clarified the molecular mechanisms by which the dominant and recessive mutations alter ion channel function and expression (Figure 4). In Thomsen's disease, the mutant subunit is expected to exert a dominant-negative effect on the associated wild-type (WT) subunit in the dimeric channel [243]. Thus, in the heterozygous carrier, the g_{Cl} is reduced by more than 50%, leading to overexcitability. This is the case of the p.T335N mutation, identified for the first time in an Italian family. This mutation induced a reduction of chloride current and exerted a dominant negative effect on the WT subunit, consistent with mild Thomsen's phenotype [244]. In contrast, *ClC-1* mutated subunits associated with recessive myotonia do not exert a significant dominant-negative effect on the associated subunit. In the heterozygous carrier, WT subunits sustain at least 50% of the g_{Cl} , and muscle function is preserved. In the compound heterozygous carrier, all the subunits are mutated, and the g_{Cl} is reduced 50% more, leading to myotonia [243].

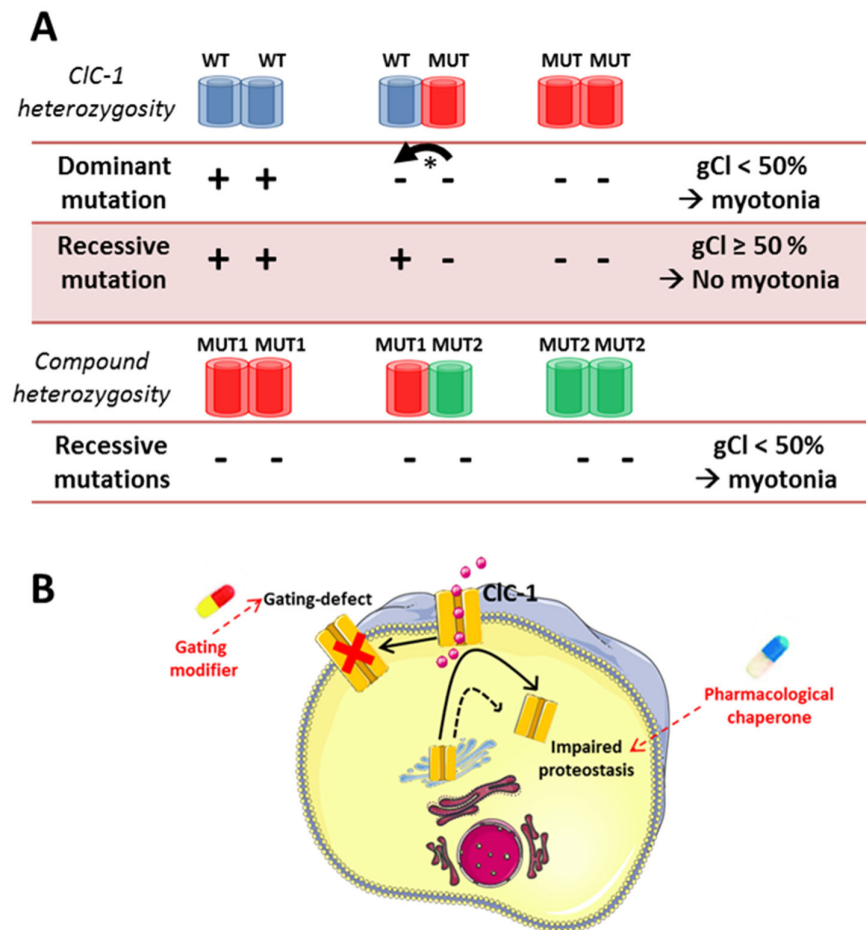


Figure 4. Pathomechanisms of CLCN1-related myotonia congenita (MC). (A) Presumed mechanism of inheritance in MC. The CIC-1 channel is a dimeric protein with a double barrel-like structure: two subunits assemble to form two parallel ion-conducting pores. In the case of heterozygosity, wild-type (WT) and mutated (MUT) CIC-1 subunits can assemble as homodimers, WT–WT and MUT–MUT, and heterodimers (WT–MUT). In autosomal dominant Thomsen’s disease, the mutated subunit is expected to exert a dominant-negative effect (*) on the associated wild-type subunit in the WT–MUT channel. This results in the reduction of sarcolemma chloride conductance (gCl) by more than 50%, leading to muscle fiber hyperexcitability and muscle stiffness. In autosomal recessive Becker’s disease, the recessive mutation is expected to have no effect on the associated WT subunit. The co-expression of the recessive mutation with the wild-type CIC-1 results at maximum in a 50% reduction of the sarcolemmal chloride conductance, which is not enough to cause myotonia. The occurrence of recessive mutations in homozygosity or in compound heterozygosity is required to reduce the sarcolemmal chloride conductance by more than 50% and to induce myotonia. (+: functional CIC-1 subunit, -: impaired CIC-1 subunit). (B). The main molecular defects of CIC-1 mutants associated with MC consist of either a defect in CIC-1 proteostasis (protein synthesis, cell trafficking, or proteolysis) or a defect in CIC-1 channel gating. Knowledge of molecular pathomechanism may guide the development of efficient mutant-targeted pharmacological treatments to restore CIC-1 function.

The majority of MC mutations are predicted to reduce chloride currents by impaired CIC-1 proteostasis (impaired synthesis, defective cell trafficking, increased degradation) or by impairing CIC-1 function through various gating defects. The latter one includes a positive shift of the voltage-dependent activation of fast and slow channel gating, reduction of single-channel conductance, altered ion selectivity, or an inverted voltage dependence (hyperpolarization-activated) [245–249,244,241]. A number of CIC-1 mutations found

in myotonic patients show no evidence of any functional defect when studied in heterologous expression systems. Notable examples include several missense mutations, such as p.T82A, p.F167L, p.R453W, p.L628P, and p.L861P [28,194,246,247]. This suggests that the defect of these variants may arise only in the skeletal muscle cells due to altered interactions with muscle proteins.

Currently, MC patients receive symptomatic treatment, which aims at dampening skeletal muscle hyperexcitability through inhibition of voltage-gated sodium channels. Thus, mexiletine was employed as the first-line therapy in MC, similarly to sodium channel myotonia and paramyotonia congenita [22]. Very recently, persistent sodium currents have been proposed to be involved in the mechanism underlying the transient weakness in recessive MC [250]. This may explain why mexiletine is greatly efficient against this debilitating symptom [238]. Similar to PMC and SCM, lamotrigine can be considered as a second choice in MC [26,27].

Besides sodium channel blockers, ACZ was reported to be efficient in small cohorts of MC patients [251,252] and could be considered a second choice. The mechanism of ACZ is not well defined, but it might stimulate the ClC-1 channel activity through intracellular acidification [39,253]. However, there is no known direct activator of ClC-1 available. The classification of ClC-1 mutations according to their functional defect would be fundamental to help the discovery of new drugs that target mutant channels' defects with the hope of ensuring a personalized treatment for MC patients. This includes the drug able to correct mutant channel gating (gating-modifiers) or to improve the expression of traffic-defective mutants (pharmacological chaperones) [231].

6. Nicotinic Receptor-Channels

Nicotinic acetylcholine receptor (AChR) is localized on the crests of the folded postsynaptic muscle membrane. The binding of acetylcholine with its receptor opens the central ion channel pore of the AChR, resulting in depolarization of the muscle membrane. The AChR is a pentamer comprising four different subunits (α , β , δ , ϵ in a ratio of 2:1:1:1), with each subunit encoded by a separate gene and forming a transmembrane ligand-gated ion channel. Congenital myasthenic syndrome (CMS) is a rare genetic disorder due to mutations in genes encoding proteins involved in the neuromuscular junction (NMJ) structure and function, causing skeletal muscle weakness and fatigability [254]. CMS may be classified based on the localization in the NMJ or the function of the mutated protein, with AChR defects accounting for around half of the CMS cases [255]. CMS related to AChR defects includes AChR deficiency and, much less frequently, AChR kinetic defects, which can be classified into slow and fast-channel syndromes. All the AChR subunits may be involved in CMS, especially the epsilon subunit gene (*CHRNE*) is mutated in about 20%–50% of the cases [255–257]. CMS related to AChR defects are recessively inherited, except for slow-channel syndrome (SCS), which is an autosomal dominant disease [254].

The clinical presentation of CMS due to AChR defects is highly variable, ranging from mild symptoms to severe manifestations, sometimes with life-threatening respiratory episodes, especially in the first decade of life. These CMS subtypes usually present at birth or in infancy, often with hypotonia in association with ocular, facial, bulbar or respiratory symptoms and followed by delayed motor milestones. Alternatively, they may present later with walking difficulty and frequent falls. Prenatal onset with arthrogryposis multiplex congenita (AMC) and fetal akinesia (FA) was originally reported on patients mutated in *CHRNA1*, coding for the gamma subunit of the fetal form of AChR [258]. No myasthenic symptoms were observed at birth or later because the adult AChR was normally expressed. AMC and FA have been reported in association with mutations in other CMS genes, including *CHRNA1* and *CHRNA1*, characterized by CMS symptoms and absence of adult AChR in the disease animal model [259,260]. CMS is usually characterized by static or slowly progressive course over the years, although acute exacerbations may be triggered by infectious episodes, surgery, or stress, sometimes leading to acute respiratory failure, in particular in the first years of life [254]. The central nervous system and

heart are not involved. The CMS diagnosis is based on clinical and electromyography findings, followed by the identification of the molecular defect, which may be guided by specific clinical, neurophysiological or histological clues [254].

Only symptomatic pharmacological therapies are available for CMS treatment. Of note, drugs with positive effects on specific forms of CMS may worsen another one, as pyridostigmine in SCS. Hence, genetic diagnosis is highly recommended to optimize pharmacologic treatment. Drugs useful to treat CMS due to AChR defects are mainly cholinergic agonists (PYR and 3,4 DAP). Adrenergic agonists (salbutamol/albuterol and ephedrine) may be used in patients not responsive to cholinergic agonists. Fluoxetine and quinidine are long-lived open-channel blockers of the AChR ion channel, and they are currently used only in SCS [254]. Salbutamol may be used even in SCS [261].

7. Concluding Remarks

The SMICs represent an expanding field; in this regard, new genes and new phenotypes have been recently discovered after the introduction of next-generation sequencing [262–265,227]. Clinical variability warrants better comprehension of genotype–phenotype correlations and of other mechanisms influencing clinical expression [266]. For instance, the coexistence of mutations in two different genes and non-genetic factors (epigenetic, environmental, and hormonal) may help the understanding of the clinical variability [24,267–269].

Up to date, most treatments are only symptomatic. However, knowledge of the pathomechanisms and detailed phenotyping may offer the possibility to develop more targeted therapies with increased efficacy and safety. Early molecular diagnosis is critical because the choice of therapeutic option may help save lives or slow down the disease progression. Ion channels are expressed on the membrane and may be easily druggable with small molecular weight molecules or monoclonal antibodies. Small compounds able to correct the specific defect induced by mutations are warranted, as it occurred for the pharmacological treatment of CFTR mutations in cystic fibrosis [270]. To this purpose, an interdisciplinary approach including both clinical, molecular, neurophysiological and pharmacological data is the only promising strategy to find efficient new treatments for SMICs.

Author Contributions: Conceptualization L.M. and J.F.D.; manuscript draft preparation S.B. and C.A.; revision and editing L.M. and J.F.D. All authors have read and agreed to the published version of the manuscript.

Funding: JFD. is supported by Association Française contre les Myopathies (grant #16123) and Bari University (grant #2017–2018).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Lorenzo Maggi is a member of the ERN Muscle Working group.

Conflicts of Interest: The authors report no disclosure relevant to the manuscript.

References

- Fontaine, B.; Khurana, T.S.; Hoffman, E.P.; Bruns, G.A.; Haines, J.L.; Trofatter, J.A.; et al. Hyperkalemic periodic paralysis and the adult muscle sodium channel alpha-subunit gene. *Science* **1990**, *250*, 1000–1002.
- Horga, A.; Raja Rayan, D.L.; Matthews, E.; Sud, R.; Fialho, D.; Durran, S.C.; et al. Prevalence study of genetically defined skeletal muscle channelopathies in England. *Neurology* **2013**, *80*, 1472–1475.
- Stunnenberg, B.C.; Raaphorst, J.; Deenen, J.C.W.; Links, T.P.; Wilde, A.A.; Verbove, D.J.; et al. Prevalence and mutation spectrum of skeletal muscle channelopathies in the Netherlands. *Neuromuscul. Disord.* **2018**, *28*, 402–407.
- Maggi, L.; Brugnoli, R.; Canioni, E.; Tonin, P.; Saletti, V.; Sola, P.; et al. Clinical and Molecular Spectrum of Myotonia and Periodic Paralysis Associated With Mutations in SCN4A in a Large Cohort of Italian Patients. *Front. Neurol.* **2020**, *11*, 646.

5. Ptáček, L.J.; George, A.L., Jr.; Griggs, R.C.; Tawil, R.; Kallen, R.G.; Barchi, R.L.; et al. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. *Cell* **1991**, *67*, 1021–1027.
6. Rojas, C.V.; Wang, J.Z.; Schwartz, L.S.; Hoffman, E.P.; Powell, B.R.; Brown, R.H., Jr. A Met-to-Val mutation in the skeletal muscle Nav channel alpha-subunit in hyperkalaemic periodic paralysis. *Nature* **1991**, *354*, 387–389.
7. Miller, T.M.; Dias da Silva, M.R.; Miller, H.A.; Kwiecinski, H.; Mendell, J.R.; Tawil, R.; et al. Correlating phenotype and genotype in the periodic paralyses. *Neurology* **2004**, *63*, 1647–1655.
8. Ptáček, L.J.; George, A.L., Jr.; Barchi, R.L.; et al. Mutations in an S4 segment of the adult skeletal muscle sodium channel cause paramyotonia congenita. *Neuron* **1992**, *8*, 891–897.
9. Matthews, E.; Fialho, D.; Tan, S.V.; Venance, S.L.; Cannon, S.C.; Sternberg, D.; CINCH Investigators; et al. The non-dystrophic myotonias: Molecular pathogenesis, diagnosis and treatment. *Brain* **2010**, *133*, 9–22.
10. Lerche, H.; Heine, R.; Pika, U.; George, A.L., Jr.; Mitrovic, N.; Browatzki, M.; et al. Human sodium channel myotonia: Slowed channel inactivation due to substitutions for a glycine within the III-IV linker. *J. Physiol.* **1993**, *470*, 13–22.
11. Trip, J.; Drost, G.; Ginjaar, H.B.; Nieman, F.H.; van der Kooi, A.J.; de Visser, M.; van Engelen, B.G.; Faber, C.G. Redefining the clinical phenotypes of non-dystrophic myotonic syndromes. *J. Neurol. Neurosurg. Psychiatry* **2009**, *80*, 647–652.
12. Cea, G.; Andreu, D.; Fletcher, E.; Ramdas, S.; Sud, R.; Hanna, M.G.; Matthews, E. Sodium channel myotonia may be associated with high-risk brief resolved unexplained events. *Wellcome Open Res.* **2020**, *5*, 57.
13. Fusco, C.; Frattini, D.; Salerno, G.G.; Canali, E.; Bernasconi, P.; Maggi, L. New phenotype and neonatal onset of sodium channel myotonia in a child with a novel mutation of SCN4A gene. *Brain Dev.* **2015**, *37*, 891–893.
14. Bednars, M.; Stunnenberg, B.C.; Kusters, B.; Kamsteeg, E.J.; Saris, C.G.; Groome, J.; et al. A novel Ile1455Thr variant in the skeletal muscle sodium channel alpha-subunit in a patient with a severe adult-onset proximal myopathy with electrical myotonia and a patient with mild paramyotonia phenotype. *Neuromuscul. Disord.* **2017**, *27*, 175–182.
15. Luo, S.; Sampedro Castañeda, M.; Matthews, E.; Sud, R.; Hanna, M.G.; Sun, J.; et al. Hypokalaemic periodic paralysis and myotonia in a patient with homozygous mutation p.R1451L in Nav1.4. *Sci. Rep.* **2018**, *8*, 9714.
16. Elia, N.; Nault, T.; McMillan, H.J.; Graham, G.E.; Huang, L.; Cannon, S.C. Myotonic myopathy with secondary joint and skeletal anomalies from the c.2386C>G, p.L769V mutation in SCN4A. *Front. Neurol.* **2020**, *11*, 77.
17. Poulin, H.; Gosselin-Badaroudine, P.; Vicart, S.; Habbout, K.; Sternberg, D.; Giuliano, S.; et al. Substitutions of the S4DIV R2 residue (R1451) in Nav1.4 lead to complex forms of paramyotonia congenita and periodic paralyses. *Sci. Rep.* **2018**, *8*, 2041.
18. Taminato, T.; Mori-Yoshimura, M.; Miki, J.; Sasaki, R.; Sato, N.; Oya, Y.; Nishino, I.; Takahashi, Y. Paramyotonia Congenita with Persistent Distal and Facial Muscle Weakness: A Case Report with Literature Review. *J. Neuromuscul. Dis.* **2020**, *7*, 193–201.
19. Cannon, S.C. Sodium channelopathies of skeletal muscle. *Handb. Exp. Pharmacol.* **2018**, *246*, 309–330.
20. Cannon, S.C.; Brown, R.H., Jr.; Corey, D.P. Theoretical reconstruction of myotonia and paralysis caused by incomplete inactivation of sodium channels. *Biophys. J.* **1993**, *65*, 270–288.
21. Hayward, L.J.; Sandoval, G.M.; Cannon, S.C. Defective slow inactivation of sodium channels contributes to familial periodic paralysis. *Neurology* **1999**, *52*, 1447–1453.
22. Statland, J.M.; Bundy, B.N.; Wang, Y.; Rayan, D.R.; Trivedi, J.R.; Sansone, V.A.; et al. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: A randomized controlled trial. *JAMA* **2012**, *308*, 1357–1365.
23. Stunnenberg, B.C.; Raaphorst, J.; Groenewoud, H.M.; Statland, J.M.; Griggs, R.C.; Woertman, W.; et al. Effect of mexiletine on muscle stiffness in patients with nondystrophic myotonia evaluated using aggregated N-of-1 trials. *JAMA* **2018**, *320*, 2344–2353.
24. Suetterlin, K.J.; Bugiardi, E.; Kaski, J.P.; Morrow, J.M.; Matthews, E.; Hanna, M.G.; et al. Long-term safety and efficacy of mexiletine for patients with skeletal muscle channelopathies. *JAMA Neurol.* **2015**, *72*, 1531–1533.
25. Modoni, A.; D'Amico, A.; Primiano, G.; Capozzoli, F.; Desaphy, J.-F.; Lo Monaco, M. Long-term safety and usefulness of mexiletine in a large cohort of patients affected by non-dystrophic myotonias. *Front. Neurol.* **2020**, *11*, 300.
26. Andersen, G.; Hedermann, G.; Witting, N.; Duno, M.; Andersen, H.; Vissing, J. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: A double-blind randomized study. *Brain* **2017**, *140*, 2295–2305.
27. Vereb, N.; Montagnese, F.; Gläser, D.; Schoser, B. Non-dystrophic myotonias: Clinical and mutation spectrum of 70 German patients. *J. Neurol.* **2021**, *268*, 1708–1720.
28. Desaphy, J.F.; Modoni, A.; Lomonaco, M.; Camerino, D.C. Dramatic improvement of myotonia permanens with flecainide: A two-case report of a possible bench-to-bedside pharmacogenetics strategy. *Eur. J. Clin. Pharmacol.* **2013**, *69*, 1037–1039.
29. Desaphy, J.F.; Carbonara, R.; D'Amico, A.; Modoni, A.; Roussel, J.; Imbrici, P.; Pagliarini, S.; Lucchiari, S.; Lo Monaco, M.; Conte Camerino, D. Translational approach to address therapy in myotonia permanens due to a new SCN4A mutation. *Neurology* **2016**, *86*, 2100–2108.
30. Farinato, A.; Altamura, C.; Imbrici, P.; Maggi, L.; Bernasconi, P.; Mantegazza, R.; et al. Pharmacogenetics of myotonic hNav1.4 sodium channel variants situated near the fast inactivation gate. *Pharmacol. Res.* **2019**, *141*, 224–235.
31. Desaphy, J.F.; Altamura, C.; Vicart, S.; Fontaine, B. Targeted Therapies for Skeletal Muscle Ion Channelopathies: Systematic Review and Steps Towards Precision Medicine. *J. Neuromuscul. Dis.* **2021**, *8*, 357–381.
32. Desaphy, J.F.; Carbonara, R.; Costanza, T.; Conte Camerino, D. Preclinical evaluation of marketed sodium channel blockers in a rat model of myotonia discloses promising antimyotonic drugs. *Exp. Neurol.* **2014**, *255*, 96–102.
33. Desaphy, J.F.; Farinato, A.; Altamura, C.; De Bellis, M.; Imbrici, P.; Tarantino, N.; et al. Safinamide's potential in treating non-dystrophic myotonias: Inhibition of skeletal muscle voltage-gated sodium channels and skeletal muscle hyperexcitability in vitro and in vivo. *Exp. Neurol.* **2020**, *328*, 113287.

34. Novak, K.R.; Norman, J.; Mitchell, J.R.; Pinter, M.J.; Rich, M.M. Sodium channel slow inactivation as a therapeutic target for myotonia congenita. *Ann. Neurol.* **2015**, *77*, 320–332.
35. Skov, M.; de Paoli, F.V.; Nielsen, O.B.; Pedersen, T.H. The anti-convulsants lacosamide, lamotrigine, and rufinamide reduce myotonia in isolated human and rat skeletal muscle. *Muscle Nerve* **2017**, *56*, 136–142.
36. De Bellis, M.; Carbonara, R.; Roussel, J.; Farinato, A.; Massari, A.; Pierno, S.; et al. Increased sodium channel use-dependent inhibition by a new potent analogue of tocainide greatly enhances in vivo antimyotonic activity. *Neuropharmacology* **2017**, *113*, 206–216.
37. De Bellis, M.; De Luca, A.; Desaphy, J.F.; Carbonara, R.; Heiny, J.A.; Kennedy, A.; et al. Combined modifications of mexiletine pharmacophores for new lead blockers of Na(v)1.4 channels. *Biophys. J.* **2013**, *104*, 344–354.
38. Tricarico, D.; Mele, A.; Conte Camerino, D. Carbonic anhydrase inhibitors ameliorate the symptoms of hypokalaemic periodic paralysis in rats by opening the muscular Ca²⁺-activated-K⁺ channels. *Neuromuscul. Disord.* **2006**, *16*, 39–45.
39. Altamura, C.; Fonzino, A.; Tarantino, N.; Conte, E.; Liantonio, A.; Imbri, P.; et al. Increased sarcolemma chloride conductance as one of the mechanisms of action of carbonic anhydrase inhibitors in muscle excitability disorders. *Exp. Neurol.* **2021**, *342*, 113758.
40. Sansone, V.A.; Burge, J.; McDermott, M.P.; Smith, P.C.; Herr, B.; Tawil, R.; et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. *Neurology* **2016**, *86*, 1408–1416.
41. Statland, J.M.; Fontaine, B.; Hanna, M.G.; Johnson, N.E.; Kissel, J.T.; Sansone, V.A.; et al. Review of the Diagnosis and Treatment of Periodic Paralysis. *Muscle Nerve* **2018**, *57*, 522–530.
42. Stunnenberg, B.C.; LoRusso, S.; Arnold, W.D.; Barohn, R.J.; Cannon, S.C.; et al. Guidelines on clinical presentation and management of nondystrophic myotonias. *Muscle Nerve* **2020**, *62*, 430–444.
43. Bulman, D.E.; Scoggan, K.A.; van Oene, M.D.; Nicolle, M.W.; Hahn, A.F.; Tollar, L.L.; Ebers, G.C. A novel sodium channel mutation in a family with hypokalemic periodic paralysis. *Neurology* **1999**, *53*, 1932–1936.
44. Jurkat-Rott, K.; Mitrovic, N.; Hang, C.; Kouzmekine, A.; Iaizzo, P.; Herzog, J.; et al. Voltage-sensor sodium channel mutations cause hypokalemic periodic paralysis type 2 by enhanced inactivation and reduced current. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9549–9554.
45. Matthews, E.; Labrum, R.; Sweeney, M.G.; Sud, R.; Haworth, A.; Chinnery, P.F.; et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. *Neurology* **2009**, *72*, 1544–1547.
46. Matthews, E.; Portaro, S.; Ke, Q.; Sud, R.; Haworth, A.; Davis, M.B.; et al. ACZ efficacy in hypokalemic periodic paralysis and the predictive role of genotype. *Neurology* **2011**, *77*, 1960–1964.
47. Tsujino, A.; Maertens, C.; Ohno, K.; Shen, X.M.; Fukuda, T.; Harper, C.M.; et al. Myasthenic syndrome caused by mutation of the SCN4A sodium channel. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7377–7382.
48. Zaharieva, I.T.; Thor, M.G.; Oates, E.C.; van Karnebeek, C.; Henderson, G.; Blom, E.; et al. Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or classical congenital myopathy. *Brain* **2016**, *139*, 674–691.
49. Thompson, R.; Bonne, G.; Missier, P.; Lochmüller, H. Targeted therapies for congenital myasthenic syndromes: Systematic review and steps towards a treatable disease. *Emerg. Top. Life Sci.* **2019**, *3*, 19–37.
50. Matthews, E.; Hartley, L.; Sud, R.; Hanna, M.G.; Muntoni, F.; Munot, P. Acetazolamide can improve symptoms and signs in ion channel-related congenital myopathy. *J. Neurol. Neurosurg. Psychiatry* **2019**, *90*, 243–245.
51. Ptacek, L.J.; Tawil, R.; Griggs, R.C.; Engel, A.G.; Layzer, R.B.; Kwiecinski, H.; et al. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. *Cell* **1994**, *77*, 863–868.
52. Holm-Yildiz, S.; Witting, N.; Dahlqvist, J.; de Stricker Borch, J.; Solheim, T.; Fornander, F.; et al. Permanent muscle weakness in hypokalemic periodic paralysis. *Neurology* **2020**, *95*, e342–e352.
53. Fan, C.; Lehmann-Horn, F.; Weber, M.A.; Bednars, M.; Groome, J.R.; Jonsson, M.K. Transient compartment-like syndrome and normokalaemic periodic paralysis due to a Ca(v)1.1 mutation. *Brain* **2013**, *136*, 3775–3786.
54. Wu, F.; Mi, W.; Hernández-Ochoa, E.O.; Burns, D.K.; Fu, Y.; Gray, H.F.; et al. A calcium channel mutant mouse model of hypokalemic periodic paralysis. *J. Clin. Invest.* **2012**, *122*, 4580–4591.
55. Scharfner, V.; Romero, N.B.; Donkervoort, S.; Treves, S.; Munot, P.; Pierson, T.M.; Dabaj, I.; et al. Dihydropyridine receptor (DHPR, CACNA1S) congenital myopathy. *Acta Neuropathol.* **2017**, *133*, 517–533.
56. Jungbluth, H.; Treves, S.; Zorzato, F.; Sarkozy, A.; Ochala, J.; Sewry, C.; Phadke, R.; Gautel, M.; Muntoni, F. Congenital myopathies: Disorders of excitation-contraction coupling and muscle contraction. *Nat. Rev. Neurol.* **2018**, *14*, 151–167.
57. Hunter, J.M.; Ahearn, M.E.; Balak, C.D.; Liang, W.S.; Kurdoglu, A.; Corneveaux, J.J.; et al. Novel pathogenic variants and genes for myopathies identified by whole exome sequencing. *Mol. Genet. Genomic Med.* **2015**, *3*, 283–301.
58. Ravenscroft, G.; Clayton, J.S.; Faiz, F.; Sivadurai, P.; Milnes, D.; Cincotta, R.; et al. Neurogenetic fetal akinesia and arthrogryposis: Genetics, expanding genotype-phenotypes and functional genomics. *J. Med. Genet.* **2020**, doi: 10.1136/jmedgenet-2020-106901.
59. Yiş, U.; Hiz, S.; Güneş, S.; Diniz, G.; Baydan, F.; Töpf, A.; et al. Dihydropyridine Receptor Congenital Myopathy In A Consanguineous Turkish Family. *J. Neuromuscul. Dis.* **2019**, *6*, 377–384.
60. Flucher, B.E.; Campiglio, M. STAC proteins: The missing link in skeletal muscle EC coupling and new regulators of calcium channel function. *Biochim. Biophys. Acta Mol. Cell. Res.* **2019**, *1866*, 1101–1110.
61. Nelson, B.R.; Wu, F.; Liu, Y.; Anderson, D.M.; McAnally, J.; Lin, W.; et al. Skeletal muscle-specific T-tubule protein STAC3 mediates voltage-induced Ca²⁺ release and contractility. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 11881–11886.

62. Horstick, E.J.; Linsley, J.W.; Dowling, J.J.; Hauser, M.A.; McDonald, K.K.; Ashley-Koch, A.; et al. Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. *Nat. Commun.* **2013**, *4*, 1952.
63. Bailey, A.G.; Bloch, E.C. Malignant hyperthermia in a three-month-old American Indian infant. *Anesth. Analg.* **1987**, *66*, 1043–1045.
64. Stewart, C.R.; Kahler, S.G.; Gilchrist, J.M. Congenital myopathy with cleft palate and increased susceptibility to malignant hyperthermia: King syndrome? *Pediatr. Neurol.* **1988**, *4*, 371–374.
65. Stamm, D.S.; Aylsworth, A.S.; Stajich, J.M.; Kahler, S.G.; Thorne, L.B.; Speer, M.C.; Powell, C.M. Native American myopathy: Congenital myopathy with cleft palate, skeletal anomalies, and susceptibility to malignant hyperthermia. *Am. J. Med. Genet. A.* **2008**, *146*, 1832–1841.
66. Flucher, B.E. Skeletal muscle Cav1.1 channelopathies. *Pflug. Arch.* **2020**, *472*, 739–754.
67. Telegrafi, A.; Webb, B.D.; Robbins, S.M.; Speck-Martins, C.E.; FitzPatrick, D.; Fleming, L.; et al. Identification of STAC3 variants in non-Native American families with overlapping features of Carey-Fineman-Ziter syndrome and Moebius syndrome. *Am. J. Med. Genet. A.* **2017**, *173*, 2763–2771.
68. Zaharieva, I.T.; Sarkozy, A.; Munot, P.; Manzur, A.; O'Grady, G.; Rendu, J.; et al. STAC3 variants cause a congenital myopathy with distinctive dysmorphic features and malignant hyperthermia susceptibility. *Hum. Mutat.* **2018**, *39*, 1980–1994.
69. Grzybowski, M.; Schänzer, A.; Pepler, A.; Heller, C.; Neubauer, B.A.; Hahn, A. Novel STAC3 Mutations in the First Non-American Indian Patient with Native American Myopathy. *Neuropediatrics* **2017**, *48*, 451–455.
70. Wong King Yuen, S.M.; Campiglio, M.; Tung, C.C.; Flucher, B.E.; Van Petegem, F. Structural insights into binding of STAC proteins to voltage-gated calcium channels. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E9520–E9528.
71. Campiglio, M.; Kaplan, M.M.; Flucher, B.E. STAC3 incorporation into skeletal muscle triads occurs independent of the dihydropyridine receptor. *J. Cell. Physiol.* **2018**, *233*, 9045–9051.
72. Hoth, M.; Penner, R. Depletion of intracellular calcium stores activates a calcium current in mast cells. *Nature* **1992**, *355*, 353–356.
73. Prakriya, M. The molecular physiology of CRAC channels. *Immunol. Rev.* **2009**, *231*, 88–98.
74. Lacruz, R.S.; Feske, S. Diseases caused by mutations in ORAI1 and STIM1. *Ann. N. Y. Acad. Sci.* **2015**, *1356*, 45–79.
75. Roos, J.; DiGregorio, P.J.; Yeromin, A.V.; Ohlsen, K.; Lioudyno, M.; Zhang, S.; et al. STIM1, an essential and conserved component of store-operated Ca²⁺ channel function. *J. Cell. Biol.* **2005**, *169*, 435–445.
76. Vig, M.; Peinelt, C.; Beck, A.; Koomoa, D.L.; Rabah, D.; Koblan-Huberson, M.; et al. CRACM1 is a plasma membrane protein essential for store-operated Ca²⁺ entry. *Science* **2006**, *312*, 1220–1223.
77. González-Sánchez, P.; Del Arco, A.; Esteban, J.A.; Satrustegui, J. Store-Operated Calcium Entry Is Required for mGluR-Dependent Long Term Depression in Cortical Neurons. *Front. Cell. Neurosci.* **2017**, *11*, 363.
78. Lunz, V.; Romanin, C.; Frischauf, I. STIM1 activation of Orai1. *Cell Calcium* **2019**, *77*, 29–38.
79. Conte, E.; Pannunzio, A.; Imbrici, P.; Camerino, G.M.; Maggi, L.; Mora, M.; et al. Gain-of-Function STIM1 L96V Mutation Causes Myogenesis Alteration in Muscle Cells From a Patient Affected by Tubular Aggregate Myopathy. *Front. Cell. Dev. Biol.* **2021**, *9*, 635063.
80. Feske, S.; Gwack, Y.; Prakriya, M.; Srikanth, S.; Puppel, S.H.; Tanasa, B.; et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature* **2006**, *441*, 179–185.
81. Hou, X.; Pedi, L.; Diver, M.M.; Long, S.B. Crystal structure of the calcium release-activated calcium channel Orai. *Science* **2012**, *338*, 1308–1313.
82. Wang, X.; Wang, Y.; Zhou, Y.; Hendron, E.; Mancarella, S.; Andrade, M.D.; Rothberg, B.S.; et al. Distinct Orai-coupling domains in STIM1 and STIM2 define the Orai-activating site. *Nat. Commun.* **2014**, *5*, 3183.
83. Schaballie, H.; Rodriguez, R.; Martin, E.; Moens, L.; Frans, G.; Lenoir, C.; et al. A novel hypomorphic mutation in STIM1 results in a late-onset immunodeficiency. *J. Allergy. Clin. Immunol.* **2015**, *136*, 816–819.
84. Stormorken, H.; Sjaastad, O.; Langslet, A.; Sulg, I.; Egge, K.; Diderichsen, J. A new syndrome: Thrombocytopathia, muscle fatigue, asplenia, miosis, migraine, dyslexia and ichthyosis. *Clin. Genet.* **1985**, *28*, 67–74.
85. Mizobuchi, M.; Tanaka, C.; Sako, K.; Murakami, N.; Nihira, A.; Abe, T.; et al. Muscle involvement of Stormorken's syndrome. *Rinsho Shinkeigaku* **2000**, *40*, 915–920.
86. Markello, T.; Chen, D.; Kwan, J.Y.; Horkayne-Szakaly, I.; Morrison, A.; Simakova, O.; et al. York platelet syndrome is a CRAC channelopathy due to gain-of-function mutations in STIM1. *Mol. Genet. Metab.* **2015**, *114*, 474–482.
87. Cameron, C.H.S.; Allen, I.V.; Patterson, V.; Avaria, M.A. Dominantly inherited tubular aggregate myopathy. *J. Pathol.* **1992**, *168*, 397–403.
88. Engel, W.K. Mitochondrial Aggregates In Muscle Disease. *J. Histochem. Cytochem.* **1964**, *12*, 46–48.
89. Nesin, V.; Wiley, G.; Kousi, M.; Ong, E.-C.; Lehmann, T.; Nicholl, D.J.; et al. Activating mutations in STIM1 and ORAI1 cause overlapping syndromes of tubular myopathy and congenital miosis. *Proc. Nat. Acad. Sci. USA* **2014**, *111*, 4197–4202.
90. Morin, G.; Bruechle, N.O.; Singh, A.R.; Knopp, C.; Jedraszak, G.; Elbracht, M.; et al. Gain-of-function mutation in STIM1 (P.R304W) is associated with Stormorken syndrome. *Hum. Mutat.* **2014**, *35*, 1221–1232.
91. Guergueltcheva, V.; Müller, J.S.; Dosl, M.; Senderek, J.; Oldfors, A.; Lindbergh, C.; et al. Congenital myasthenic syndrome with tubular aggregates caused by GFPT1 mutations. *J. Neurol.* **2012**, *259*, 838–850.
92. Belaya, K.; Finlayson, S.; Slater, C.R.; Cossins, J.; Liu, W.W.; Maxwell, S.; et al. Mutations in DPAGT1 cause a limb-girdle congenital myasthenic syndrome with tubular aggregates. *Am. J. Hum. Genet.* **2012**, *91*, 193–201.

93. Sternberg, D.; Maisonobe, T.; Jurkat-Rott, K.; Nicole, S.; Launay, E.; Chauveau, D.; et al. Hypokalaemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. *Brain* **2001**, *124*, 1091–1099.
94. Böhm, J.; Chevessier, F.; Maues De Paula, A.; Koch, C.; Attarian, S.; Feger, C.; et al. Constitutive activation of the calcium sensor STIM1 causes tubular-aggregate myopathy. *Am. J. Hum. Genet.* **2013**, *92*, 271–278.
95. Böhm, J.; Chevessier, F.; Koch, C.; Peche, G.A.; Mora, M.; Morandi, L.; et al. Clinical, histological and genetic characterisation of patients with tubular aggregate myopathy caused by mutations in STIM1. *J. Med. Genet.* **2014**, *51*, 824–833.
96. Hedberg, C.; Niceta, M.; Fattori, F.; Lindvall, B.; Ciolfi, A.; D'Amico, A.; et al. Childhood onset tubular aggregate myopathy associated with de novo STIM1 mutations. *J. Neurol.* **2014**, *261*, 870–876.
97. Claeys, T.; Goossens, V.; Racé, V.; Theys, T.; Thal, D.R.; Depuydt, C.E.; Claeys, K.G. Clinical and muscle MRI features in a family with tubular aggregate myopathy and novel STIM1 mutation. *Neuromuscul. Disord.* **2020**, *30*, 709–718.
98. Silva-Rojas, R.; Laporte, J.; Böhm, J. STIM1/ORAI1 Loss-of-Function and Gain-of-Function Mutations Inversely Impact on SOCE and Calcium Homeostasis and Cause Multi-Systemic Mirror Diseases. *Front. Physiol.* **2020**, *11*, 604941.
99. Misceo, D.; Holmgren, A.; Louch, W.E.; Holme, P.A.; Mizobuchi, M.; Morales, R.J.; et al. A dominant STIM1 mutation causes Stormorken syndrome. *Hum. Mutat.* **2014**, *35*, 556–564.
100. Endo, Y.; Noguchi, S.; Hara, Y.; Hayashi, Y.K.; Motomura, K.; Miyatake, S.; et al. Dominant mutations in ORAI1 cause tubular aggregate myopathy with hypocalcemia via constitutive activation of store-operated Ca(2)(+) channels. *Hum. Mol. Genet.* **2015**, *24*, 637–648.
101. Böhm, J.; Bulla, M.; Urquhart, J.E.; Malfatti, E.; Williams, S.G.; O'Sullivan, J.; et al. ORAI1 Mutations with Distinct Channel Gating Defects in Tubular Aggregate Myopathy. *Hum. Mutat.* **2017**, *38*, 426–438.
102. Garibaldi, M.; Fattori, F.; Riva, B.; Labasse, C.; Brochier, G.; Ottaviani, P.; et al. A novel gain-of-function mutation in ORAI1 causes late-onset tubular aggregate myopathy and congenital miosis. *Clin. Genet.* **2017**, *91*, 780–786.
103. Stauderman, K.A. CRAC channels as targets for drug discovery and development. *Cell. Calcium.* **2018**, *74*, 147–159.
104. Phillips, M.S.; Fujii, J.; Khanna, V.K.; DeLeon, S.; Yokobata, K.; de Jong, P.J.; MacLennan, D.H. The structural organization of the human skeletal muscle ryanodine receptor (RYR1) gene. *Genomics* **1996**, *34*, 24–41.
105. Dowling, J.J.; D. Gonorazky, H.; Cohn, R.D.; Campbell, C. Treating pediatric neuromuscular disorders: The future is now. *Am. J. Med. Genet. A* **2018**, *176*, 804–841.
106. Klein, A.; Lillis, S.; Munteanu, I.; Scoto, M.; Zhou, H.; Quinlivan, R.; et al. Clinical and genetic findings in a large cohort of patients with ryanodine receptor 1 gene-associated myopathies. *Hum. Mutat.* **2012**, *33*, 981–988.
107. Dlamini, N.; Voermans, N.C.; Lillis, S.; Stewart, K.; Kamsteeg, E.J.; Drost, G.; et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul. Disord.* **2013**, *23*, 540–548.
108. Løseth, S.; Voermans, N.C.; Torbergson, T.; Lillis, S.; Jonsrud, C.; Lindal, S.; et al. A novel late-onset axial myopathy associated with mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *J. Neurol.* **2013**, *260*, 1504–1510.
109. Zou, Y.; Liang, Y.; Gong, H.; Zhou, N.; Ma, H.; Guan, A.; et al. Ryanodine receptor type 2 is required for the development of pressure overload-induced cardiac hypertrophy. *Hypertension* **2011**, *58*, 1099–1110.
110. Zhou, H.; Rokach, O.; Feng, L.; Munteanu, I.; Mamchaoui, K.; Wilmshurst, J.M.; et al. RyR1 deficiency in congenital myopathies disrupts excitation-contraction coupling. *Hum. Mutat.* **2013**, *34*, 986–996.
111. Garibaldi, M.; Rendu, J.; Brocard, J.; Lacene, E.; Fauré, J.; Brochier, G.; et al. Dusty core disease (DuCD): Expanding morphological spectrum of RYR1 recessive myopathies. *Acta Neuropathol. Commun.* **2019**, *7*, 3.
112. Matthews, E.; Neuwirth, C.; Jaffer, F.; Scalco, R.S.; Fialho, D.; Parton, M.; et al. Atypical periodic paralysis and myalgia: A novel RYR1 phenotype. *Neurology* **2018**, *90*, e412–e418.
113. Lawal, T.A.; Todd, J.J.; Witherspoon, J.W.; Bönnemann, C.G.; Dowling, J.J.; Hamilton, S.L.; et al. Ryanodine receptor 1-related disorders: An historical perspective and proposal for a unified nomenclature. *Skelet. Muscle* **2020**, *10*, 32.
114. Davis, M.R.; Haan, E.; Jungbluth, H.; Sewry, C.; North, K.; Muntoni, F.; et al. Principal mutation hotspot for central core disease and related myopathies in the C-terminal transmembrane region of the RYR1 gene. *Neuromuscul. Disord.* **2003**, *13*, 151–157.
115. Levano, S.; Vukcevic, M.; Singer, M.; Matter, A.; Treves, S.; Urwyler, A.; Girard, T. Increasing the number of diagnostic mutations in malignant hyperthermia. *Hum. Mutat.* **2009**, *30*, 590–598.
116. Robinson, R.; Carpenter, D.; Shaw, M.A.; Halsall, J.; Hopkins, P. Mutations in RYR1 in malignant hyperthermia and central core disease. *Hum. Mutat.* **2006**, *27*, 977–989.
117. Wu, S.; Ibarra, M.C.; Malicdan, M.C.; Murayama, K.; Ichihara, Y.; Kikuchi, H.; et al. Central core disease is due to RYR1 mutations in more than 90% of patients. *Brain* **2006**, *129*, 1470–1480.
118. Zhou, H.; Jungbluth, H.; Sewry, C.A.; Feng, L.; Bertini, E.; Bushby, K.; et al. Molecular mechanisms and phenotypic variation in RYR1-related congenital myopathies. *Brain* **2007**, *130*, 2024–2036.
119. Maggi, L.; Scoto, M.; Cirak, S.; Robb, S.A.; Klein, A.; Lillis, S.; et al. Congenital myopathies—clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. *Neuromuscul. Disord.* **2013**, *23*, 195–205.
120. Colombo, I.; Scoto, M.; Manzur, A.Y.; Robb, S.A.; Maggi, L.; Gowda, V.; et al. Congenital myopathies: Natural history of a large pediatric cohort. *Neurology* **2015**, *84*, 28–35.
121. Jungbluth, H. Central core disease. *Orphanet J. Rare Dis.* **2007**, *2*, 25.
122. Jungbluth, H. Multi-minicore disease. *Orphanet J. Rare Dis.* **2007**, *2*, 31.
123. Clarke, N.F.; Waddell, L.B.; Cooper, S.T.; Perry, M.; Smith, R.L.; Kornberg, A.J.; et al. Recessive mutations in RYR1 are a common cause of congenital fibre type disproportion. *Hum. Mutat.* **2010**, *31*, e1544–e1550.

124. Monnier, N.; Marty, I.; Faure, J.; Castiglioni, C.; Desnuelle, C.; Sacconi, S.; et al. Null mutations causing depletion of the type 1 ryanodine receptor (RYR1) are commonly associated with recessive structural congenital myopathies with cores. *Hum. Mutat.* **2008**, *29*, 670–678.
125. Monnier, N.; Romero, N.B.; Lerale, J.; Nivoche, Y.; Qi, D.; MacLennan, D.H.; et al. An autosomal dominant congenital myopathy with cores and rods is associated with a neomutation in the RYR1 gene encoding the skeletal muscle ryanodine receptor. *Hum. Mol. Genet.* **2000**, *9*, 2599–2608.
126. Jungbluth, H.; Dowling, J.J.; Ferreira, A.; Muntoni, F. 182nd ENMC International Workshop: RYR1-related myopathies, 15–17th April 2011, Naarden, The Netherlands. *Neuromuscul. Disord.* **2012**, *22*, 453–462.
127. Wilmschurst, J.M.; Lillis, S.; Zhou, H.; Pillay, K.; Henderson, H.; Kress, W.; et al. RYR1 mutations are a common cause of congenital myopathies with central nuclei. *Ann. Neurol.* **2010**, *68*, 717–726.
128. Ferreira, A.; Monnier, N.; Romero, N.B.; Leroy, J.P.; Bonnemant, C.; Haenggeli, C.A.; et al. A recessive form of central core disease, transiently presenting as multi-minicore disease, is associated with a homozygous mutation in the ryanodine receptor type 1 gene. *Ann. Neurol.* **2002**, *51*, 750–759.
129. Romero, N.B.; Monnier, N.; Viollet, L.; Cortey, A.; Chevallay, M.; Leroy, J.P.; et al. Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. *Brain* **2003**, *126*, 2341–2349.
130. De Wel, B.; Claeys, K.G. Malignant hyperthermia: Still an issue for neuromuscular diseases? *Curr. Opin. Neurol.* **2018**, *31*, 628–634.
131. Carpenter, D.; Robinson, R.L.; Quinnell, R.J.; Ringrose, C.; Hogg, M.; Casson, F.; et al. Genetic variation in RYR1 and malignant hyperthermia phenotypes. *Br. J. Anaesth.* **2009**, *103*, 538–548.
132. Rosenberg, H.; Pollock, N.; Schiemann, A.; Bulger, T.; Stowell, K. Malignant hyperthermia: A review. *Orphanet J. Rare Dis.* **2015**, *10*, 93.
133. Lehmann-Horn, F.; Iaizzo, P.A. Are myotonias and periodic paralyses associated with susceptibility to malignant hyper—thermia? *Br. J. Anaesth.* **1990**, *65*, 692–697.
134. Dowling, J.J.; Lillis, S.; Amburgey, K.; Zhou, H.; Al-Sarraj, S.; Buk, S.J.; et al. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul. Disord.* **2011**, *21*, 420–427.
135. Jungbluth, H.; Lillis, S.; Zhou, H.; Abbs, S.; Sewry, C.; Swash, M.; Muntoni, F. Late-onset axial myopathy with cores due to a novel heterozygous dominant mutation in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul. Disord.* **2009**, *19*, 344–347.
136. Zhou, H.; Lillis, S.; Loy, R.E.; Ghassemi, F.; Rose, M.R.; Norwood, F.; et al. Multi-minicore disease and atypical periodic paralysis associated with novel mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul. Disord.* **2010**, *20*, 166–173.
137. Bertocchini, F.; Ovitt, C.E.; Conti, A.; Barone, V.; Scholer, H.R.; Bottinelli, R.; et al. Requirement for the ryanodine receptor type 3 for efficient contraction in neonatal skeletal muscles. *EMBO J.* **1997**, *16*, 6956–6963.
138. Perez, C.F.; López, J.R.; Allen, P.D. Expression levels of RyR1 and RyR3 control resting free Ca²⁺ in skeletal muscle. *Am. J. Physiol. Cell. Physiol.* **2005**, *88*, C640–C649.
139. Nilipour, Y.; Nafissi, S.; Tjust, A.E.; Ravenscroft, G.; Hossein Nejad Nedai, H.; Taylor, R.L.; et al. Ryanodine receptor type 3 (RYR3) as a novel gene associated with a myopathy with nemaline bodies. *Europ. J. Neurol.* **2018**, *25*, 841–847.
140. Krüger, J.; Kunert-Keil, C.; Bisping, F.; Brinkmeier, H. Transient receptor potential cation channels in normal and dystrophic mdx muscle. *Neuromuscul. Disord.* **2008**, *18*, 501–513.
141. Ho, T.C.; Horn, N.A.; Huynh, T.; Kelava, L.; Lansman, J.B. Evidence TRPV4 contributes to mechanosensitive ion channels in mouse skeletal muscle fibers. *Channels* **2012**, *6*, 246–254.
142. Pritschow, B.W.; Lange, T.; Kasch, J.; Kunert-Keil, C.; Liedtke, W.; Brinkmeier, H. Functional TRPV4 channels are expressed in mouse skeletal muscle and can modulate resting Ca²⁺ influx and muscle fatigue. *Pflug. Arch.* **2011**, *46*, 115–122.
143. Auer-Grumbach, M.; Olschewski, A.; Papić, L.; Kremer, H.; McEntagart, M.E.; Uhrig, S.; et al. Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C. *Nat. Genet.* **2010**, *42*, 160–164.
144. Deng, H.X.; Klein, C.J.; Yan, J.; Shi, Y.; Wu, Y.; Fecto, F.; et al. Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by alterations in TRPV4. *Nat. Genet.* **2010**, *42*, 165–169.
145. Landouré, G.; Zdebik, A.A.; Martinez, T.L.; Burnett, B.G.; Stanescu, H.C.; Inada, H.; et al. Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. *Nat. Genet.* **2010**, *42*, 170–174.
146. Zimoń, M.; Baets, J.; Auer-Grumbach, M.; Berciano, J.; Garcia, A.; Lopez-Laso, E.; et al. Dominant mutations in the cation channel gene transient receptor potential vanilloid 4 cause an unusual spectrum of neuropathies. *Brain* **2010**, *133*, 1798–1809.
147. Rock, M.J.; Prenen, J.; Funari, V.A.; Funari, T.L.; Merriman, B.; Nelson, S.F.; et al. Gain-of-function mutations in TRPV4 cause autosomal dominant brachyolmia. *Nat. Genet.* **2008**, *40*, 999–1003.
148. Krakow, D.; Vriens, J.; Camacho, N.; Luong, P.; Deixler, H.; Funari, T.L.; et al. Mutations in the gene encoding the calcium-permeable ion channel TRPV4 produce spondylometaphyseal dysplasia, Kozłowski type and metatropic dysplasia. *Am. J. Hum. Genet.* **2009**, *84*, 307–315.
149. Cho, T.J.; Matsumoto, K.; Fano, V.; Dai, J.; Kim, O.H.; Chae, J.H.; et al. TRPV4-pathway manifesting both skeletal dysplasia and peripheral neuropathy: A report of three patients. *Am. J. Med. Genet. A.* **2012**, *158A*, 795–802.
150. Echaniz-Laguna, A.; Dubourg, O.; Carlier, P.; Carlier, R.Y.; Sabouraud, P.; Péréon, Y.; et al. Phenotypic spectrum and incidence of TRPV4 mutations in patients with inherited axonal neuropathy. *Neurology* **2014**, *82*, 1919–1926.

151. Oonk, A.M.; Ekker, M.S.; Huygen, P.L.; Kunst, H.P.; Kremer, H.; Schelhaas, J.J.; Pennings, R.J. Intrafamilial variable hearing loss in TRPV4 induced spinal muscular atrophy. *Ann. Otol. Rhinol. Laryngol.* **2014**, *123*, 859–865.
152. Evangelista, T.; Bansagi, B.; Pyle, A.; Griffin, H.; Douroudis, K.; Polvikoski, T.; et al. Phenotypic variability of TRPV4 related neuropathies. *Neuromuscul. Disord.* **2015**, *25*, 516–521.
153. Koutsis, G.; Lynch, D.; Manole, A.; Karadima, G.; Reilly, M.M.; Houlden, H.; Panas, M. Charcot-Marie-Tooth disease type 2C and scapuloperoneal muscular atrophy overlap syndrome in a patient with the R232C TRPV4 mutation. *J. Neurol.* **2015**, *262*, 1972–1975.
154. Ürel-Demir, G.; Şimşek-Kiper, P.Ö.; Öncel, İ.; Utine, G.E.; Haliloğlu, G.; Boduroğlu, K. Natural history of TRPV4-Related disorders: From skeletal dysplasia to neuromuscular phenotype. *Eur. J. Paediatr. Neurol.* **2021**, *32*, 46–55.
155. Sullivan, J.M.; Zimanyi, C.M.; Aisenberg, W.; Bears, B.; Chen, D.H.; Day, J.W.; et al. Novel mutations highlight the key role of the ankyrin repeat domain in TRPV4-mediated neuropathy. *Neurol. Genet.* **2015**, *1*, e29.
156. Woolums, B.M.; McCray, B.A.; Sung, H.; Tabuchi, M.; Sullivan, J.M.; Ruppell, K.T.; et al. TRPV4 disrupts mitochondrial transport and causes axonal degeneration via a CaMKII-dependent elevation of intracellular Ca²⁺. *Nat. Commun.* **2020**, *11*, 2679.
157. Dupont, C.; Novak, K.; Denman, K.; Myers, J.H.; Sullivan, J.M.; Walker, P.V., 2nd. TRPV4 Antagonism Prevents Mechanically Induced Myotonia. *Ann. Neurol.* **2020**, *88*, 297–308.
158. Goyal, N.; Skrdla, P.; Schroyer, R.; Kumar, S.; Fernando, D.; Oughton, A.; et al. Clinical Pharmacokinetics, Safety, and Tolerability of a Novel, First-in-Class TRPV4 Ion Channel Inhibitor, GSK2798745, in Healthy and Heart Failure Subjects. *Am. J. Cardiovasc. Drugs* **2019**, *19*, 335–342.
159. Carter, M.T.; McMillan, H.J.; Tomin, A.; Weiss, N. Compound heterozygous CACNA1H mutations associated with severe congenital amyotrophy. *Channels* **2019**, *13*, 153–161.
160. Tawil, R.; Ptacek, L.J.; Pavlakis, S.G.; DeVivo, D.C.; Penn, A.S.; Ozdemir, C.; Griggs, R.C. Andersen's syndrome: Potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. *Ann. Neurol.* **1994**, *35*, 326–330.
161. Sansone, V.; Tawil, R. Management and treatment of Andersen-Tawil syndrome (ATS). *Neurotherapeutics* **2007**, *4*, 233–237.
162. Pérez-Riera, A.R.; Barbosa-Barros, R.; Samesina, N.; Pastore, C.A.; Scanavacca, M.; Daminello-Raimundo, R.; et al. Andersen-Tawil Syndrome: A Comprehensive Review. *Cardiol. Rev.* **2021**, *29*, 165–177.
163. Nguyen, H.L.; Pieper, G.H.; Wilders, R. Andersen-Tawil syndrome: Clinical and molecular aspects. *Int. J. Cardiol.* **2013**, *170*, 1–16.
164. Child, N.D.; Cleland, J.C.; Roxburgh, R. Andersen-Tawil syndrome presenting as a fixed myopathy. *Muscle Nerve* **2013**, *48*, 623.
165. Lefter, S.; Hardiman, O.; Costigan, D.; Lynch, B.; McConville, J.; Hand, C.K.; Ryan, A.M. Andersen-Tawil syndrome with early fixed myopathy. *J. Clin. Neuromuscul. Dis.* **2014**, *16*, 79–82.
166. Oz Tuncer, G.; Teber, S.; Kutluk, M.G.; Albayrak, P.; Deda, G. Andersen-Tawil Syndrome with Early Onset Myopathy: 2 Cases. *J. Neuromuscul. Dis.* **2017**, *4*, 93–95.
167. Wu, L.; Fang, Y.; Zhang, B.R. Andersen-Tawil syndrome associated with myopathy. *World J. Emerg. Med.* **2020**, *11*, 267–269.
168. Hiraide, T.; Fukumura, S.; Yamamoto, A.; Nakashima, M.; Saitsu, H. Familial periodic paralysis associated with a rare KCNJ5 variant that supposed to have incomplete penetrance. *Brain. Dev.* **2021**, *43*, 470–474.
169. Plaster, N.M.; Tawil, R.; Tristani-Firouzi, M.; Canún, S.; Bendahhou, S.; Tsunoda, A.; et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* **2001**, *105*, 511–519.
170. Lopes, C.M.; Zhang, H.; Rohacs, T.; Jin, T.; Yang, J.; Logothetis, D.E. Alterations in conserved Kir channel-PIP2 interactions underlie channelopathies. *Neuron* **2002**, *34*, 933–944.
171. Ballester, L.Y.; Benson, D.W.; Wong, B.; Law, I.H.; Mathews, K.D.; Vanoye, C.G.; George, A.L., Jr. Trafficking-competent and trafficking-defective KCNJ2 mutations in Andersen syndrome. *Hum. Mutat.* **2006**, *27*, 388.
172. Ma, D.; Tang, X.D.; Rogers, T.B.; Welling, P.A. An andersen-Tawil syndrome mutation in Kir2.1 (V302M) alters the G-loop cytoplasmic K⁺ conduction pathway. *J. Biol. Chem.* **2007**, *282*, 5781–5789.
173. Handklo-Jamal, R.; Meisel, E.; Yakubovich, D.; Vysochek, L.; Beinart, R.; Glikson, M.; et al. Andersen-Tawil Syndrome Is Associated With Impaired PIP2 Regulation of the Potassium Channel Kir2.1. *Front. Pharmacol.* **2020**, *11*, 672.
174. Bendahhou, S.; Donaldson, M.R.; Plaster, N.M.; Tristani-Firouzi, M.; Fu, Y.H.; Ptáček, L.J. Defective potassium channel Kir2.1 trafficking underlies Andersen-Tawil syndrome. *J. Biol. Chem.* **2003**, *278*, 51779–51785.
175. Bendahhou, S.; Fournier, E.; Sternberg, D.; Bassez, G.; Furby, A.; Sereni, C.; et al. In vivo and in vitro functional characterization of Andersen's syndrome mutations. *J. Physiol.* **2005**, *565*, 731–741.
176. Sacco, S.; Giuliano, S.; Sacconi, S.; Desnuelle, C.; Barhanin, J.; Amri, E.Z.; Bendahhou, S. The inward rectifier potassium channel Kir2.1 is required for osteoblastogenesis. *Hum. Mol. Genet.* **2015**, *24*, 471–479.
177. Belus, M.T.; Rogers, M.A.; Elzubeir, A.; Josey, M.; Rose, S.; Andreeva, V.; et al. Kir2.1 is important for efficient BMP signaling in mammalian face development. *Dev. Biol.* **2018**, *444*, S297–S307.
178. Pini, J.; Giuliano, S.; Matonti, J.; Gannoun, L.; Simkin, D.; Rouleau, M.; Bendahhou, S. Osteogenic and Chondrogenic Master Genes Expression Is Dependent on the Kir2.1 Potassium Channel Through the Bone Morphogenetic Protein Pathway. *J. Bone Miner. Res.* **2018**, *33*, 1826–1841.
179. Preisig-Müller, R.; Schlichthörl, G.; Goerge, T.; Heinen, S.; Brüggemann, A.; Rajan, S.; et al. Heteromerization of Kir2.x potassium channels contributes to the phenotype of Andersen's syndrome. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 7774–7779.
180. Decher, N.; Renigunta, V.; Zuzarte, M.; Soom, M.; Heinemann, S.H.; Timothy, K.W.; et al. Impaired interaction between the slide helix and the C-terminus of Kir2.1: A novel mechanism of Andersen syndrome. *Cardiovasc. Res.* **2007**, *75*, 748–757.

181. Jagodzińska, M.; Szperl, M.; Ponińska, J.; Kosiec, A.; Gajda, R.; Kukla, P.; Biernacka, E.K. Coexistence of Andersen-Tawil Syndrome with Polymorphisms in hERG1 Gene (K897T) and SCN5A Gene (H558R) in One Family. *Ann. Noninvasive Electrocardiol.* **2016**, *21*, 189–195.
182. Polyak, M.E.; Shestak, A.; Podolyak, D.; Zaklyazminskaya, E. Compound heterozygous mutations in KCNJ2 and KCNH2 in a patient with severe Andersen-Tawil syndrome. *BMJ Case Rep.* **2020**, *13*, e235703.
183. Priori, S.G.; Pandit, S.V.; Rivolta, I.; Berenfeld, O.; Ronchetti, E.; Dhamoon, A.; et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ. Res.* **2005**, *96*, 800–807.
184. Xia, M.; Jin, Q.; Bendahhou, S.; He, Y.; Larroque, M.M.; Chen, Y.; et al. A Kir2.1 gain-of-function mutation underlies familial atrial fibrillation. *Biochem. Biophys. Res. Commun.* **2005**, *332*, 1012–1019.
185. Yang, Y.; Liang, B.; Liu, J.; Li, J.; Grunnet, M.; Olesen, S.P.; et al. Identification of a Kir3.4 mutation in congenital long QT syndrome. *Am. J. Hum. Genet.* **2010**, *86*, 872–880.
186. Kokunai, Y.; Nakata, T.; Furuta, M.; Sakata, S.; Kimura, H.; Aiba, T.; et al. A Kir3.4 mutation causes Andersen-Tawil syndrome by an inhibitory effect on Kir2.1. *Neurology* **2014**, *82*, 1058–1064.
187. Nagamine, S.; Sakoda, S.; Koide, R.; Kawata, A.; Yuan, J.; Takashima, H.; Nakano, I. A case of Andersen-Tawil syndrome presenting periodic paralysis exacerbated by ACZ. *J. Neurol. Sci.* **2014**, *347*, 385–386.
188. Abott, G.W.; Butler, M.H.; Bendahhou, S.; Dalakas, M.C.; Ptacek, L.J.; Goldstein, S.A. MiRP2 forms potassium channels in skeletal muscle with Kv3.4 and is associated with periodic paralysis. *Cell* **2001**, *104*, 217–231.
189. Dias Da Silva, M.R.; Cerutti, J.M.; Arnaldi, L.A.; Maciel, R.M. A mutation in the KCNE3 potassium channel gene is associated with susceptibility to thyrotoxic hypokalemic periodic paralysis. *J. Clin. Endocrinol. Metab.* **2002**, *87*, 4881–4884.
190. Sternberg, D.; Tabti, N.; Fournier, E.; Hainque, B.; Fontaine, B. Lack of association of the potassium channel-associated peptide MiRP2-R83H variant with periodic paralysis. *Neurology* **2003**, *61*, 857–859.
191. Jurkat-Rott, K.; Lehmann-Horn, F. Periodic paralysis mutation MiRP2-R83H in controls: Interpretations and general recommendation. *Neurology* **2004**, *62*, 1012–1015.
192. Tang, N.L.; Chow, C.C.; Ko, G.T.; Tai, M.H.; Kwok, R.; Yao, X.Q.; Cockram, C.S. No mutation in the KCNE3 potassium channel gene in Chinese thyrotoxic hypokalaemic periodic paralysis patients. *Clin. Endocrinol.* **2004**, *61*, 109–112.
193. Abbott, G.W.; Butler, M.H.; Goldstein, S.A. Phosphorylation and protonation of neighboring MiRP2 sites: Function and pathophysiology of MiRP2-Kv3.4 potassium channels in periodic paralysis. *FASEB J.* **2006**, *20*, 293–301.
194. Portaro, S.; Altamura, C.; Licata, N.; Camerino, G.M.; Imbrici, P.; Musumeci, O.; et al. Clinical, Molecular, and Functional Characterization of CLCN1 Mutations in Three Families with Recessive Myotonia Congenita. *Neuromol. Med.* **2015**, *17*, 285–296.
195. Imbrici, P.; Accogli, A.; Blunck, R.; Altamura, C.; Iacomino, M.; D'adamo, M.C.; Allegri, A. et al. Musculoskeletal Features without Ataxia Associated with a Novel de novo Mutation in KCNA1 Impairing the Voltage Sensitivity of Kv1.1 Channel. *Biomedicines* **2021**, *9*, 75.
196. Salih, M.; van Kinschot, C.M.J.; Peeters, R.P.; de Herder, W.W.; Duschek, E.J.J.; van der Linden, J.; et al. Thyrotoxic periodic paralysis: An unusual presentation of hyperthyroidism. *Neth. J. Med.* **2017**, *75*, 315–320.
197. Chu, P.Y.; Cheng, C.J.; Tseng, M.H.; Yang, S.S.; Chen, H.C.; Lin, S.H. Genetic variant rs623011 (17q24.3) associates with non-familial thyrotoxic and sporadic hypokalemic paralysis. *Clin. Chim. Acta.* **2012**, *414*, 105–108.
198. Song, I.W.; Sung, C.C.; Chen, C.H.; Cheng, C.J.; Yang, S.S.; Chou, Y.C.; et al. Novel susceptibility gene for nonfamilial hypokalemic periodic paralysis. *Neurology* **2016**, *86*, 1190–1198.
199. Nakaza, M.; Kitamura, Y.; Furuta, M.; Kubota, T.; Sasaki, R.; Takahashi, M.P. Analysis of the genetic background associated with sporadic periodic paralysis in Japanese patients. *J. Neurol. Sci.* **2020**, *412*, 116795.
200. Cannon, S.C. Further evidence for shared genetic susceptibility in both sporadic and thyrotoxic periodic paralysis. *J. Neurol. Sci.* **2020**, *412*, 116794.
201. Ryan, D.P.; da Silva, M.R.; Soong, T.W.; Fontaine, B.; Donaldson, M.R.; Kung, A.W.; et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell* **2010**, *140*, 88–98.
202. Cheng, C.J.; Lin, S.H.; Lo, Y.F.; Yang, S.S.; Hsu, Y.J.; Cannon, S.C.; Huang, C.L. Identification and functional characterization of Kir2.6 mutations associated with non-familial hypokalemic periodic paralysis. *J. Biol. Chem.* **2011**, *286*, 27425–27435.
203. Zheng, J.; Liang, Z.; Hou, Y.; Liu, F.; Hu, Y.; Lin, P.; Yan, C. A novel Kir2.6 mutation associated with hypokalemic periodic paralysis. *Clin. Neurophysiol.* **2016**, *127*, 2503–2508.
204. Paninka, R.M.; Carlos-Lima, E.; Lindsey, S.C.; Kunii, I.S.; Dias-da-Silva, M.R.; Arcisio-Miranda, M. Down-regulation of Kir2.6 channel by c-termini mutation D252N and its association with the susceptibility to Thyrotoxic Periodic Paralysis. *Neuroscience* **2017**, *346*, 197–202.
205. Cheung, C.L.; Lau, K.S.; Ho, A.Y.; Lee, K.K.; Tiu, S.C.; Lau, E.Y.; et al. Genome-wide association study identifies a susceptibility locus for thyrotoxic periodic paralysis at 17q24.3. *Nat. Genet.* **2012**, *44*, 1026–1029.
206. Jongjaroenprasert, W.; Phusantisampan, T.; Mahasirimongkol, S.; Mushiroda, T.; Hirankarn, N.; Snabboon, T.; et al. A genome-wide association study identifies novel susceptibility genetic variation for thyrotoxic hypokalemic periodic paralysis. *J. Hum. Genet.* **2012**, *57*, 301–304.
207. Li, X.; Yao, S.; Xiang, Y.; Zhang, X.; Wu, X.; Luo, L.; et al. The clinical and genetic features in a cohort of mainland Chinese patients with thyrotoxic periodic paralysis. *BMC Neurol.* **2015**, *15*, 38.
208. Rolim, A.L.; Lindsey, S.C.; Kunii, I.S.; Crispim, F.; Moisés, R.C.; Maciel, R.M.; Dias-da-Silva, M.R. The insulin-sensitivity sulphonylurea receptor variant is associated with thyrotoxic paralysis. *J. Mol. Endocrinol.* **2014**, *53*, 295–301.

209. Kuhn, M.; Jurkat-Rott, K.; Lehmann-Horn, F. Rare KCNJ18 variants do not explain hypokalaemic periodic paralysis in 263 unrelated patients. *J. Neurol. Neurosurg. Psychiatry*. **2016**, *87*, 49–52.
210. Paninka, R.M.; Mazzotti, D.R.; Kizys, M.M.; Vidi, A.C.; Rodrigues, H.; Silva, S.P.; et al. Whole genome and exome sequencing realignment supports the assignment of KCNJ12, KCNJ17, and KCNJ18 paralogous genes in thyrotoxic periodic paralysis locus: Functional characterization of two polymorphic Kir2.6 isoforms. *Mol. Genet. Genomics* **2016**, *291*, 1535–1544.
211. Smeland, M.F.; McClenaghan, C.; Roessler, H.I.; Savelberg, S.; Hansen, G.Å.M.; et al. ABCC9-related Intellectual disability Myopathy Syndrome is a KATP channelopathy with loss-of-function mutations in ABCC9. *Nat. Commun.* **2019**, *10*, 4457.
212. Tricarico, D.; Mele, A.; Lundquist, A.L.; Desai, R.R.; George, A.L., Jr.; Conte Camerino, D. Hybrid assemblies of ATP-sensitive K⁺ channels determine their muscle-type-dependent biophysical and pharmacological properties. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1118–1123.
213. Flagg, T.P.; Enkvetchakul, D.; Koster, J.C.; Nichols, C.G. Muscle KATP channels: Recent insights to energy sensing and myo-protection. *Physiol. Rev.* **2010**, *90*, 799–829.
214. Browne, D.L.; Ganchar, S.T.; Nutt, J.G.; Brunt, E.R.; Smith, E.A.; Kramer, P.; Litt, M. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat. Genet.* **1994**, *8*, 136–140.
215. Adelman, J.P.; Bond, C.T.; Pessia, M.; Maylie, J. Episodic ataxia results from voltage-dependent potassium channels with altered functions. *Neuron* **1995**, *15*, 1449–1454.
216. D'Adamo, M.C.; Liantonio, A.; Rolland, J.F.; Pessia, M.; Imbrici, P. Kv1.1 Channelopathies: Pathophysiological Mechanisms and Therapeutic Approaches. *Int. J. Mol. Sci.* **2020**, *21*, 2935.
217. Paulhus, K.; Ammerman, L.; Glasscock, E. Clinical Spectrum of KCNA1 Mutations: New Insights into Episodic Ataxia and Epilepsy Comorbidity. *Int. J. Mol. Sci.* **2020**, *21*, 2802.
218. Herson, P.S.; Virk, M.; Rustay, N.R.; Bond, C.T.; Crabbe, J.C.; Adelman, J.P.; Maylie, J. A mouse model of episodic ataxia type-1. *Nat. Neurosci.* **2003**, *6*, 378–383.
219. Begum, R.; Bakiri, Y.; Volynski, K.E.; Kullmann, D.M. Action potential broadening in a presynaptic channelopathy. *Nat. Commun.* **2016**, *7*, 12102.
220. Brunetti, O.; Imbrici, P.; Botti, F.M.; Pettorossi, V.E.; D'Adamo, M.C.; Valentino, M.; et al. Kv1.1 knock-in ataxic mice exhibit spontaneous myokymic activity exacerbated by fatigue, ischemia and low temperature. *Neurobiol. Dis.* **2012**, *47*, 310–321.
221. Eunson, L.H.; Rea, R.; Zuberi, S.M.; Youroukos, S.; Panayiotopoulos, C.P.; Liguori, R.; et al. Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability. *Ann. Neurol.* **2000**, *48*, 647–656.
222. Kinali, M.; Jungbluth, H.; Eunson, L.H.; Sewry, C.A.; Manzur, A.Y.; Mercuri, E.; et al. Expanding the phenotype of potassium channelopathy: Severe neuromyotonia and skeletal deformities without prominent Episodic Ataxia. *Neuromuscul. Disord.* **2004**, *14*, 689–693.
223. Chen, H.; von Hehn, C.; Kaczmarek, L.K.; Ment, L.R.; Pober, B.R.; Hisama, F.M. Functional analysis of a novel potassium channel (KCNA1) mutation in hereditary myokymia. *Neurogenetics* **2007**, *8*, 131–135.
224. Rogers, A.; Golumbek, P.; Cellini, E.; Doccini, V.; Guerrini, R.; Wallgren-Pettersson, C.; Thureson, A.C.; Gurnett, C.A. De novo KCNA1 variants in the PVP motif cause infantile epileptic encephalopathy and cognitive impairment similar to recurrent KCNA2 variants. *Am. J. Med. Genet. A* **2018**, *176*, 1748–1752.
225. Russo, A.; Gobbi, G.; Pini, A.; Möller, R.S.; Rubboli, G. Encephalopathy related to status epilepticus during sleep due to a de novo KCNA1 variant in the Kv-specific Pro-Val-Pro motif: Phenotypic description and remarkable electroclinical response to ACTH. *Epileptic. Disord.* **2020**, *22*, 802–806.
226. Trosclair, K.; Dhaibar, H.A.; Gautier, N.M.; Mishra, V.; Glasscock, E. Neuron-specific Kv1.1 deficiency is sufficient to cause epilepsy, premature death, and cardiorespiratory dysregulation. *Neurobiol. Dis.* **2020**, *137*, 104759.
227. Brugnani, R.; Maggi, L.; Canioni, E.; Verde, F.; Gallone, A.; Ariatti, A.; et al. Next-generation sequencing application to investigate skeletal muscle channelopathies in a large cohort of Italian patients. *Neuromuscul. Disord.* **2021**, *31*, 336–347.
228. Graves, T.D.; Cha, Y.H.; Hahn, A.F.; Barohn, R.; Salajegheh, M.K.; Griggs, R.C.; et al. Episodic ataxia type 1: Clinical characterization, quality of life and genotype-phenotype correlation. *Brain* **2014**, *137*, 1009–1018.
229. D'Adamo, M.C.; Hasan, S.; Guglielmi, L.; Servettini, I.; Cenciarini, M.; Catacuzzeno, L.; Franciolini, F. New insights into the pathogenesis and therapeutics of episodic ataxia type 1. *Front. Cell. Neurosci.* **2015**, *9*, 317.
230. Jentsch, T.J.; Pusch, M. CLC Chloride Channels and Transporters: Structure, Function, Physiology, and Disease. *Physiol. Rev.* **2018**, *98*, 1493–1590.
231. Altamura, C.; Desaphy, J.F.; Conte, D.; De Luca, A.; Imbrici, P. Skeletal muscle CIC-1 chloride channels in health and diseases. *Pflug. Arch.* **2020**, *472*, 961–975.
232. Steinmeyer, K.; Ortland, C.; Jentsch, T.J. Primary structure and functional expression of a developmentally regulated skeletal muscle chloride channel. *Nature* **1991**, *354*, 301–304.
233. Park, E.; MacKinnon, R. Structure of the CLC-1 chloride channel from Homo sapiens. *Elife* **2018**, *7*, e36629.
234. Wang, K.; Preisler, S.S.; Zhang, L.; Cui, Y.; Missel, J.W.; Grønberg, C.; et al. Structure of the human CIC-1 chloride channel. *PLoS Biol.* **2019**, *17*, e3000218.
235. Koch, M.C.; Steinmeyer, K.; Lorenz, C.; Ricker, K.; Wolf, F.; Otto, M.; et al. The skeletal muscle chloride channel in dominant and recessive human myotonia. *Science* **1992**, *257*, 797–800.
236. George, A.L., Jr.; Crackower, M.A.; Abdalla, J.A.; Hudson, A.J.; Ebers, G.C. Molecular basis of Thomsen's disease (autosomal dominant myotonia congenita). *Nat. Genet.* **1993**, *3*, 305–310.

237. Trivedi, J.R.; Bundy, B.; Statland, J.; Salajegheh, M.; Rayan, D.R.; Venance, S.L.; et al. Non-dystrophic myotonia: Prospective study of objective and patient reported outcomes. *Brain* **2013**, *136*, 2189–2200.
238. Lo Monaco, M.; D'Amico, A.; Luigetti, M.; Desaphy, J.F.; Modoni, A. Effect of mexiletine on transitory depression of compound motor action potential in recessive myotonia congenita. *Clin. Neurophysiol.* **2015**, *126*, 399–403.
239. Fialho, D.; Schorge, S.; Pucovska, U.; Davies, N.P.; Labrum, R.; Haworth, A.; et al. Chloride channel myotonia: Exon 8 hot-spot for dominant-negative interactions. *Brain* **2007**, *130*, 3265–3274.
240. Brugnoli, R.; Kapetis, D.; Imbrici, P.; Pessia, M.; Canioni, E.; Colleoni, L.; et al. A large cohort of myotonia congenita probands: Novel mutations and a high-frequency mutation region in exons 4 and 5 of the CLCN1 gene. *J. Hum. Genet.* **2013**, *58*, 581–587.
241. Altamura, C.; Ivanova, E.A.; Imbrici, P.; Conte, E.; Camerino, G.M.; Dadali, E.L.; et al. Pathomechanisms of a CLCN1 Mutation Found in a Russian Family Suffering From Becker's Myotonia. *Front. Neurol.* **2020**, *11*, 1019.
242. Raja Rayan, D.L.; Haworth, A.; Sud, R.; Matthews, E.; Fialho, D.; Burge, J.; et al. A new explanation for recessive myotonia congenita: Exon deletions and duplications in CLCN1. *Neurology* **2012**, *78*, 1953–1958.
243. Saviane, C.; Conti, F.; Pusch, M. The muscle chloride channel ClC-1 has a double-barreled appearance that is differentially affected in dominant and recessive myotonia. *J. Gen. Physiol.* **1999**, *113*, 457–468.
244. Imbrici, P.; Altamura, C.; Camerino, G.M.; Mangiatordi, G.F.; Conte, E.; Maggi, L.; et al. Multidisciplinary study of a new ClC-1 mutation causing myotonia congenita: A paradigm to understand and treat ion channelopathies. *FASEB J.* **2016**, *30*, 3285–3295.
245. Desaphy, J.F.; Gramegna, G.; Altamura, C.; Dinardo, M.M.; Imbrici, P.; George, A.L., Jr.; et al. Functional characterization of ClC-1 mutations from patients affected by recessive myotonia congenita presenting with different clinical phenotypes. *Exp. Neurol.* **2013**, *248*, 530–540.
246. Altamura, C.; Lucchiari, S.; Sahbani, D.; Ulzi, G.; Comi, G.P.; D'Ambrosio, P.; et al. The analysis of myotonia congenita mutations discloses functional clusters of amino acids within the CBS2 domain and the C-terminal peptide of the ClC-1 channel. *Hum. Mutat.* **2018**, *39*, 1273–1283.
247. Imbrici, P.; Maggi, L.; Mangiatordi, G.F.; Dinardo, M.M.; Altamura, C.; Brugnoli, R.; et al. ClC-1 mutations in myotonia congenita patients: Insights into molecular gating mechanisms and genotype-phenotype correlation. *J. Physiol.* **2015**, *593*, 4181–4199.
248. Weinberger, S.; Wojciechowski, D.; Sternberg, D.; Lehmann-Horn, F.; Jurkat-Rott, K.; Becher, T.; et al. Disease-causing mutations C277R and C277Y modify gating of human ClC-1 chloride channels in myotonia congenita. *J. Physiol.* **2012**, *590*, 3449–3464.
249. Jeng, C.J.; Fu, S.J.; You, C.Y.; Peng, Y.J.; Hsiao, C.T.; Chen, T.Y.; Tang, C.Y. Defective Gating and Proteostasis of Human ClC-1 Chloride Channel: Molecular Pathophysiology of Myotonia Congenita. *Front. Neurol.* **2020**, *11*, 76.
250. Myers, J.H.; Denman, K.; DuPont, C.; Hawash, A.A.; Novak, K.R.; Koesters, A.; et al. The mechanism underlying transient weakness in myotonia congenita. *Elife* **2021**, *10*, e65691.
251. Markhorst, J.M.; Stunnenberg, B.C.; Ginjaar, I.B.; Drost, G.; Erasmus, C.E.; Sie, L.T. Clinical experience with long-term ACZ treatment in children with nondystrophic myotonias: A three-case report. *Pediatr. Neurol.* **2014**, *51*, 537–541.
252. Moreira, S.D.; Barreto, R.; Roriz, J.M. Becker myotonia—a recently identified mutation in Iberian descendants with apparent ACZ-responsive phenotype. *Muscle Nerve* **2015**, *51*, 933–934.
253. Eguchi, H.; Tsujino, A.; Kaibara, M.; Eguchi, H.; Nakayama, S.; Sato, K.; et al. ACZ acts directly on the human skeletal muscle chloride channel. *Muscle Nerve* **2006**, *34*, 292–297.
254. Maggi, L.; Bernasconi, P.; D'Amico, A.; Brugnoli, R.; Fiorillo, C.; Garibaldi, M.; et al. Italian recommendations for diagnosis and management of congenital myasthenic syndromes. *Neurol. Sci.* **2019**, *40*, 457–468.
255. Engel, A.G.; Shen, X.M.; Selcen, D.; Sine, S.M. Congenital myasthenic syndromes: Pathogenesis, diagnosis, and treatment. *Lancet. Neurol.* **2015**, *14*, 420–434. Erratum in: *Lancet Neurol.* **2015**, *14*, 461.
256. Finlayson, S.; Beeson, D.; Palace, J. Congenital myasthenic syndromes: An update. *Pract. Neurol.* **2013**, *13*, 80–91.
257. Abicht, A.; Dösl, M.; Gallenmüller, C.; Guergueltcheva, V.; Schara, U.; Della Marina, A.; et al. Congenital myasthenic syndromes: Achievements and limitations of phenotype-guided gene-after-gene sequencing in diagnostic practice: A study of 680 patients. *Hum. Mutat.* **2012**, *33*, 1474–1484.
258. Hoffmann, K.; Müller, J.S.; Stricker, S.; Megarbane, A.; Rajab, A.; Lindner, T.H.; et al. Escobar syndrome is a prenatal myasthenia caused by disruption of the acetylcholine receptor fetal gamma subunit. *Am. J. Hum. Genet.* **2006**, *79*, 303–312.
259. Vogt, J.; Harrison, B.J.; Spearman, H.; Cossins, J.; Vermeer, S.; ten Cate, L.N. Mutation analysis of CHRNA1, CHRNB1, CHRND, and RAPSN genes in multiple pterygium syndrome/fetal akinesia patients. *Am. J. Hum. Genet.* **2008**, *82*, 222–227.
260. Michalk, A.; Stricker, S.; Becker, J.; Rupps, R.; Pantzar, T.; Miertus, J.; et al. Acetylcholine receptor pathway mutations explain various fetal akinesia deformation sequence disorders. *Am. J. Hum. Genet.* **2008**, *82*, 464–476.
261. Santovito, L.S.; Brugnoli, R.; Banfi, P.; Maggi, L. Salbutamol as effective treatment in slow-channel syndrome—first report. *Neurol. Sci.* **2021**, *42*, 1611–1612.
262. Nigro, V.; Savarese, M. Next-generation sequencing approaches for the diagnosis of skeletal muscle disorders. *Curr. Opin. Neurol.* **2016**, *29*, 621–627.
263. Ferradini, V.; Cassone, M.; Nuovo, S.; Bagni, I.; D'Apice, M.R.; Botta, A.; et al. Targeted Next Generation Sequencing in patients with Myotonia Congenita. *Clin. Chim. Acta.* **2017**, *470*, 1–7.
264. Vivekanandam, V.; Männikkö, R.; Matthews, E.; Hanna, M.G. Improving genetic diagnostics of skeletal muscle channelopathies. *Expert. Rev. Mol. Diagn.* **2020**, *20*, 725–736.

-
265. Yeh, H.M.; Liao, M.H.; Chu, C.L.; Lin, Y.H.; Sun, W.Z.; Lai, L.P.; Chen, P.L. Next-generation sequencing and bioinformatics to identify genetic causes of malignant hyperthermia. *J. Formos. Med. Assoc.* **2021**, *120*, 883–892.
 266. Morales, F.; Pusch, M. An Up-to-Date Overview of the Complexity of Genotype-Phenotype Relationships in Myotonic Channelopathies. *Front. Neurol.* **2020**, *10*, 1404.
 267. Maggi, L.; Ravaglia, S.; Farinato, A.; Brugnoli, R.; Altamura, C.; Imbrici, P.; et al. Coexistence of CLCN1 and SCN4A mutations in one family suffering from myotonia. *Neurogenetics* **2017**, *18*, 219–225.
 268. Thor, M.G.; Vivekanandam, V.; Sampedro-Castañeda, M.; Tan, S.V.; Suetterlin, K.; Sud, R.; et al. Myotonia in a patient with a mutation in an S4 arginine residue associated with hypokalaemic periodic paralysis and a concomitant synonymous CLCN1 mutation. *Sci. Rep.* **2019**, *9*, 17560.
 269. Brenes, O.; Barbieri, R.; Vázquez, M.; Vindas-Smith, R.; Roig, J.; Romero, A.; et al. Functional and Structural Characterization of CIC-1 and Nav1.4 Channels Resulting from CLCN1 and SCN4A Mutations Identified Alone and Coexisting in Myotonic Patients. *Cells* **2021**, *10*, 374.
 270. Mall, M.A.; Mayer-Hamblett, N.; Rowe, S.M. Cystic Fibrosis: Emergence of Highly Effective Targeted Therapeutics and Potential Clinical Implications. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 1193–1208.