# Hereditary nondystrophic myotonias and periodic paralyses

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The hereditary disorders of muscle excitability are now recognized to be caused by defects in the genes encoding muscle ion channels. This led to a new classification of this disease group. The pathophysiology of these disorders has been elucidated on the molecular level to an extent that exceeds the understanding of the disease mechanisms of most other neuromuscular diseases. The seemingly minor variants of the symptom of myotonia were found to be caused by the remarkable difference that either chloride or sodium channel function is impaired. Even more surprising, the basic defects for hyper- and hypokalemic periodic paralysis, often clinically very difficult to distinguish, turned out to be in the sodium and calcium channels, respectively; these channels are considered to have very different functions in muscle physiology. Three new types of myotonic disease, that is, myotonia, fluctuans, myotonia permanens and proximal myotonic myopathy were discovered. An explanation has been provided as to why myotonia congenita may be transmitted as a dominant or recessive trait.

Current Opinion in Neurology 1995, **8**:402–410

## Introduction

The hereditary nondystrophic myotonias and periodic paralyses have only recently been grouped together. Formerly, myotonia and paramyotonia congenita were lumped with myotonic dystrophy, whereas the periodic paralyses were sometimes dealt with under metabolic diseases. The new classification was made on the basis of the understanding that the nondystrophic myotonias and periodic paralyses are all caused by mutations in genes that code for muscle chloride, sodium, or calcium ion channels and this has also led to the new designations of 'ion channel diseases' or 'channelopathies' for this group [1,2].

Clinical studies, pharmacology, in-vitro electrophysiology, genetic linkage studies and molecular biology have contributed to an elucidation of the pathophysiology of the ion channel diseases. In particular, the affected genes, the various mutations and the gene products are all known for the prominent members of the group, that is, autosomal dominant and recessive myotonia congenita (Thomsen and Becker myotonia), paramyotonia congenita (Eulenburg), and hyperkalemic and hypokalemic periodic paralysis. Moreover, three new types of myotonic disease were discovered by the combined use of molecular biological methods and refined clinical examination. Thus, myotonia fluctuans was separated from dominant myotonia congenita [3], myotonia permanens from the Schwartz–Jampel syndrome [4], and proximal myotonic myopathy from myotonic dystrophy [5••,6]. Table 1 provides an overview of the whole group.

**Table 1.** Muscle ion channel diseases: myotonias and periodic paralyses.

| |
|---|
| **Chloride channel diseases** |
| Myotonia congenita |
| Dominant (Thomsen) |
| Recessive (Becker) |
| **Sodium channel diseases** |
| Hyperkalemic periodic paralysis |
| Paramyotonia congenita |
| Myotonia fluctuans |
| Myotonia permanens |
| Acetazolamine-responsive myotonia |
| **Calcium channel diseases** |
| Hypokalemic periodic paralysis |

## Chloride channel diseases: Thomsen's disease, Becker-type myotonia, and deJong's myotonia levior

On the basis of pharmacological experiments, Bryant [7] suggested that the typical sign of myotonia congenita, that is, muscle stiffness, is caused by an abnormally low chloride conductance of the muscle fiber membranes. In agreement with this hypothesis, both the dominant and recessive type of myotonia congenita have now been established to be caused by mutations in *CLCN1*, the gene (on 7q32) encoding the skeletal muscle chloride channel protein, ClC-1 [8].

Fourteen missense mutations, three nonsense mutations, and two deletions in various exons of *CLCN1* have

**Abbreviations**

**ClC-1**—major muscle chloride channel; **DM**—myotonic dystrophy.



 ISSN 1350-7540

been discovered (Figure 1A and Table 2). Six point mutations exert dominant effects; five of them are missense mutations, such as Gly230Glu [13], Pro480Leu [17•], Ile290Met [14•], Gln552Arg [14•], and Gly200Arg [10]; and the sixth is a nonsense mutation which causes truncation at the very end of the protein: Arg894Stop [12]. Pro480Leu is present in Dr Thomsen's offspring; Gln552Arg was found in a family with myotonia levior, a term coined by deJong for a dominant myotonia variant characterized by mild symptoms, late onset of myotonia and absence of muscle hypertrophy. With the exception of Gly230Glu, which was detected in three Canadian families, each mutation was only discovered in one single family.

The other point mutations, that is, Phe413Cys [8], Val327Ile, Arg496Ser [15], Phe167Leu, Arg300Stop, Arg338Gln [12], Asp136Gly [11•], Gln74Stop, Tyr150Cys, Tyr261Cys, and Ala415Val [10] and the 4bp [11•] and 14 bp deletions [17•] were detected in (approximately 60) Becker-type patients. The majority of them were heterozygous for a mutation and supposed to carry a second, not yet identified mutation. Only thirteen index patients, most of them offspring of consanguinous parents, were homozygous [8,10,11•,14•,17•] or compound heterozygous [10,14•,15].

Interesting consequences as regards dominant and recessive mode of inheritance follow from the possibility that functional channels are complexes composed of two or four ClC-1 monomers [18••]. The effect of a particular mutation on the inheritance pattern depends on the ability of mutant ClC-1 to interact with other monomers and change the function of the channel complex. Mutant ClC-1 unable to polymerize, for example, severely truncated proteins, allow normal ClC-1 monomers (expressed by the other allele) to form normal complexes, although reduced in number (50%). If there are no compensatory mechanisms effective, clinically normal heterozygous carriers of such mutations would have 50% muscle chloride conductance; effects of such mutations would be recessive. In contrast, mutant ClC-1 able to interact with normal ClC-1 may destroy or change the function of the complex. If all monomers need to be mutants for an effect, mutation of one allele leaves the majority of the complexes functional (75% with dimers, 94% with tetramers) and exerts recessive effects. If one mutant monomer is sufficient for an effect, only a minority of complexes will be functional (25% with dimers, 6% with tetramers). Such mutations exert dominant effects unless the mutant complexes function partially. An interesting hypothesis was deduced from gene dosage effects on the current amplitude of functionally expressed mutant channels [16••]: one monomer of Pro480Leu, the mutation in Dr Thomsen's family, seems to be sufficient to destroy the function of a tetrameric channel complex, whereas two monomers of Gly230Glu, the 'Canadian' mutation, are needed for functional destruction of the complex. It remains to be determined if Gly230Glu and the myotonia levior mutation Gln552Arg are similar in their potency.

ClC-1 is special in that its gene belongs to a novel family not related to any other ion channel gene families,

**Table 2.** *CLCN1* mutations causing dominant and recessive myotonia congentia.

| Domain | Exon no. | Base exchange | Amino acid substitution | Phenotype | Carrier reported | First report |
|---|---|---|---|---|---|---|
| N-T | 2 | C220T | Gln74Stop | Recessive | Homozygous | [10] |
| $1_e$ | 3 | A407G | Asp136Gly | Recessive | Homozygous | [11•] |
| 1/2 | 4 | A449G | Tyr150Cys | Recessive | Compound heterozygous | [10] |
| 2 | 4 | C501G | Phe167Leu | Recessive | Heterozygous | [12] |
| 2/3 | 5 | G598A | Gly200Arg | Dominant | Heterozygous | [10] |
| 3/4 | 5 | G689A | Gly230Glu | Dominant | Heterozygous | [13] |
| 4/5 | 7 | A782G | Tyr261Cys | Recessive | Compound heterozygous | [10] |
| 5/6 | 8 | C870G | Ile290Met | Dominant | Heterozygous | [14•] |
| 5/6 | 8 | G898T | Arg300Stop | Recessive | Compound heterozygous | [12] |
| 6/7 | 8 | G979A | Val327Ile | Recessive | Compound heterozygous | [15] |
| 6/7 | 9 | G1013A | Arg338Gln | Recessive | Compound heterozygous | [12] |
| $8_e$ | 11 | T1238G | Phe413Cys | Recessive | Homozygous/heterozygous | [8] |
| $8_e$ | 11 | C1244T | Ala415Val | Recessive | Homozygous/heterozygous | [11] |
| 8/9 | 12 | 1282-85 | Deletion | Recessive | Homozygous | [11] |
| 9/10 | 13 | C1439T | Pro480Leu | Dominant | Heterozygous | [16•] |
| 9/10 | 13 | 1437-50 | Deletion | Recessive | Homozygous/heterozygous | [17•] |
| 10/11 | 14 | G1488T | Arg496Ser | Recessive | Compound heterozygous | [15] |
| $12_e$ | 15 | A1655G | Gln552Arg | Dominant 'levior' | Heterozygous | [14•] |
| C-T | 23 | C2680T | Arg894Stop | Dominant | Heterozygous | [12] |

C-T, carboxyl-terminal; $_e$, extracellular end; N-T, amino-terminal.

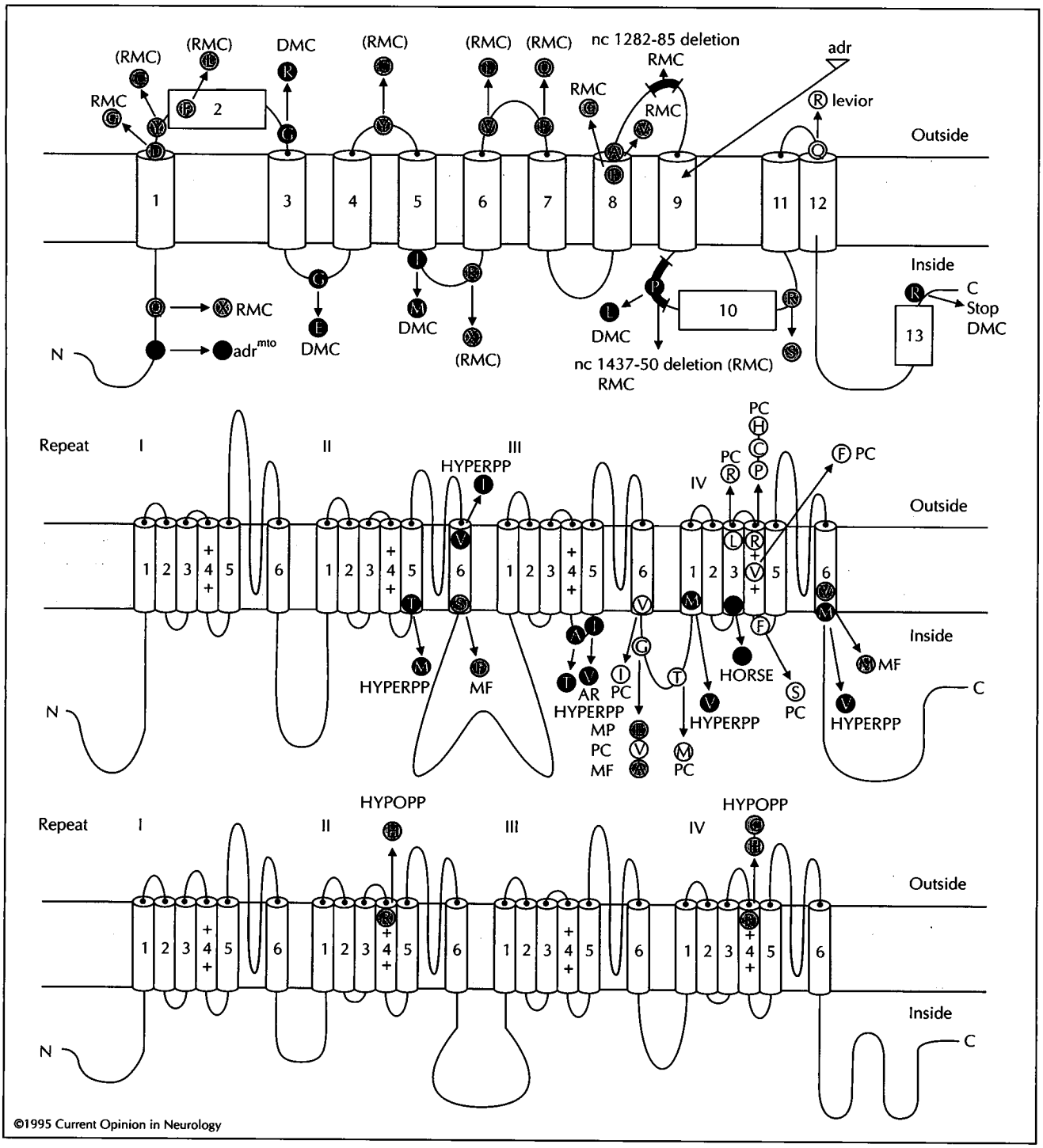


**Fig. 1.** Amino acid changes predicted in voltage-gated ion channel proteins of skeletal muscle (transmembrane segments indicated by cylinders). Abbreviations used in cartoon for chloride channel (upper panel, modified after Middleton *et al.* [9•]): adr, position of insert in adr myotonic mouse; DMC, dominant myotonia congenita; RMC, homozygous mutations in recessive myotonia congenita, (RMC), heterozygous mutations in recessive myotonia congenita. Abbreviations used in cartoon for sodium channel α subunit, center panel): AR, acetazolamide-responsive myotonia; HORSE, position of the mutation causing hyperkalemic periodic paralysis in Quarter horses; HYPERPP, hyperkalemic periodic paralysis; MF, myotonia fluctuans; MP, myotonia permanens; PC, paramyotonia congenita. Abbreviation used in cartoon for calcium channel α1 subunit, lower panel): HYPOPP, hypokalemic periodic paralysis. In all panels the conventional 1-letter abbreviations are used for wild-type and substituted amino acids (indicated by arrows).

including that for epithelial chloride channels (such as the one involved in cystic fibrosis). Studies of naturally occurring mutations leading to myotonia have helped to reveal the functional details of the chloride channel [19•].

## Sodium channel diseases: myotonia fluctuans, myotonia permanens, paramyotonia congenita, and hyperkalemic periodic paralysis

Functional abnormality of the muscle sodium channels in paramyotonia and hyperkalemic paralysis was predicted on the basis of classical electrophysiology before the era of molecular biology [20–23]. Nineteen point mutations discovered in *SCN4A*, the gene encoding the α subunit of the skeletal muscle sodium channel, confirmed this prediction (Figure 1**(b)** and Table 3). Five mutations lead to myotonias (fluctuans, permanens, acetazolamide-responsive), nine lead to paramyotonia congenita, and five lead to hyperkalemic periodic paralysis (Table 3). Some of them are in the part of the gene encoding the loop connecting repeats III and IV, the supposed inactivation gate of the channel. Others situated at intracellular ends of transmembrane segments may be related to the acceptor of the gate at the inner mouth of the pore. Finally, some mutations are in the voltage sensor IVS4 or adjacent transmembrane segments.

Studies on heterologously expressed mutant sodium channels confirmed the early results of incomplete channel inactivation in native fibers and revealed additional mechanisms of sodium channel dysfunction such as shift in gating modes, accelerated recovery from inactivation, increase in window current, and uncoupling of activation from inactivation [36,37,38•–41•] (Fig. 2). Incomplete sodium channel inactivation causes increased sodium membrane conductance and the resulting sodium influx generates depolarization and repetitive action potentials. If depolarization is mild, the result is long-lasting hyperexcitability. If it is strong, the normally functioning sodium channels that are also expressed in these autosomal dominant disorders become inactivated. Thus, the muscle cells become inexcitable, and this is the basis of the muscle weakness. Extracellular potassium had no direct effects on heterologously expressed mutant channels investigated under voltage-clamp conditions [38•–41•]. The myotonia-triggering effect of increased $[K^+]_e$ *in vivo* and in excised muscle fibers [20,21], is probably mediated via membrane depolarization.

### Myotonia fluctuans

Shortly after this disease was first described by Ricker *et al.* in 1990 [42], three mutations in *SCN4A* were found responsible for it, that is, Val1589Met [35,39•], Gly1306Ala [3,4,41•,43], and Ser804Phe [3]. A family

**Table 3.** *SCN4A* point mutations causing hyperkalemic periodic paralysis, paramyotonia congentia, and the sodium channel myotonias myotonia fluctuans and myotonia permanens.

| Genotype | Channel part | Substitution | Exon no. | Phenotype | First report |
|---|---|---|---|---|---|
| **Hyperkalemic period paralysis** | | | | | |
| C2188T | $IIS5_i$ | Thr704Met | 13 | Permanent weakness (non)-myotonic most frequent | [24] |
| G2341A | IIS6 | Val781Ile | 13 | Cardiomyopathy? | [25] |
| G3466A | $(IIIS4/5)_i$ | Ala1156Thr | 19 | Reduced penetrance | [26] |
| A4078G | IVS1 | Met1360Val | 23 | Reduced penetrance | [27] |
| A4774G | $IVS6_i$ | Met1592Val | 24 | Myotonic, frequent | [28] |
| **Paramyotonia congenita** | | | | | |
| G3877A | $IIIS6_i$ | Val1293Ile | 21 | Borderline myotonia | [29] |
| G3917A | $(III/IV)_i$ | Gly1306Val | 22 | Borderline myotonia | [30] |
| C3938T | $(III/IV)_i$ | Thr1313Met | 22 | Frequent | [30] |
| T4298G | IVS3 | Leu1433Arg | 24 | | [31] |
| C4342T | IVS4 | Arg1448Cys | 24 | | [32] |
| G4343A | IVS4 | Arg1448His | 24 | | [32] |
| G4343C | IVS4 | Arg1448Pro | 24 | Atrophy? | [33] |
| G4372T | IVS4 | Val1458Phe | 24 | | [29] |
| T4418C | $IVS4/5_i$ | Phe1473Ser | 24 | | [29] |
| **Sodium channel myotonias** | | | | | |
| C2411T | $IIS6_i$ | Ser804Phe | 14 | Borderline paramyotonia<br>Myotonia fluctuans | [26]<br>[3] |
| A3478G | $(IIIS4/5)_i$ | Ile1160Val | 19 | Acetazolamide-responsive | [34•] |
| G3917A | $(III/IV)_i$ | Gly1306Glu | 22 | Myotonia permanens | [4] |
| G3917C | $(III/IV)_i$ | Gly1306Ala | 22 | Myotonia fluctuans | [4] |
| G4765A | $IVS6_i$ | val1589Met | 24 | | |

Borderline, overlapping two diseases; i, intracellular end.

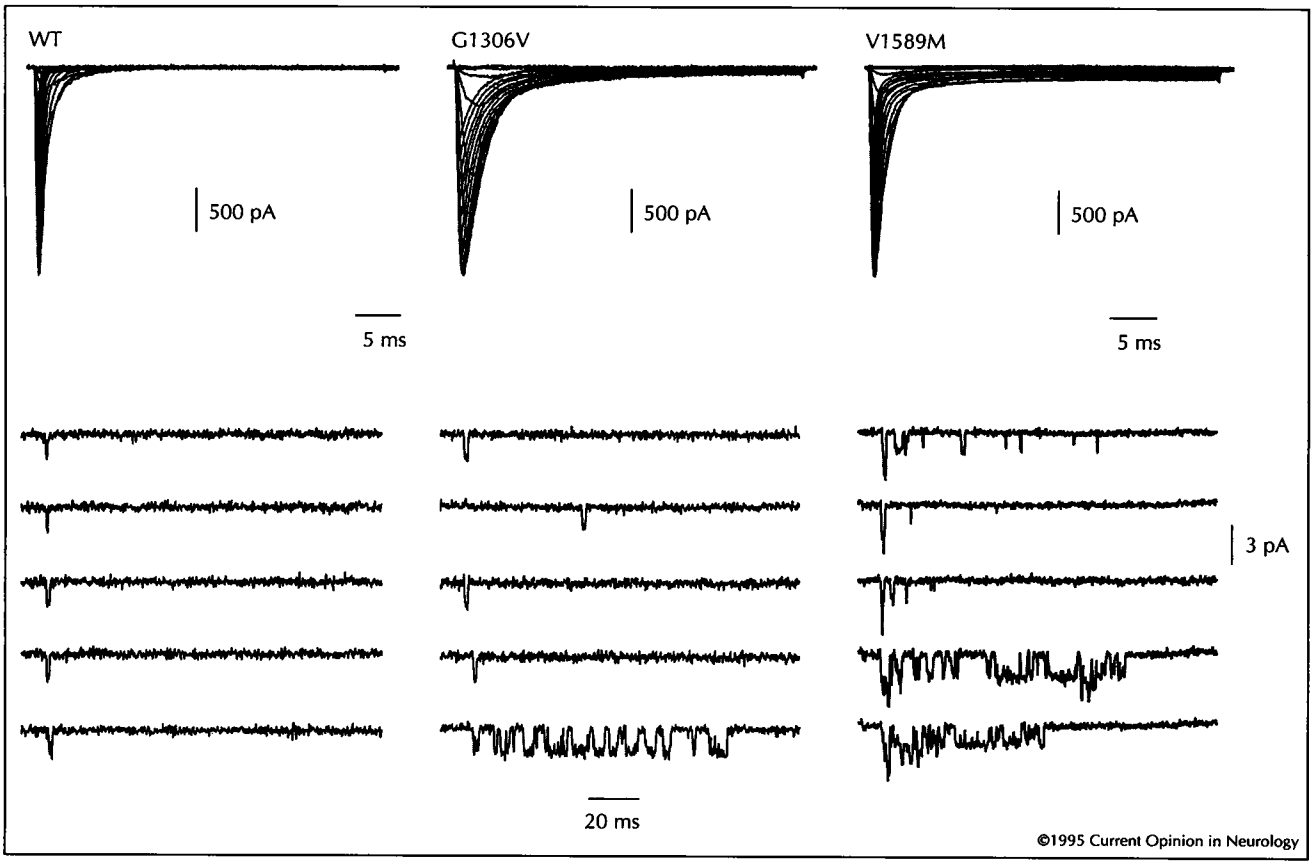


**Fig. 2.** Two examples of faulty inactivation of mutant sodium channels. Patch clamp recordings from normal (wild-type), Gly1306Val and Val1589Met channels expressed in HEK293 cells. Upper panels: families of sodium currents recorded at various test potentials in the whole cell mode show slowed decay and failure to return completely to baseline. Slowed inactivation is more pronounced with Gly1306Val, persistent inward sodium current is larger for Val1589Met. Lower panels: traces of 5 single-channel recordings each obtained by clamping the membrane potential to 20 mV. Mutant channels show re-openings which are the reason for the 'macroscopic' current alterations shown in the upper panels. Modified after Mitrovic [39•,41•].

having mutation Ser804Phe had earlier been described as having features of paramyotonia congenita and myotonia congenita [26]. The clinical signs resemble those of myotonia congenita with the peculiarity that the stiffness tends to fluctuate from day to day. The patients never experience muscle weakness and are not very sensitive to cold as regards muscle stiffness. Their muscle stiffness is provoked by exercise: usually it occurs during rest about half an hour after the exercise and lasts for approximately another hour. Ingestion of potassium aggravates myotonia but does not induce weakness as in hyperkalemic periodic paralysis. Also, other depolarizing agents such as suxamethonium can induce or aggravate myotonia so that severe ventilation problems may occur during general anesthesia because neither the patient nor the anesthetist may be aware of the genetic disposition [3,43,44]. Another subtype, named 'acetazolamide-responsive myotonia' [34•], seems also to belong to this group of sodium channel myotonias.

One of the mutations is in the region coding for the inactivation gate. This site is particularly remarkable because three mutations of the same nucleotide result in a different amino acid substitute for one of a pair of glycines (Gly1306/07) supposed to act as the hinge of the inactivation gate. Length, ramification, and charge of the side-chains in the substitutes correlate with both the degree of membrane hyperexcitability and the clinical phenotype. Alanine, distinguished by a short side-chain, is the substitute in myotonia fluctuans, the most moderate form of sodium channel myotona. Valine, an amino acid with a side-chain of intermediate size, results in paramyotonia congenita (see below), and glutamic acid, an amino acid with a long side-chain and a negative charge, causes myotonia permanens [4,41•].

## Myotonia permanens

The definition of this disease is the consequence of genotyping a patient earlier thought to have a 'myogenic' type of Schwartz–Jampel syndrome [45]; as detected later he was carrying the above-mentioned Gly1306Glu mutation affecting the inactivation gate [4,41•]. Continuous myotonic activity is detectable in the electromyogram of these patients causing persistent severe myotonia. Muscle hypertrophy, particularly in the neck and shoulder, is very marked. During attacks of

severe muscle stiffness the patients suffer from impaired ventilation; they could probably not survive without persisting treatment.

## Paramyotonia congenita

With the new myotonic sodium channel diseases described above it seems necessary to repeat the diagnostic criteria for the classical myotonic disorder first described by Eulenburg, that is, paradoxical myotonia (muscle stiffness that increases with continued exercise), increase of myotonia in the cold, prevailing of myotonia in the face, neck, and distal upper extremity muscles, and weakness induced by prolonged exercise in a cold environment. The weakness may last for several hours, even if the muscles are rewarmed after its onset. In a number of patients the spectrum of symptoms is somewhat different: (i) some experience myotonic stiffness during work even under warm conditions; (ii) in others, cold induces stiffness but no weakness; (iii) still others are immediately paralyzed by cold; and (iv) some patients also experience temperature-independent paralytic attacks, resembling those in hyperkalemic periodic paralysis (see below). These attacks usually begin early in the day and do not last longer than a few minutes. They may be precipitated by oral intake of potassium [46].

Nine of the 19 point mutations detected in different parts of *SCN4A* have been reported to lead to paramyotonia congenita. Three of them involve Arg1448 (situated in segment IVS4) replacing it by histidine, cysteine or proline [32,33,47–49]. A frequent mutation results in Thr1313Met [30,31,50,51] and a less frequent one in Gly1306Val [4,30,51]. Both affect the cytoplasmic loop between repeats III and IV, that is, the inactivation gate. Other mutations predict Leu1433Arg in IVS3 [31], Val1293Ile in IIIS6 [29], Val1458Phe in IVS4 [29], and Phe1473Ser in the intracellular loop connecting S4 and S5 of repeat IV [29].

## Hyperkalemic periodic paralysis

The most common mutation causing hyperkalemic periodic paralysis is Thr704Met. The mutation may cause the myotonic or the non-myotonic form of the disease [24,47,51,52]. In either case progressive myopathy is found in older and sometimes even in younger patients. The second most common mutation, Met1592Val, is always associated with myotonia and does not lead to permanent weakness [28,47,52]. The rare third and fourth mutations, Ala1156Thr [30] and Met1360Val [27] are characterized by incomplete clinical penetrance in females, although 'unaffected' family members show electrical myotonia in the EMG, indicating that penetrance is really 100% [27]. The fifth mutation, Val783Ile, is a sporadic case with hyperkalemic periodic paralysis and cardiac dysrhythmia [25]. One family that was convincingly diagnosed as having hyperkalemic periodic paralysis was not linked to *SCN4A* [47]. Genetic heterogeneity is the most probable explanation.

## Calcium channel disease: hypokalemic periodic paralysis

A systematic genome analysis linked this disease to chromosome 1q31-32 [53•], a region containing the gene encoding the α1 subunit of the L-type calcium channel of skeletal muscle. This subunit is part of the dihydropyridine receptor/calcium channel complex, which is located in the transverse tubular system and consists of 5 subunits: α1, α2/δ, β, and γ. The α1 subunit [Fig. 1(c)] contains the receptor for dihydropyridines and other calcium channel antagonists, the pore and several voltage sensors for excitation–contraction coupling. It is involved in voltage-dependent calcium release from the sarcoplasmic reticulum, mediating contraction [54••]. As in the sodium channel, these voltage sensors are supposed to be in the S4 segments of the protein (Fig. 1(c)).

Three similar mutations, Arg528His and Arg1239His/Gly, in two S4 segments have been detected [55•,56•], the majority of families carrying either Arg528His or Arg1239His [57]. The arginine-to-histidine exchanges seem to enhance inactivation of the L-type calcium channel but, contrary to expectation, do not alter activation [58•,59]. How inactivation of the L-type calcium current is related to hypokalemia-induced attacks of muscle weakness which characterize familial hypokalemic periodic paralysis can only be speculated upon. Because the dihydropyridine receptor has been proposed to act as a calcium channel and as a control device for internal calcium release, both functions may be affected. The hypokalemia-induced membrane depolarization observed in excised muscle fibres [60] might reduce calcium release by inactivating sodium channels as well as by a direct effect on its voltage control.

## Proximal myotonic myopathy

The attempt to genotype patients clinically diagnosed as having myotonic dystrophy (DM) revealed families with normal length of CTG repeats in the DM gene [5••,61,62]. Linkage of the disease in such families to the DM gene, or to the sodium or chloride channel genes was excluded [5••]. Careful clinical evaluation of these patients revealed a nosological entity slightly different from DM. Patients present with myotonia and peculiar muscle pain in early adulthood, later in life develop weakness of the thigh muscles. Muscle wasting is mild or absent. Cataracts indistinguishable from those in DM are frequent. Creatine kinase and gamma-glutamyl transferase may be slightly elevated, immunoglobuline levels slightly reduced. Anticipation or the existence of a congenital form have not been described. Usually, the disease progresses very slowly with muscle weakness developing typically after 30 years

of age. Therefore, Ricker *et al.* [5••,6] coined the term 'proximal myotonic myopathy'.

## Suggestions for diagnosis and therapy

With most of the mutations known, exact diagnosis should now be made by one of the specialized laboratories using molecular biologic methodology. For the few cases that cannot yet be identified, provocative tests are recommended [46]. Muscle biopsy is not specific and patients should be spared the discomfort.

For intermittent or long-term therapy of myotonia, mexiletine is now the drug of choice, if necessary. Long-term medication is needed for myotonia permanens and many Becker myotonia patients. As mexiteline has a narrow therapeutical range, its serum levels should be controlled. Carbamazepine or acetazolamide have also proved successful. yperkalemic periodic paralysis patients should be long-term treated with diuretics lowering serum potassium. Hypokalemic periodic paralysis also responds to carboanhydrase inhibitors such as acetazolamide or diclofenamide.

## Conclusion

With the exception of proximal myotonic myopathy, the mutated genes and their products for all hereditary nondystrophic myotonias and periodic paralyses are now known. Although some research is still directed at finding more mutations by investigating more families, the end of this period of investigation is very close. Currently, construction of the mutant genes and expression in various heterologous systems, such as Xenopus oocytes or human embryonic kidney cells, is carried out in several laboratories for investigation of both the structure–function relationships of the various channels and the detailed pathomechanism of the various diseases. Further detailed clinical investigations of patients, as well as *in vitro* experiments on excised muscle specimens, such as those that have provided so many clues in the times before the advent of molecular biology, might be necessary again for a complete understanding of all facets of this fascinating group of diseases.

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- •• of outstanding interest


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