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The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment

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The non-dystrophic myotonias are an important group of skeletal muscle channelopathies electrophysiologically characterized by altered membrane excitability. Many distinct clinical phenotypes are now recognized and range in severity from severe neonatal myotonia with respiratory compromise through to milder late-onset myotonic muscle stiffness. Specific genetic mutations in the major skeletal muscle voltage gated chloride channel gene and in the voltage gated sodium channel gene are causative in most patients. Recent work has allowed more precise correlations between the genotype and the electrophysiological and clinical phenotype. The majority of patients with myotonia have either a primary or secondary loss of membrane chloride conductance predicted to result in reduction of the resting membrane potential. Causative mutations in the sodium channel gene result in an abnormal gain of sodium channel function that may show marked temperature dependence. Despite significant advances in the clinical, genetic and molecular pathophysiological understanding of these disorders, which we review here, there are important unresolved issues we address: (i) recent work suggests that specialized clinical neurophysiology can identify channel specific patterns and aid genetic diagnosis in many cases however, it is not yet clear if such techniques can be refined to predict the causative gene in all cases or even predict the precise genotype; (ii) although clinical experience indicates these patients can have significant progressive morbidity, the detailed natural history and determinants of morbidity have not been specifically studied in a prospective fashion; (iii) some patients develop myopathy, but its frequency, severity and possible response to treatment remains undetermined, furthermore, the pathophysiological link between ion channel dysfunction and muscle degeneration is unknown; (iv) there is currently insufficient clinical trial evidence to recommend a standard treatment. Limited data suggest that sodium channel blocking agents have some efficacy. However, establishing the effectiveness of a therapy requires completion of multi-centre randomized controlled trials employing accurate outcome measures including reliable quantitation of myotonia. More specific pharmacological approaches are required and could include those which might preferentially reduce

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persistent muscle sodium currents or enhance the conductance of mutant chloride channels. Alternative strategies may be directed at preventing premature mutant channel degradation or correcting the mis-targeting of the mutant channels.

Keywords: ion channels; neuromuscular; genetics; EMG

Abbreviations: *CLCN-1* = skeletal muscle voltage gated chloride channel gene; CMAP = compound muscle action potential; *SCN4A* = skeletal muscle voltage gated sodium channel gene

Introduction

The non-dystrophic myotonias are skeletal muscle ion channel disorders traditionally considered to be distinct from myotonic dystrophy because of the absence of progressive weakness and systemic features. The non-dystrophic myotonias are now known to be caused by dysfunction of key skeletal muscle ion channels and include myotonia congenita, paramyotonia congenita and the sodium channel myotonias. The worldwide prevalence of non-dystrophic myotonia has been estimated to be ~1 in 100 000 (Emery, 1991). However, the prevalence seems to vary considerably between geographical regions. For example, myotonia congenita alone was estimated to have a prevalence of between 7 and 10 in 100 000 in Scandinavia (Baumann *et al*., 1998; Sun *et al*., 2001).

The major clinical manifestation of the non-dystrophic myotonias is muscle stiffness as a consequence of the myotonia. Additional common symptoms include pain, weakness and fatigue (Walsh *et al*., 2007; Trivedi *et al*., 2008; Wang *et al*., 2008*c*). Myotonia can be demonstrated on examination as delayed muscle relaxation following muscle contraction or following mechanical stimulation such as percussion. The underlying muscle membrane hyper-excitability manifests neurophysiologically as repetitive muscle fibre after-discharges on EMG. Recent studies have revealed a wide range of clinical phenotypes which may present diagnostic difficulty. Importantly, it has also been observed that patients with myotonic dystrophy type II may present with a clinical phenotype that is difficult to distinguish from myotonia congenita (Fialho *et al*., 2007). It is now clear that the clinical severity of these disorders can range from a neonatal life threatening presentation through to mild late-onset symptoms. The application of specialized electrophysiological protocols can reveal gene-specific patterns which can be used to direct DNA-based diagnosis (Fournier *et al*., 2004).

Myotonia congenita is caused by mutations in the skeletal muscle chloride channel gene (*CLCN-1*) and inherited in a dominant or in a recessive fashion. Paramyotonia congenita and the sodium channel myotonias are allelic, autosomal dominant disorders caused by point mutations in the skeletal muscle sodium channel gene (*SCN4A*). Hyperkalaemic periodic paralysis is also caused by mutations in *SCN4A* and may be accompanied by myotonia in some cases, although episodic paralysis is usually the dominant feature (Venance *et al*., 2006).

Here we review clinical presentations, genetics, electrodiagnosis and molecular pathogenesis of these disorders. We highlight important largely unresolved questions in relation to morbidity and natural history, mechanisms of muscle degeneration and treatment.

Clinical features

Myotonia congenita

Myotonia congenita is the most common inherited skeletal muscle channelopathy. The autosomal dominant form was first described in the 19th century by the Danish physician Julius Thomsen in himself and his family (Thomsen, 1876). In the 1970s, the German Physician P.E. Becker fully documented the existence of the recessive form of myotonia congenita (Becker, 1977). In both forms muscle stiffness is most pronounced during rapid voluntary movements following a period of rest but improves with repeated activity—the so-called 'warm-up' phenomenon (Walsh *et al*., 2007; Trivedi *et al*., 2008; Wang *et al*., 2008*c*). Some clinical findings are more common in the recessive than in the dominant form but considerable overlap exists. Recessive myotonia congenita tends to be more severe, is more frequently associated with muscle hypertrophy and with depressed tendon reflexes (Becker, 1977; Fialho *et al*., 2007). Patients with recessive myotonia congenita typically experience a peculiar transient weakness on initiating an action, which is only rarely seen in dominant myotonia congenita. Although Becker found that most patients with recessive myotonia congenita presented between the ages 4 and 12 years while the dominant form usually manifested before the age of 3 years (Becker, 1977), we found no difference in the age of onset (Fialho *et al*., 2007).

Myotonic dystrophy types I and II can often be differentiated from myotonia congenita by the presence of systemic features. However, cases of myotonic dystrophy type II in which myotonia is the predominant complaint without any overt systemic features have been described (Fialho *et al*., 2007) and can lead to diagnostic difficulty.

Paramyotonia congenita

Eulenburg first used the term paramyotonia congenita in 1886 to describe a syndrome of episodic muscle cramps and paralysis profoundly exacerbated by cold and exercise in six generations of a German family (Eulenburg, 1886). The inheritance is autosomal dominant and symptoms usually manifest in the first decade of life. The facial, tongue, and hand muscles are predominantly affected and the lower limbs are generally only mildly affected (Miller *et al*., 2004). The myotonia can last seconds to minutes but the weakness may persist for hours and occasionally days. Paradoxical myotonia that worsens with exercise can be demonstrated at the bedside in most patients (Trivedi *et al*., 2008). Muscle hypertrophy is less frequent than in myotonia congenita but in our recent series we found it to be present in ~30% of patients (Matthews *et al*., 2008*b*).

Sodium channel myotonia

In 1987, prior to the availability of genetic testing, it was observed that there was a group of myotonic patients who seemed clinically distinct from either myotonia congenita or paramyotonia congenita. The first kindred reported exhibited autosomal dominant inheritance of a phenotype characterized by cold insensitive painful myotonia that was markedly exacerbated by potassium ingestion. None of the affected family members reported attacks of weakness but all experienced a significant improvement in myotonic symptoms with acetazolamide treatment. The term 'acetazolamide-responsive' myotonia congenita was coined to describe this family (Trudell *et al*., 1987; Ptacek *et al*., 1994). Subsequent reports described patients with a cold insensitive pure myotonic phenotype who did not experience weakness but whose myotonia fluctuated dramatically and was profoundly worsened by potassium ingestion. Notably the myotonia tended to occur with a more delayed (10–30 min) onset after exercise rather than with the initiation of movement after rest as seen in myotonia congenita, or within seconds of exercise as seen in paramyotonia congenita. This phenotype was classified as myotonia fluctuans (Ricker *et al*., 1990, 1994; Lennox *et al*., 1992). The term myotonia permanens was introduced to describe patients with a third clinical variant characterized by very severe persistent myotonia which significantly impaired respiration (McClatchey *et al*., 1992*b*; Lerche *et al*., 1993). These three purely myotonic disorders shared the potassium aggravation and the absence of sensitivity to cold. Together they have become known as the potassium aggravated myotonias. Additional pure myotonic phenotypes have been described but these differ from the potassium aggravated myotonia phenotypes in that they have been reported to be cold-sensitive (Heine *et al*., 1993; Koch *et al*., 1995; Wu *et al*., 2001). All these pure myotonic phenotypes have now been shown to be caused by allelic point mutations in the gene encoding *SCN4A*.

We consider that from a practical clinical viewpoint a simplified classification of sodium channel myotonic disorders into two broad groups based on the presence or absence of episodic weakness is helpful:

Group 1 Paramyotonia congenita—characterized by a marked worsening of myotonia by cold and by the presence of clear episodes of weakness;

Group 2 Sodium channel myotonia—notable for the absence of episodic weakness but may have cold sensitivity. This includes all the pure myotonic phenotypes, including the potassium aggravated myotonias (Fournier *et al*., 2004, 2006).

Distinguishing chloride from sodium channel myotonias is often possible on clinical grounds alone as indicated in Table 1. However, difficulty may arise as some cases with sodium channel myotonia may have clinical features that are very similar to those seen in some cases of dominant myotonia congenita (see Table 1). For example, sodium channel myotonia may exhibit the presence of the warm up phenomenon, have minimal or absent sensitivity to cold, and have an upper limb/facial distribution of myotonia that is indistinguishable from dominant myotonia congenita (see Table 1).

In such cases the presence of transient weakness would point to dominant myotonia congenita whereas the presence of eyelid myotonia is more suggestive of sodium channel myotonia (Trip *et al*., 2009*b*). In addition specialized electrophysiological protocols can be helpful.

Myopathy

Myopathy may develop in some patients with non-dystrophic myotonia (Becker, 1977; Plassart *et al*., 1996; Nagamitsu *et al*., 2000). In a series of 49 genetically confirmed paramyotonia congenita cases, 'myopathic biopsy findings' were reported in 33% of those biopsied although full clinical details of the degree of weakness were not available (Miller *et al*., 2004). Permanent severe myopathy seems to be more common in patients with periodic paralysis than in the non-dystrophic myotonias (Miller *et al*., 2004). In periodic paralysis it has been postulated that the severity of myopathy may not relate to paralytic attack frequency (Buruma *et al*., 1978; Links *et al*., 1990) but the exact relationship remains unclear. There is some evidence that the severity of myopathy associated with periodic paralysis does correlate with increasing age (Links *et al*., 1990; Plassart *et al*., 1994). It is not known if a similar relationship between age and severity of myopathy exists in the non-dystrophic myotonias or if symptom frequency or severity has a direct influence on the development of myopathy. In periodic paralysis there is some evidence that the frequency of paralytic attacks may decline with age (Miller *et al*., 2004). However, it is not established if myotonia severity alters over time in patients with non-dystrophic myotonia. Importantly, there are no published studies to provide accurate detailed data on the natural history of the non-dystrophic myotonias in order to address the above questions. Such a large natural history study is currently in progress as part of the Consortium for Clinical Investigation of Neurological Channelopathies (http://rarediseasesnetwork.epi.usf.edu).

Mechanisms of muscle degeneration

Patients with periodic paralysis have been frequently reported to exhibit vacuoles and/or tubular aggregates on muscle biopsy. However, the myopathological findings in non-dystrophic myotonias are not defined well and are often reported to be non-specific (Miller *et al*., 2004). Furthermore, with the characteristic clinical history and examination findings coupled with the recent advances in electrophysiological techniques a diagnosis of non-dystrophic myotonia is usually apparent and it is now rare that a muscle biopsy will be performed in such patients other than as a research procedure.

It is clear muscle damage can occur in the non-dystrophic myotonias but its pathomechansim and frequency are unknown. It has been postulated that the abnormally prolonged intramuscular

Table 1 **Common clinical features and electrophysiological patterns of the sub-groups of non-dystrophic myotonia**

	Recessive myotonia congenita	Dominant myotonia congenita	Paramyotonia congenita	Sodium channel myotonia
Inheritance	Recessive	Dominant	Dominant	Dominant
Causative gene	*CLCN-1*	*CLCN-1*	*SCN4A*	*SCN4A*
Myotonia distribution	Lower limbs more than upper limbs	Upper limbs more than lower limbs Facial muscles may be involved	Upper limbs and face more than lower limbs	Upper limbs, face and extraocular, more than lower limbs
Myotonia cold sensitivity	None or minimal	None or minimal	Yes—often dramatic	Variable—ranging from none to severe
Warm up phenomenon	Present	Present	Absent	May be present
Paradoxical myotonia	Absent	Absent	Present	May be present
Delayed onset myotonia after exercise[a]	Absent	Absent	Absent	May be present Characteristic of myotonia fluctuans
Episodic muscle weakness	Common, develops on initiation of movement but transient and improves rapidly	Uncommon	Common often exacerbated by cold and/or exercise and frequently prolonged for several hours	Not reported
Eyelid myotonia	Infrequent	Infrequent	Common	Common
Short exercise test without cooling	Early decrement in CMAP with rapid recovery Decrement reduces with repetition (see Fig. 1)	Little or no decrement in CMAP (see Fig. 2)	Gradual and persistent reduction in CMAP enhanced by repetition (see Fig. 4)	No significant change of the CMAP from baseline[b] (see Fig. 3)
Short exercise test with cooling	Cooling has little further effect (see Fig. 1)	Early decrement with rapid recovery and reduction with repetition may be seen (see Fig. 2)	Gradual and persistent reduction in CMAP enhanced further by cooling (see Fig. 4)	No significant change of the CMAP from baseline[b] (see Fig. 3)
Fournier pattern	II	II/III	I	III

a Myotonia typically develops after a short period of exercise e.g. 10 min or on resting after a period of exercise.

b This same pattern may be observed in dominant myotonia congenita. CMAP = compound muscle action potential.

influx of sodium that is known to occur via the mutant sodium channels may be responsible for muscle degeneration (Bradley *et al*., 1990). There is evidence for increased intracellular sodium contributing to cell necrosis in the mouse model of Duchenne muscular dystrophy (Hirn *et al*., 2008). One recent study has employed ultrasound to assess permanent muscle changes in the non-dystrophic myotonias. Using ultrasound measurements of eight muscles (four upper limb and four lower limb), in a group of 63 patients with genetically confirmed non-dystrophic myotonia an increase in the mean echo intensity compared with controls from all muscles examined except the *rectus femoris* was observed. The ultrasound changes were considered to indicate structural muscle damage such as fatty infiltration or fibrosis. This change was most marked in the forearm flexors where the increased echogenicity correlated negatively with muscle power. There was no positive correlation between echo intensity and age for individual muscles except the *rectus femoris* although the sum of the scores did show a significant positive correlation (Trip *et al*., 2009*c*).

Recently, a mouse model of hyperkalaemic periodic paralysis has been engineered by introducing the murine equivalent of the *SCN4A* mis-sense mutation M1592V (Hayward *et al*., 2008). This mutation causes both myotonia and paralysis in humans (Rojas *et al*., 1991; Kelly *et al*., 1997) and was demonstrated to produce the same symptoms in the mouse indicating the validity of the model. At a few months of age the heterozygous mice displayed subtle myopathic changes. In homozygous mice significant muscle abnormalities were seen including an increase in fibre size variability, frequent internal nuclei and large scattered vacuoles. These changes were present before any spontaneous episodes of paralysis had been observed. Furthermore, they were shown to increase with age in the heterozygotes while muscle force generation declined (Hayward *et al*., 2008). These findings support the clinical observations that myopathy increases with age (Links *et al*., 1990; Plassart *et al*., 1994) and that it may be independent of paralytic attacks in the periodic paralyses (Buruma *et al*., 1978; Links *et al*., 1990).

It seems likely that future insights into muscle degeneration gained from the study of this model will also have implications for our understanding of paramyotonia congenita and sodium channel myotonia associated with the same *SCN4A* gene. The possibility that myopathy develops independently of symptom frequency or severity may influence future approaches to therapy which is currently aimed at relieving symptoms. At present many patients with minimal or manageable symptoms decline pharmacological treatment but it is possible that treatment may have a role in preventing subsequent myopathy.

Morbidity in the non-dystrophic myotonias

Very little is known about the impact of non-dystrophic myotonias on quality of life and these disorders have often been regarded as benign. A single study has recently examined this in a group of 62 patients with genetically confirmed non-dystrophic myotonia and found painful myotonia and fatigue to be the best predictors of poor general health perception and physical functioning (Trip *et al*., 2009*a*). In this study painful myotonia was reported in 28% of those with myotonia congenita and 57% with sodium channelopathy. In addition, there are numerous case reports where severe pain is described (Ptacek *et al*., 1994; Rosenfeld *et al*., 1997; Vicart *et al*., 2004; Jorgensen *et al*., 2006; Colding-Fialho *et al*., 2007; Walsh *et al*., 2007; Wang *et al*., 2008*c*). This suggests that pain is a frequent symptom that may have been previously under-recognized and possibly undertreated in the non-dystrophic myotonias.

Clinical electrophysiology

Recently, specialized clinical neurophysiology protocols have aided precise diagnosis in muscle channelopathies by directing genetic testing based on channel-specific electrophysiological patterns. Sarcolemmal excitability can be measured indirectly as the variability of the compound muscle action potential (CMAP) following different stimuli. The CMAP size varies in skeletal muscle channelopathies in response to short (10–20 s) or long (3–5 min) exercise tests (Streib, 1982; McManis *et al*., 1986). Using these exercise protocols in combination with muscle cooling, distinct electrophysiological patterns—termed patterns I, II and III—are now recognized for each of the non-dystrophic myotonia groups (Fournier *et al*., 2004, 2006). For clinical diagnosis the repeat short exercise test with muscle cooling is of great value in the non-dystrophic myotonias.

Patients with chloride channel myotonia can show one of two patterns. The most common is pattern II (Fournier *et al*., 2004) in which at room temperature there is an immediate CMAP decrement after exercise which recovers quickly and diminishes with repetition, reflecting the transient weakness observed clinically (Fig. 1). This pattern is most frequently seen in recessive myotonia congenita but can be observed in any muscle ion channel disorder in which there is a loss of sarcolemmal chloride conductance. It is therefore also seen in dominant myotonia congenita and in both myotonic dystrophy types I and II. That this pattern may be seen in myotonic dystrophy types I and II is not unexpected as there is now clear evidence that the myotonia in these dystrophies is secondary to reduced chloride conductance (Charlet *et al*., 2002). In recessive myotonia congenita cooling has little further effect (Fig. 1). However, in dominant myotonia congenita, the CMAP decrement may be worsened or only seen with cooling (Fournier *et al*., 2006) making it essential to perform the short exercise test at both room temperature and with the muscle cooled (Fig. 2). Occasional patients with dominant myotonia congenita show a normal response [pattern III (Fournier *et al*., 2006)] to all provocative tests, even with muscle cooling which is indistinguishable electrophysiologically from sodium channel myotonia (Fig. 3).

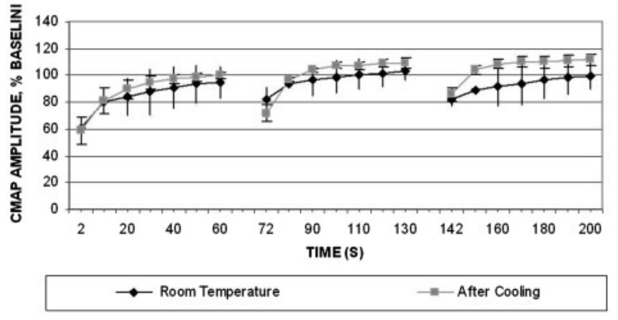

Figure 1 Autosomal recessive myotonia congenita: short exercise test (mean CMAP amplitudes) at room temperature and after cooling.

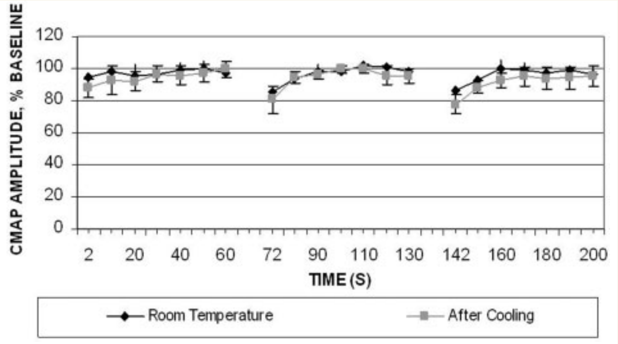

Figure 2 Autosomal dominant myotonia congenita: short exercise test (mean CMAP amplitudes) at room temperature and after cooling.

Patients with paramyotonia congenita typically have a gradual and prolonged decrement in CMAP after exercise, termed pattern I (Fournier *et al*., 2004). This decrement is exacerbated with repeat testing and muscle cooling (Fig. 4) reflecting the clinically observed cold- and exercise-induced weakness. Some genotypes only display this typical pattern when the short exercise test is performed with the muscle cooled (Fournier *et al*., 2006) again emphasizing the importance in diagnosis of performing a short exercise test at both room temperature and with the muscle cooled.

The sodium channel myotonias are separated clinically from paramyotonia congenita by their lack of weakness. This is illustrated by pattern III, normal responses to all provocative tests (Fig. 3) with EMG myotonia as usually the only positive electrophysiological finding. This is the characteristic finding in sodium channel myotonia but is not absolute and there are some variations for certain genotypes (Fournier *et al*., 2006). It is notable that this is the same pattern observed in a minority of cases with dominant myotonia congenita.

The similarities between sodium channel myotonia and dominant myotonia congenita can lead to difficulty in prioritizing genetic testing. Clinical history and examination considered in

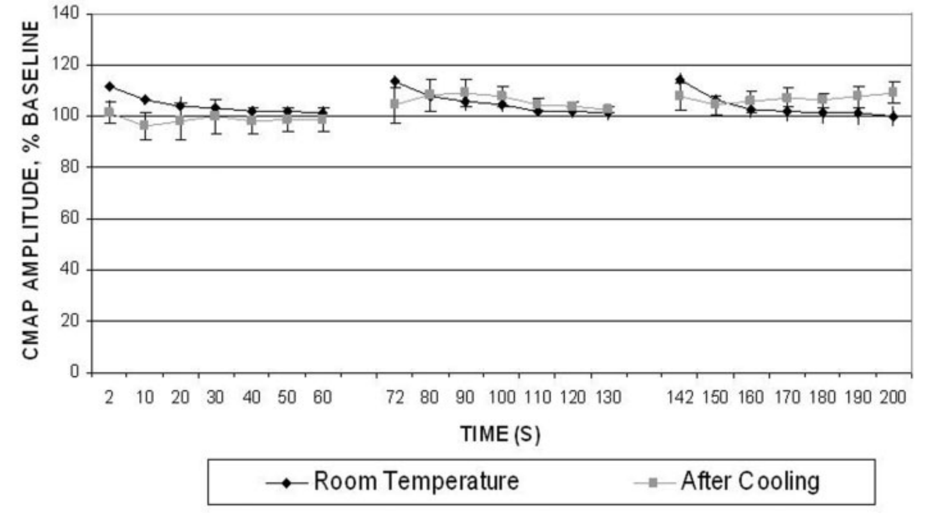

Figure 3 Sodium channel myotonia: short exercise test (mean CMAP amplitudes) at room temperature and after cooling

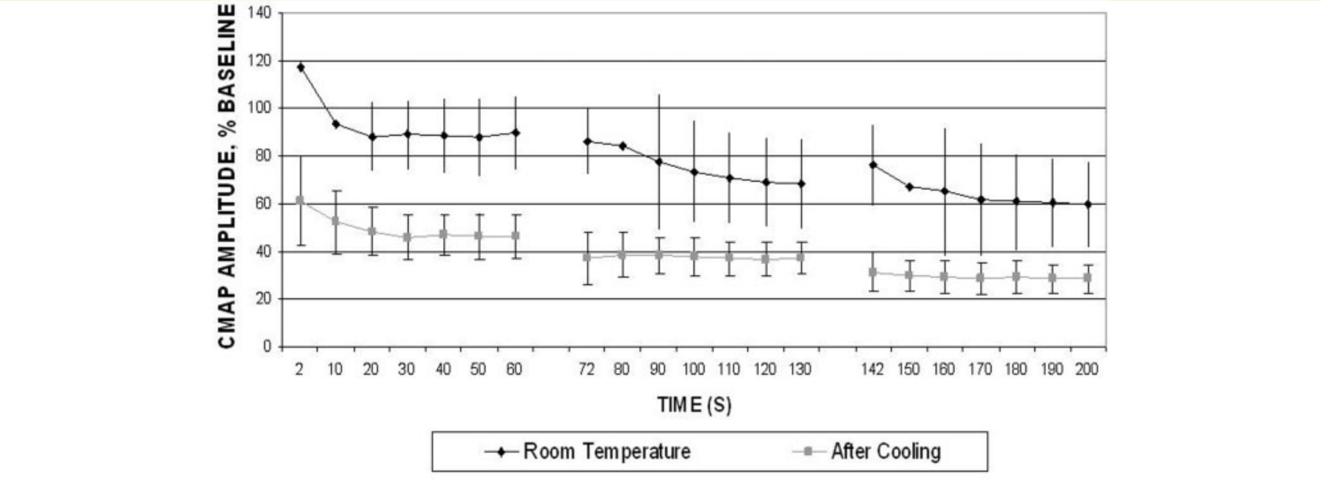

Figure 4 Paramyotonia congenita: short exercise test (mean CMAP amplitudes) at room temperature and after cooling.

conjunction with EMG findings (see Table 1) can improve the ability to distinguish between the two and guide genetic analysis, but in some cases screening of both the *CLCN-1* and *SCN4A* genes will be required.

Variability exists in the response of the non-dystrophic myotonia subgroups to exercise testing and where muscle cooling has already proven useful in improving diagnosis, repetitive nerve stimulation may have a future role to play in distinguishing the sub-types of non-dystrophic myotonia. There is some evidence that a reduction in CMAP may be provoked by repetitive nerve stimulation in certain cases of recessive myotonia congenita where exercise testing even with the muscle cooled has failed to produce any such decrement (Michel *et al*., 2007). In this way, repetitive nerve stimulation may become an additional future tool to guide the genetic analysis towards recessive myotonia congenita, in cases that may otherwise be thought to be dominant myotonia congenita or sodium channel myotonia. There is currently no distinguishing electrophysiological test for myotonic dystrophy type II and this diagnosis should be considered for patients with a myotonic disorder in whom no mutations are found in *CLCN-1* or *SCN4A*.

Genetics

Skeletal muscle chloride channel

Recessive and dominant myotonia congenita are caused by mutations in the voltage gated chloride channel gene on chromosome 7q35. (Koch *et al*., 1992; George *et al*., 1993). The functional chloride channel exists as a dimeric structure with two gating pores. To date, over 100 missense, non-sense, insertions, deletions and splice site mutations have been identified throughout *CLCN-1*. Many patients carry ‘private’ mutations. It is a particular feature of myotonia congenita that several mutations have been reported to be inherited in both an autosomal dominant and autosomal recessive manner in different families (George *et al*., 1994; Meyer-Kleine *et al*., 1995; Zhang *et al*., 1996; Papponen *et al*., 1999; Sun *et al*., 2001). The advent of molecular genetic testing has demonstrated that familial non-dystrophic myotonia with dominant inheritance is often caused by missense mutations in *SCN4A*. Those *CLCN-1* mutations that do cause dominant myotonia congenita seem to cluster in exon 8 of the gene (Fialho *et al*., 2007)

A recent report indicates that there is a higher frequency of recessive *CLCN-1* mutations in myotonic dystrophy type II patients from Finnish and German populations. In the cases described, co-segregation of the CCTG expansion in the first intron of *zinc finger protein-9* and a *CLCN-1* mutation produced more severe myotonia than is commonly encountered in myotonic dystrophy type II. However, the number of cases was too small for this finding to be statistically significant (Suominen *et al*., 2008). It is therefore not yet established if the presence of a *CLCN-1* mutation is a genetic modifier of the myotonic dystrophy type II phenotype. This is an attractive hypothesis since both genetic changes would be predicted additively to impair chloride channel function. These findings also suggest that analysis of the myotonic dystrophy type II gene expansion should be considered in patients with myotonia only harboring a single recessive *CLCN-1* mutation.

Skeletal muscle sodium channel

Hyperkalaemic periodic paralysis was the first of the sodium channel disorders to be linked to the *SCN4A* gene on chromosome 17 which encodes the skeletal muscle voltage gated sodium channel Nav1.4 (Fontaine *et al*., 1990; Koch *et al*., 1991*b*; Ptacek *et al*., 1991*c*). Given some of the shared clinical features of hyperkalaemic periodic paralysis and paramyotonia congenita and the recognition of abnormal sodium conductance in both (Lehmann-Horn *et al*., 1981, 1987*a*, *b*) it was proposed and subsequently confirmed that paramyotonia congenita and hyperkalaemic periodic paralysis were allelic disorders (Koch *et al*., 1991*a*; Ptacek *et al*., 1991*a*, *b*; Rojas *et al*., 1991; McClatchey *et al*., 1992*a*, *b*). Later the phenotypes grouped together as the potassium aggravated myotonias were also shown to be sodium channel disorders (Lerche *et al*., 1993; Ptacek *et al*., 1994; Ricker *et al*., 1994)

All the skeletal muscle sodium channelopathies are autosomal dominant conditions and *de novo* mutations can occur. In a proportion of patients with a phenotype typical for paramyotonia congenita no mutation has been identified in *SCN4A* raising the possibility of further genetic heterogeneity (Miller *et al*., 2004). Virtually all described mutations are missense with the only exception being a three base pair deletion (Michel *et al*., 2007).

Over 40 different mutations including those responsible for periodic paralysis have been reported in the *SCN4A* gene. Exons 22 and 24 are recognized as ‘hot spots’ for paramyotonia congenita, particularly the T1313M mutation and amino acid substitutions at the R1448 position (Matthews *et al*., 2008*b*). The most common sodium channel myotonia mutations are V1589M and those at the G1306 position (Vicart *et al*., 2005).

Genetic diagnosis

Although there are many clinical and electrophysiological indicators to help prioritize genetic testing in the non-dystrophic myotonias the difficulties described in distinguishing sodium channel myotonia from dominant myotonia congenita indicate that a proportion of patients will require screening of both the *CLCN-1* and *SCN4A* genes (Trip *et al*., 2008). In some cases of recessive myotonia congenita, only one *CLCN-1* mutant allele has been identified despite analysis of all coding exons (Trip *et al*., 2008). This indicates that mutations may be present in deeper intronic regions or possibly in promoter regions, although none have been reported. Another possibility is that there may be as yet unidentified large scale deletions in *CLCN-1*. Although it is recognized that some cases diagnosed clinically as non-dystrophic myotonia will have myotonic dystrophy type II, it is not known how frequent this is. Considering the importance of appropriate cardiac evaluation in myotonic dystrophy type II, we suggest that if *CLCN-1* and/or *SCN4A* screening is negative, *zinc finger protein-9* gene analysis should be undertaken.

Genotype–phenotype correlations

Marked phenotypic heterogeneity is common in the skeletal muscle channelopathies even in kindreds with the same mutation. Clinical and electrophysiological findings can help to distinguish between dominant and recessive myotonia congenita but since the same mutation can be inherited in a dominant or recessive manner this doesn’t necessarily narrow the possible genotypes. From a genetic point of view, non-sense mutations, small deletions and insertions leading to frameshift or mutations interrupting splice sites are usually associated with recessive myotonia congenita. However, missense mutations can lead to either recessive or dominant myotonia congenita depending on their location and the effect of the amino acid substitution on channel gating. Dominant mutations are clustered around the dimer interface of the channel (Duffield *et al*., 2003; Fialho *et al*., 2007) but are also found in other regions of the channel. R894X is the most studied mutation causing recessive and dominant myotonia congenita in different families. It is a non-sense mutation located within the C-terminus of the channel. Due to its location within the last exon of the *CLCN-1* gene the mRNA does not undergo the usual non-sense mediated decay typically induced by earlier premature stop-codons. Duno *et al*. (2004) compared two families with dominant myotonia congenita and two families with recessive myotonia congenita carrying the R894X mutation. There was no direct relation between levels of CLCN-1 mRNA and inheritance type excluding differential allelic expression as an explanation for the varying inheritance mode. However, the most severely affected dominant case expressed more than twice the amount of mutant mRNA compared to the recessive families raising the possibility that this may contribute to phenotypic variability particularly within dominant pedigrees (Duno *et al*., 2004).

Paramyotonia congenita and sodium channel myotonia can usually be reliably distinguished from each other by the presence or absence of weakness from clinical and EMG findings. This narrows down the likely genotype to a certain degree but within each group there are still a number of possibilities. Supplementary Table 2 outlines the phenotypes reported for each mutation.

Now, there is evidence that certain *SCN4A* genotypes are associated with a severe neonatal phenotype. A fatal case of myotonia with significant respiratory muscle involvement was described in an infant with a *de novo* N1297K mutation (Gay *et al*., 2008). We observed the I693T mutation linked to spontaneously resolving neonatal hypotonia with variable feeding and respiratory difficulties in four unrelated families (Matthews *et al*., 2008*a*). The recognition that sodium channelopathies may present in such a way is important in order to provide appropriate prenatal advice for mothers known to carry these mutations and neonatal care for their children.

A further example of the phenotypic variability that can be observed with the same genotype is provided by G1306E mutation. The original phenotype reported with this was so severe the individual suffered permanent myotonia that included the respiratory muscles and which lead to hypoxia and acidosis requiring ventilatory support (Lerche *et al*., 1993). In contrast, a more recent report observed that although affected individuals had relatively severe myotonia they did not exhibit respiratory involvement and were able to carry out daily activities including work without treatment (Colding-Jorgensen *et al*., 2006). See Supplementary Table 2 for more detail of phenotypes reported in different kindreds with the same *SCN4A* mutation.

One limitation in studying genotype–phenotype correlations has been the lack of availability of sufficient numbers of individuals carrying each mutation. The large multicentre natural history trial currently being run by the Consortium for Clinical Investigation of Neurological Channelopathies aims to address these issues.

Molecular pathophysiology

In a normal muscle fibre, a single nerve stimulus depolarizes the sarcolemma propagating a single action potential that results in a single muscle contraction followed by rapid relaxation. Myotonia results from an increased excitability of the muscle fibre membrane such that a single electrical stimulus triggers a repetitive train of action potentials.

In myotonia congenita, the enhanced excitability is due to reduced sarcolemmal chloride conductance and was initially demonstrated in muscles of myotonic goats (Lipicky *et al*., 1966; Bryant., 1969) and later in humans (Lipicky *et al*., 1971). Compared with other excitable cells, skeletal muscle has an unusually high chloride conductance, accounting for up to 85% of the resting membrane conductance (Bryant *et al*., 1971). The high chloride conductance is especially important in view of the large size of the muscle fibers which require the T-tubule system to propagate an action potential into the depth of the cell to initiate a synchronous contraction. Although T-tubules are directly connected to the extracellular space, they represent a significant diffusion barrier. Consequently with repeated membrane discharges, a build-up of potassium ions within the T-tubule system due to the repolarizing potassium ion currents increases the probability of additional spikes. The membrane depolarization as a consequence of potassium ion accumulation in the T-tubules is normally counteracted by the chloride conductance.

The chloride channel is an antiparallel assembled homodimer consisting of two identical subunits each with their own ion conducting pore (Fig. 5A). There are two main gating modes referred to as the fast gate, which can open and close the two pores independently, and a slow gating mechanism or ‘common gate’ which causes deactivation of both pores simultaneously. While all chloride channel mutations lead to loss of function, recessive mutations usually exert their effect by loss of function of the

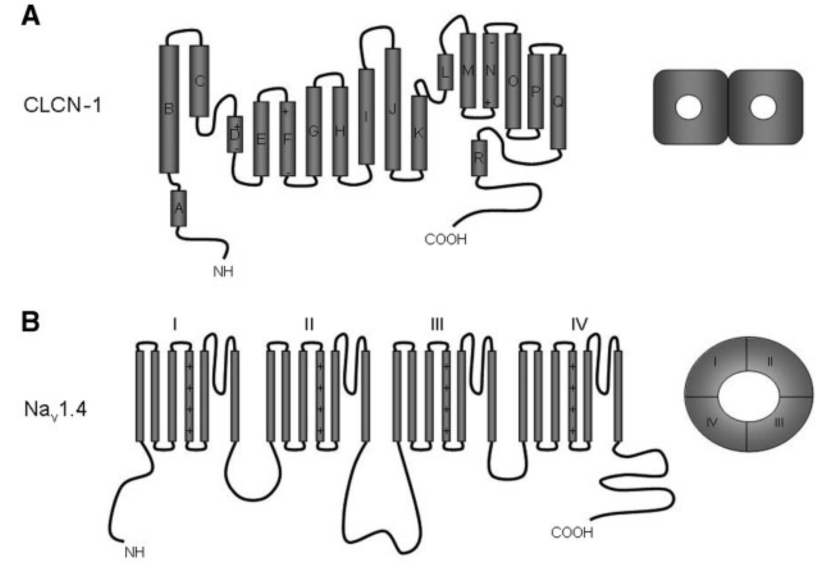

Figure 5 Diagramatic representation of (**A**) *CLCN*-1 and (**B**) Nav1.4 channels.

mutated subunit, while the mutant subunit in dominant disease tends to have an adverse effect on the function of the co-expressed wild-type subunit, i.e. a dominant negative effect (Pusch *et al*., 1995). The majority of dominant myotonia congenita mutations shift the voltage dependence of CLCN-1 to more positive voltages (Pusch *et al*., 1995; Kubisch *et al*., 1998). Using a mathematical model, Barchi (1975) showed that decreasing the chloride conductance to 20% is sufficient to trigger myotonic discharges following a single stimulus. A similar hyperexcitability threshold of 25% was predicted by graded pharmacological inhibition of muscle CLCN-1 conductance (Kwiecinski *et al*., 1988). Clinically, a reduction to 50% does not seem to cause myotonia as evidenced by the majority of asymptomatic carriers of recessive myotonia congenita mutations. However, this assumes a 1:1 allelic expression in these cases, which may not always be the case (Chen *et al*., 1997). Supplementary Table 3 outlines details of known functional effects of all reported *CLCN-1* mutations.

In contrast to the chloride channel, the voltage gated skeletal muscle sodium channel comprises a single ion conducting pore formed by the interaction between four homologous domains (Fig. 5B). All of the mutations associated with paramyotonia congenita and sodium channel myotonia produce ‘gain of function’ defects either by impaired inactivation or enhanced activation of the Nav1.4 channel (see Table 2 Supplementary Data**)**. Impaired inactivation can either involve delayed inactivation or incomplete inactivation. Delayed inactivation of the skeletal muscle sodium channel causes increased excitability of the muscle fibre membrane and myotonia (Yang *et al*., 1994). The increased availability of sodium channels immediately after an action potential renders the fibre susceptible to sustained trains of repetitive discharges (Cannon, 2000), the electrophysiological hallmark of myotonia. In contrast to the repetitive firing seen in myotonia, the paralytic attacks experienced in paramyotonia congenita and in the allelic disorder hyperkalaemic periodic paralysis, are caused by episodic loss of fibre excitability. This sustained depolarization of the resting potential is due to sodium channels that do not inactivate completely, thereby conducting a persistent inward sodium current that depolarizes the fibre. (Bendahhou *et al*., 2002; Cannon, 2006).

Sodium channels also undergo a second, mechanistically distinct form of inactivation on a much slower time scale of seconds termed slow inactivation. Defects of slow inactivation increase the propensity for depolarization-induced attacks of weakness, and missense mutations of *SCN4A* that disrupt slow inactivation always result in a paralytic phenotype (Hayward *et al*., 1999).

Animal models

There are several animal models of myotonia congenita. The myotonic goat was bred by Dr H. H. Mayberry in Tenessee in the 1800s. This myotonic goat has been shown to harbour an alanine to proline substitution in the carboxyl terminus of the chloride channel (Beck *et al*., 1996). Other animal models include the arrested development of righting mouse which is caused by an insertion of a transposon element (Steinmeyer *et al*., 1991). More recently two different myotonic canine models have been described; the miniature Schnauzer and the Australian cattle dog with recessive missense mutations in *CLCN-1* (Rhodes *et al*., 1999; Finnigan *et al*., 2007). The small size of the myotonic mouse makes it a difficult model upon which to undertake *in vivo* electrophysiology. Muscles from myotonic goats were very useful in the early experiments to elucidate the pathophysiology of myotonia congenita. However, in view of the substantial resource implications of goat care, goats are not considered ideal as a potential model for therapeutic trials. The maintenance of the myotonic dog models is also a major undertaking, but since many other canine models of disease have been extensively studied, greater technical experience is available indicating that myotonic dogs may be a more attractive model for future studies including therapeutic trials.

Hyperkalaemic periodic paralysis has been described in quarter horses. A single point mutation has been identified in the equine skeletal muscle sodium channel gene that substitutes a phenylalanine for a leucine in the DIV/S3 segment of the protein (Rudolph *et al*., 1992). Recently a mouse model of hyperkalaemic periodic paralysis was successfully engineered by introducing the equivalent of the common human M1592V mutation into the murine SCN4A gene (Hayward *et al*., 2008). The mouse was shown to display similar clinical and biopsy findings to those seen in human cases of hyperkalaemic periodic paralysis validating it as a reasonable animal model. New insights into the beneficial effects of elevated extracellular calcium levels and detrimental effects of impairing the sodium/potassium pump in the pathophysiology of hyperkalaemic periodic paralysis have already been determined (Hayward *et al*., 2008). This knock-in mouse offers potential for developing an increased understanding of the pathophysiology of hyperkalaemic periodic paralysis and possibly the development of future therapies.

Although hyperkalaemic periodic paralysis is allelic to paramyotonia congenita and sodium channel myotonia, no such phenotypes have been described in animal models. Myotonia does occur in horses but in conjunction with multisystem defects; the phenotype seems more like one of equine myotonic dystrophy (Reed *et al*., 1988).

Treatment

For those patients with mild symptoms no specific drug treatment may be needed, although it is important to provide advice regarding the avoidance of precipitating factors such as cold exposure or strenuous exercise. In those patients with significant symptoms and disability from myotonia, a variety of agents have been suggested which we outline in chronological order.

In early studies, procainamide, quinine and glucocorticosteroids were employed. A small randomized double blind trial compared the efficacy of each of these treatments in relation to placebo in 20 individuals with myotonic disorder (16 myotonic dystrophy, 4 myotonia congenita). The diagnosis was made on a clinical basis without genetic confirmation. The trial lasted 12 weeks and all participants received each of the four treatments for a 3 week period with no washout period. An end-point of at least a 50% reduction in the duration of hand grip myotonia, measured by EMG and timed clinically, was employed. Using this endpoint, 6/20 participants taking quinine, 15/20 taking procainamide, 15/19 taking prednisone (one patient did not receive prednisone) and 0/20 taking placebo showed improvement (Leyburn and Walton, 1959). This study, although imperfect, illustrated a low efficacy of quinine. Despite the suggested benefits of procainamide and prednisone the side effect profile of both these drugs restricts their use and they are no longer recommended as therapeutic agents in the non-dystrophic myotonias.

The carbonic anhydrase inhibitor acetazolamide is commonly used in the periodic paralyses and has been reported to be beneficial in the non-dystrophic myotonias (Trudell *et al*., 1987; Ferriby *et al*., 2006). In a small series of nine patients with myotonia, seven diagnosed clinically with myotonia congenita and two with paramyotonia congenita, all cases reported a subjective and objective (timed measurements of myotonia) improvement in myotonia with acetazolamide. However, one individual with paramyotonia congenita developed quadrapareses 12 h after the ingestion of acetazolamide (Griggs *et al*., 1978). Larger studies of acetazolamide use in the non-dystrophic myotonias have not been performed, and while there is evidence of some benefit, it is not generally considered as a first line agent for the treatment of myotonia.

Anti-convulsants, local anaesthetics and anti-arrhythmic drugs which block sodium channels are the most frequently used agents in the treatment of myotonia. There are currently no safe drugs which specifically act on the chloride channel CLCN-1 (Verkman *et al*., 2009). Phenytoin has been shown to improve the righting time of myotonic mice turned onto their backs (Aichele *et al*., 1985). Ricker *et al*. (1978) reported subjective improvement in muscle stiffness and an improved timed walk in one patient with myotonia congenita and a dose dependant improvement in isometric force in another. The lignocaine derivative tocainide gave encouraging results initially (Rudel *et al*., 1980; Streib, 1987) but was eventually withdrawn from the market due to the risk of potentially fatal agranulocytosis (Volosin *et al*., 1985). Synthesis of tocainide analogues has been attempted *in vitro* and it may be of value for future study as anti-myotonic agents if the efficacy and side effect profiles are favourable (Catalano *et al*., 2008).

More recently class I anti-arryhthmics have offered potential for treatment. Flecainide, a class Ic anti-arrhythmic, has been shown to be effective *in vitro* (Aoike *et al*., 2006) although its use in clinical practice as an anti-myotonic agent is rarely reported (Rosenfeld *et al*., 1997). An improvement in clinical symptoms and cold induced EMG findings with propafenone, another class Ic anti-arrhythmic has been reported in a single case of paramyotonia congenita (Alfonsi *et al*., 2007).

The class Ib anti-arrhythmic mexiletine is generally considered to be the first-line treatment of choice by myologists but a randomized controlled trial is required. It is usually well tolerated with only minor side effects reported. Importantly it has pro-arrhythmic potential and therefore pre- and post-treatment ECGs are essential to ensure satisfactory QT interval. More extensive cardiac evaluation prior to commencement is important if there is an abnormal baseline ECG or a history of cardiac disease. Single case reports have shown that mexiletine is effective in treating myotonia in both sodium and chloride channel disorders (Ceccarelli *et al*., 1992; Jackson *et al*., 1994). However, a recent Cochrane review highlighted the lack of adequate randomized double blind placebo controlled trials to prove efficacy (Trip *et al*., 2006). The ability to conduct such trials is partly hampered by the difficulty in quantitating myotonia (Torres *et al*., 1983; Hammaren *et al*., 2005; Logigian *et al*., 2005; Moxley *et al*., 2007; Hogrel, 2009) and in recruiting adequate numbers of patients to achieve statistical power. A recent study employed trunk sway analysis to measure the warm up phenomenon in recessive myotonia congenita and proposed that with further evaluation this may offer an alternative potential end-point for therapeutic trials (Horlings *et al*., 2009).

Sodium MRI has also recently been proposed as a possible outcome measure in patients with sodium channel diseases. An increase in intramuscular sodium content was demonstrated to accompany muscle weakness following exercise of cooled muscles in paramyotonia congenita. In a small group of patients this increase was significantly reduced following treatment with mexiletine (Weber *et al*., 2006). It is possible this technique could be used to monitor response to treatment in both a clinical and research setting. The Consortium for Clinical Investigation of Neurologic Channelopathies is currently performing a double-blind, placebo-controlled cross-over study of mexiletine for non-dystrophic myotonias (see clinicaltrials.gov) and will study 60 subjects with paramyotonia congenita and myotonia congenita. The primary endpoint measurement is patient stiffness as reported in the interactive voice response system (Wang, 2008*c*). The interactive voice response was chosen as the primary endpoint for this study as quantification of myotonia using handgrip devices has not consistently demonstrated the delayed relaxation phenomenon in patients with non-dystrophic myotonia (Wang, 2008*c*). It is hypothesized that patients' self-reported responses of stiffness will be a more consistent and reliable endpoint measurement in order to determine efficacy of drug response.

In vitro studies continue to identify pharmacological agents that preferentially block sodium channels in the open state, thereby targeting persistent sodium currents (Wang *et al*., 2008*a*, *b*). These studies may identify future therapies.

No drugs are available which specifically act on the *CLCN-1* channel. A number of experimental approaches may have future implications for the treatment of myotonia congenita (Cleland *et al*., 2008). It has been shown that alternative splicing of the *CLCN-1* gene contributes to the myotonia in myotonic dystrophy type I and that directed anti-sense morpholino oligonucleotides to skip exon 7a restores chloride channel function and abolishes myotonia in a mouse model of myotonic dystrophy type I (Wheeler *et al*., 2007). It is possible that the development of this technique and its delivery could be a potential treatment for those cases of myotonia congenita due to splice site mutations.

Trans-splicing is a natural form of RNA processing where exons from two separate RNA transcripts are joined together. This can be manipulated to restore normal RNA processing of a mutant transcript. Such a technique has been employed using a *trans*-splicing ribozyme to restore a mutant chloride channel transcript in a cellular model. Although a good recovery of chloride channel function was observed in individual cells the efficiency of RNA repair in the cell culture as a whole was only 1.2% (Rogers *et al*., 2002).

Improving defective CLCN-1 channel protein transport from the endoplasmic reticulum to the Golgi apparatus is another potential therapeutic strategy. Defective transport has been demonstrated for the F413C and A531V *CLCN-1* mutations associated with recessive myotonia congenita (Papponen *et al*., 2008). Furthermore, functional expression of the F413C mutation *in vitro* showed only a minimal shift in chloride conductance (Zhang *et al*., 2000). This suggests that if the protein could be restored to the muscle membrane, this may result in an at least partial restoration of chloride conductance. Pharmacological therapies need to be developed that promote correct trafficking and which also build on the partial success of trans-splicing techniques safely.

It remains to be established if more specific therapies will not only reduce myotonic symptoms but, if given prophylactically, will also reduce the probability of developing a fixed myopathy.

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Supplementary material

Supplementary material is available at Brain online.

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Appendix 1

This report summarizes the findings presented at the International Conference on Non-Dystrophic Myotonias (Kansas, June 2007). The conference was generously supported by a National Institutes of Health conference grant [R13 NS057 995].

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Anthony Amato (Brigham and Women's Hospital), Marianne Arzel-Hezode (Pitie-Salpetriere, France), Tetsuo Ashizawa (University of Texas), Richard Barohn (University of Kansas), Brian Bundy (DTCC, Florida), Steve Cannon (University of Texas Southwestern), Yoon-Hee Cha (UCLA), James Cleland (University of Rochester), John Day (University of Minnesota), Robert Dirksen (University of Rochester), Christoph Fahlke (Institute of Neurophysiology, Hannover, Germany), Doreen Fialho (Institute of Neurology, UK), Bertrand Fontaine (Pitie-Salpetriere, France), Alfred L. George (Vanderbilt University, Nashville), Tracey Graves (Institute of Neurology, UK), Robert Griggs (University of Rochester), Angelika Hahn (London Health Science Centre, Canada), Michael G. Hanna (Institute of Neurology, UK), Laura Herbelin (University of Kansas), Barbara Herr (University of Rochester), Jeffrey Krischer (DTCC, Florida), Robert Layzer (University of California), Emma Matthews (Institute of Neurology, UK), Giovanni Meola (University of Milan, Italy), Richard T. Moxley III(University of Rochester), Shree Pandya (University of Rochester), Ming Qi (University of Rochester), Sanjeev Rajakulendran (Institute of Neurology, UK), Jeffrey Ralph (University of California), Mohammed Salajegheh (Brigham and Women's Hospital), David Saperstein (University of Kansas), Patty Smith (University of Rochester), Damien Sternberg (Pitie-Salpetriere, France), Rabi Tawil (University of Rochester), Charles Thornton (University of Rochester), Susie Tomlinson (Institute of Neurology, UK), Jaya Trivedi (University of Texas Southwestern), Paul Twydell (University of Rochester), Shannon Venance (London Health Science Centre, Canada), Julio Vergara (University of California), Savine Vicart(Pitie-Salpetriere, France), Ronan Walsh (Brigham and Women's Hospital), Yunxia Wang (University of Kansas), Thurman Wheeler (University of Rochester).