Hum Genet (1994) 94:551–556

SHORT COMMUNICATION

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Genetic heterogeneity in hypokalemic periodic paralysis (hypoPP)

Received: 5 March 1994 / Revised: 30 April 1994

Abstract Hypokalemic periodic paralysis (hypoPP) is an autosomal dominant disorder belonging to a group of muscle diseases known to involve an abnormal function of ion channels. The latter includes hypokalemic and hyperkalemic periodic paralyses, and non-dystrophic myotonias. We recently showed genetic linkage of hypoPP to loci on chromosome 1q31–32, co-localized with the DHP-sensitive calcium channel CACNL1A3. We propose to term this locus hypoPP-1. Using extended haplotypes with new markers located on chromosome 1q31–32, we now report the detailed mapping of hypoPP-1 within a 7 cM interval. Two recombinants between hypoPP-1 and the flanking markers D1S413 and D1S510 should help to reduce further the hypoPP-1 interval. We used this new information to demonstrate that a large family of French origin displaying hypoPP is not genetically linked to hypoPP-1. We excluded genetic linkage over the entire hypoPP-1 interval showing for the first time genetic heterogeneity in hypoPP.

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Introduction

Periodic paralyses and non-dystrophic myotonias constitute a group of hereditary muscle disorders implicating an abnormal function of ion channels. These ion channelopathies include hypokalemic and hyperkalemic periodic paralysis, paramyotonia congenita, and myotonia congenita.

Hyperkalemic periodic paralysis (MIM 170500, McKusick 1990), paramyotonia congenita (MIM 168300, McKusick 1990) and their variants are transmitted with an autosomal dominant inheritance with complete penetrance and variable expressivity. By a candidate gene approach, these muscle disorders were shown to be caused by allelic mutations of the muscle sodium channel gene SCN4A located on chromosome 17q22–23 (Fontaine et al. 1990; George et al. 1991; Barchi 1992; Ptacek et al. 1993; Fontaine 1993; Hoffman and Wang 1993; Rüdel et al. 1993; Heine et al. 1993; Plassart et al. 1994).

Myotonia congenita displays both autosomal dominant (MIM 160800, McKusick 1990) and recessive (MIM 255 700, McKusick 1990) modes of transmission. By analogy with a murine model of myotonia congenita and using interspecies conservation of syntenic loci, both forms of myotonia were shown to implicate the muscle chloride channel CLCN1 (Abdalla et al. 1992; Koch et al. 1992, 1993; George et al. 1993).

The last member of this group of muscle disorders is hypokalemic periodic paralysis (hypoPP). HypoPP (MIM 170400, McKusick 1990) is of autosomal dominant inheritance. The onset of the disease is usually in the second decade. Patients present with acute and reversible attacks of muscle weakness accompanied by a fall in blood potassium levels. Muscle weakness during attacks is due to the persistent depolarization of the sarcolemmal membrane (Rüdel and Ricker 1985). An abnormal influx of sodium was recorded in muscle fibers of hypoPP patients when decreasing the extracellular level of potassium (Lehmann-Horn et al. 1987). The nature of the abnormal ion channel and the mechanisms leading to hypokalemia

are still unknown. However, sarcolemmal ion channels or the genes regulating their function are candidate genes for the defect. In this context, hypoPP was shown to be non-allelic to the other ion channelopathies (Fontaine et al. 1990, 1991; Casley et al. 1992). Using highly polymorphic dinucleotide repeats, we recently mapped one hypoPP locus (hypoPP-1) to chromosome 1q31–32 co-localized with the α1 subunit of the DHP-sensitive calcium channel (CACNL1A3) in three hypoPP families of European origin (Fontaine et al. 1994). In this article, we present a finer mapping of the hypoPP-1 locus by analysis of extended haplotypes in recombinant individuals with closely linked markers. Moreover, we demonstrate the existence of a second locus in one family of French origin.

Subjects and methods

Clinical evaluation

Family A has already been described by Fontaine et al. (1994). In order to permit comparison with the data reported in Fontaine et al. (1994), we kept the same numbering for the families and the individuals presented in the former article. Therefore, the second family described in this paper was referred to as family D. Diagnostic criteria were those described by Buruna and Schipperheyn (1979), McKusick (1990), and Lehmann-Horn et al. (1993). Clinical characteristics of families A and D are summarized in Table 1 and the pedigrees are shown in Fig. 1.

DNA analysis

Blood samples were collected from all participating individuals after they had given their written informed consent. The protocol of this study was approved by the ethics committee of La Salpêtrière Hospital and is in accord with the 1964 Declaration of Helsinki. DNA was prepared using standard methods (Gusella 1986). Genetic markers and genetic maps used in this study were described in Weissenbach et al. (1992) and Gyapay et al. (1994). The chromosome 1q map with the relative position of the markers is shown in Fig. 2. D1S477, D1S510 and D1S456 (Gyapay et al. 1994) were used in addition to markers typed in Fontaine et al. (1994). The likelihood of the order of the loci and distances were established with odds over 10^3: 1. Genotyping was performed by the polymerase chain reaction (PCR)/blotting technique of Hazan et al. (1992).

Linkage analysis

Pairwise lod scores were calculated using the MLINK program of the LINKAGE package (version 5.1) (Lathrop et al. 1985). The mode of inheritance of the disease was considered to be autosomal dominant with a frequency of 0.0001. To take into account incomplete penetrance in women, penetrances of 100% and 90% were chosen for men and women respectively as described in Fontaine et al. (1994). Lod scores were calculated both with the assumption of equal allele frequencies, and with the allele frequencies determined in C.E.P.H. pedigrees. Lod scores were similar with both methods. Recombination fractions were converted to map distances using the Haldane mapping function. The HOMOG program (version 3.10) was used to test genetic homogeneity (Ott 1991).

Results

Two crucial recombination events bracket the hypoPP-1 locus on chromosome 1

Four markers located between the flanking markers of the hypoPP locus D1S413 and D1S249 (Fontaine et al. 1994) were tested in this study. For families B and C described in Fontaine et al. (1994), no more information was obtained than that reported in Fontaine et al. (1994) (data not shown). As expected in family A, two-point lod scores were positive for all markers located between D1S413 and D1S249 (Table 2). The haplotypes are shown in Fig. 1A. Two affected individuals bear recombinant haplotypes important for localizing the hypoPP locus. The recombinations occurred in individual AII2 (visible in individuals AIII2 and AIII8). The recombination is located telomeric to D1S413 and centromeric to D1S510 for AIII2 and AIII8 respectively (Fig. 1A). The two crucial recombinants localize the hypoPP-1 locus on chromosome 1 within a 7 cM interval flanked by D1S413 and D1S510 (Fig. 2).

In our initial study, an ambiguity remained concerning individual AIII1 (Fontaine et al. 1994). A recombination centromeric to D1S245 occurred in individual AII2 visible in AIII1. AIII1 is a clinically unaffected woman. However, given the known incomplete penetrance of hypoPP in women, we could not discriminate between a recombination centromeric to the hypoPP locus in an affected but asymptomatic woman, or telomeric to the hypoPP locus in an unaffected woman. We clearly show that the recombination event in AIII1 occurred telomeric to D1S456, at a distance from the hypoPP locus. This result is in accord with the unaffected status of AIII1.

Genetic heterogeneity in hypoPP

We first excluded genetic linkage of hypoPP to the muscle sodium channel SCN4A with an intragenic microsatellite

Table 1 Summary of the clinical features

	Family A (n = 15)	Family D (n = 9)
Mean age of onset in years (range)	11 (2–15)	10 (7–15)
Mean duration in years (range)	37 (1–72)	20 (2–53)
Duration of attacks	3 to 60 h	4 to 36 h
Pattern of weakness	Quadriparesia	Quadriparesia
Provocating factors	Exercise Cold Carbohydrates Alcohol	Exercise Cold Carbohydrates
Documented hypokalemia during attacks	n = 4	n =3
Permanent muscle weakness	n =4	n =2
Response to acetazolamide	Positive	Not tested

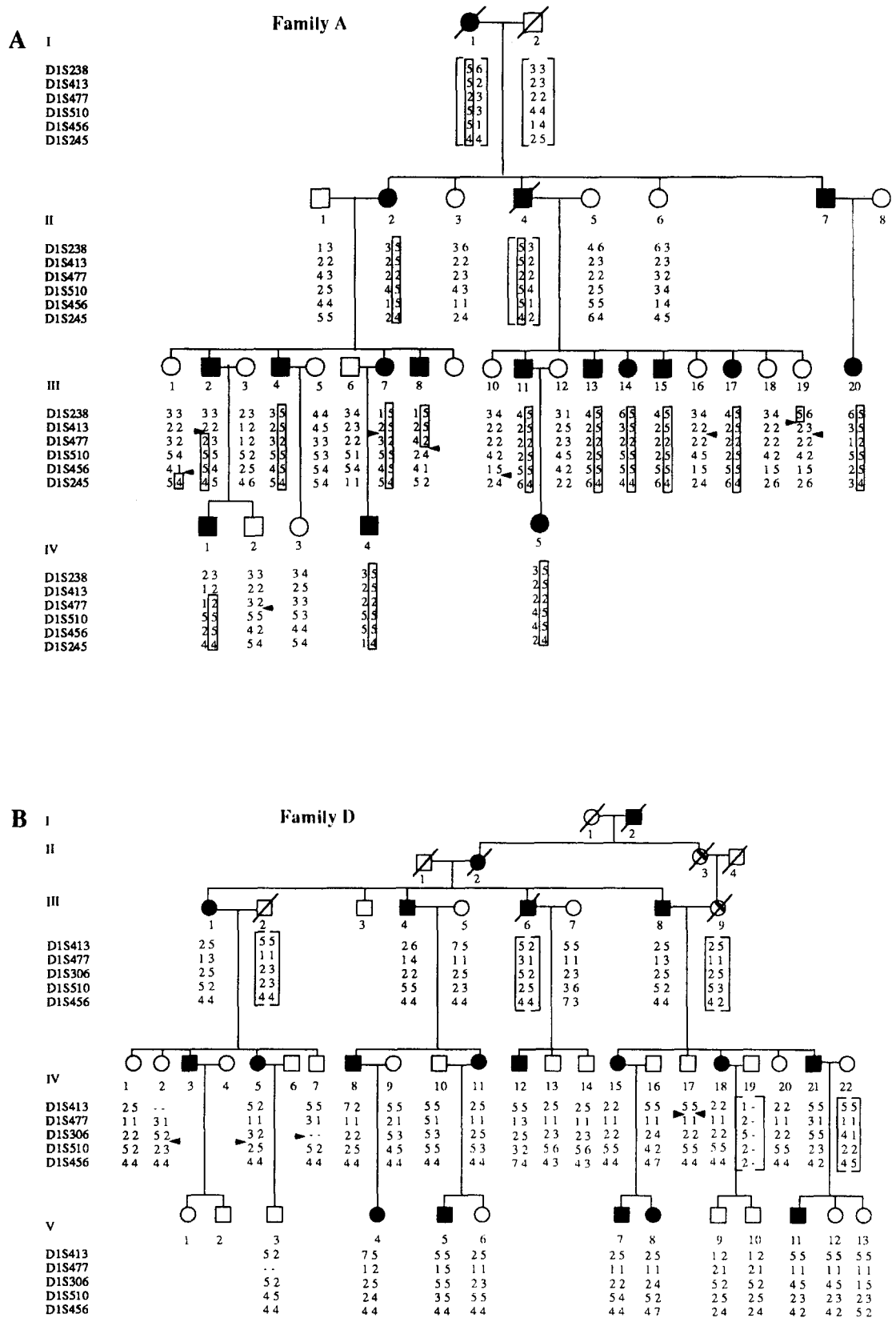

Fig. 1 A,B Pedigrees of two families with hypokalemic periodic paralysis (hypoPP). Affected individuals and unaffected individuals are represented by *black* and *open symbols* respectively. Individuals DII3 and DIII9 were reported to be asymptomatic throughout their life by the other members of the family but no definitive clinical report was available. They are represented by a *hatched symbol* (status unknown in the linkage analysis). Genotypes for microsatellite markers D1S413, D1S477, D1S306, D1S510, D1S456, are shown for both families. Genotypes for D1S238 and D1S245 are indicated only for family A. The haplotype segregating with HypoPP in family A is *boxed*. Haplotypes between *brackets* are deduced. Recombination events are indicated by *arrowheads*

Table 2 Pairwise lod scores between chromosome 1q markers and hypoPP in Families A and D

Locus		Recombination fraction								
		0.00	0.01	0.05	0.10	0.20	0.30	0.40	*t*max	zmax
D1S413	A	$-\infty$	3.83	4.15	3.96	3.19	2.17	0.98	0.05	4.16
	D	$-\infty$	–8.80	–4.87	–3.05	–1.37	–0.59	–0.21		
D1S477	A	1.46	1.44	1.34	1.21	0.92	0.62	0.30	0.01	1.15
	D	$-\infty$	–2.94	–1.64	–1.09	–0.48	–0.15	–0.03		
D1S306	A	Non-informative								
	D	$-\infty$	–6.52	–3.62	–2.36	–1.16	–0.58	–0.25		
D1S510	A	$-\infty$	1.94	2.40	2.37	1.95	1.32	0.56	0.08	2.55
	D	$-\infty$	–8.20	–4.61	–3.02	–1.49	–0.70	–0.25		
D1S456	A	$-\infty$	3.49	3.92	3.82	3.16	2.19	1.00	0.06	3.92
	D	Non-informative								

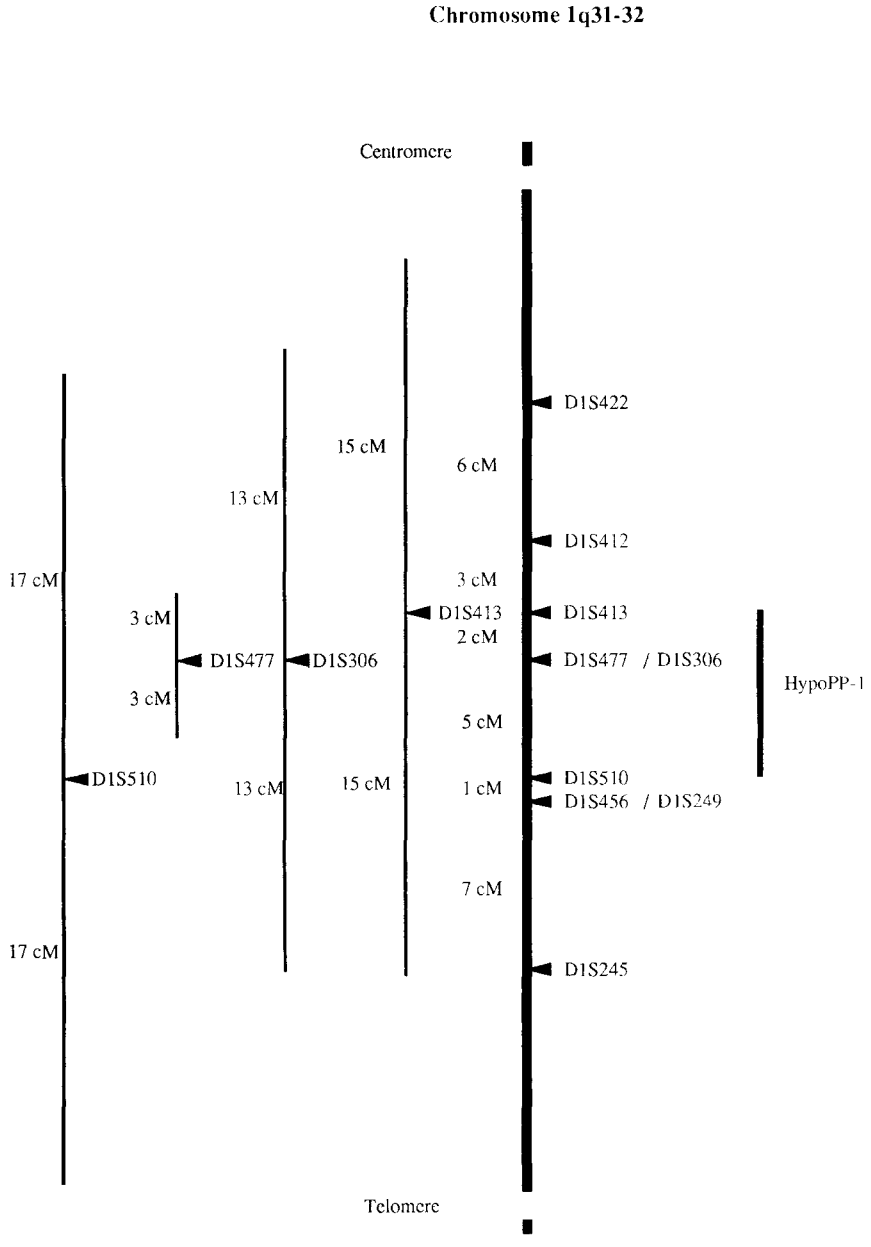

Fig. 2 Genetic regional map of chromosome 1q. Markers used for the linkage analysis are indicated with their respective genetic distances. The most likely localization of hypoPP-1 is indicated in the right part of the figure. In the left part of the figure, the intervals of exclusion, as determined by the pairwise lod score analysis, are shown for family D

(McClatchey et al. 1992) in family D (data not shown). Family D was then analyzed with the markers located within, and flanking, the hypoPP-1 interval (Fig. 2). As shown in Table 2, pairwise lod scores were negative. The distance of exclusion as defined by genetic intervals with lod scores below -2.00 as 15 cM for D1S413, 3 cM for D1S477, 13 cM for D1S306 and 17 cM for D1S510 (Fig. 2). Therefore, the 7 cM interval flanked by D1S413 and D1S510, which defines the hypoPP-1 locus is entirely excluded by these intervals of exclusion (Fig. 2). A multipoint analysis could not be performed with the available programs and computers because of the consanguinity loop in family D. Breaking the loop resulted in more negative pairwise lod-scores, which led to an overestimation of the excluded interval (data not shown). Therefore, we chose the most conservative option, which is the pairwise lod-score analysis shown in Fig. 2.

To confirm the results of the pairwise lod-score analysis, we performed a homogeneity test with the program HOMOG, taking into account the families linked to the hypoPP-1 described in Fontaine et al. (1994). Posterior probabilities of linked type to D1S413, D1S477, D1S306 and D1S510 were 0.00 for family D. Haplotypes were reconstructed (Fig. 1B). No co-segregation between a haplotype and hypoPP was observed in family D (Fig. 1B). The most likely interpretation of the pairwise lod scores, the HOMOG analysis, and the reconstruction of haplotypes is that hypoPP is a genetically heterogeneous disorder.

Discussion

We localized the hypoPP-1 locus to chromosome 1q31–32 (Fontaine et al. 1994). In our initial study, we also reported the co-localization of the hypoPP-1 locus and the DHP-sensitive calcium channel α1 subunit (CACNL1A3) (Fontaine et al. 1994). To define further the hypoPP-1 locus, we set up a genetic study with extended haplotypes using new markers. In addition to the markers used in Fontaine et al. (1994), three recently described markers mapping within the interval defined by D1S413 and D1S249 were used in this study (Gyapay et al. 1994). The hypoPP-1 locus was reduced to 7 cM and two important recombinants were identified on both sides of the locus in family A (AIII2 and AIII8). These two recombinants will be crucial to orient the progression toward the hypoPP gene. However, AIII2 is recombinant with D1S413 and uninformative for the available DNA polymorphisms for CACNL1A3 (Fontaine et al. 1994). Because the most likely localization of CACNL1A3 is either centromeric or telomeric to D1S413 (Fontaine et al. 1994), we still do not know whether CACNL1A3 only maps within the hypoPP-1 interval. Answering this question will require development of new microsatellites in the region and new DNA polymorphisms in CACNL1A3.

The second important set of results reported in this article is the evidence of the existence of a second hypoPP locus in family D. Family D is of French origin and displays hypoPP. Hypokalemia was indeed demonstrated during attacks in at least three different index cases. No clinical peculiarities were noted in family D. The age of onset, the duration of the attacks, and the provocative factors were similar to those of the other hypoPP families. Patients in family D were successfully treated by potassium salt supplementation. Therefore, the acetazolamide response was not tested. As in other families, some patients displayed, in addition to attacks, a fixed muscle weakness due to a vacuolar myopathic process (Links et al. 1990). So, although almost clinically similar to the other hypoPP families, family D did not show genetic linkage to the hypoPP-1 locus. Moreover, genetic linkage was excluded over the entire hypoPP-1 interval. A similar situation has been described for sodium channelopathies. Although the vast majority of normokalemic and hyperkalemic periodic paralysis families are genetically linked and demonstrate mutations in SCN4A, one hyperkalemic periodic paralysis family of Yugoslavian origin did not show genetic linkage to SCN4A (Wang et al. 1993). In chloride channelopathies however, no evidence of genetic heterogeneity was reported (Koch et al. 1993). Another disease implicating ion channels is malignant hyperthermia susceptibility (MHS). MHS is a potentially lethal disorder of autosomal dominant inheritance. The gene defect has been mapped to chromosome 19q12–13.2 and mutations were discovered in the skeletal muscle calcium release channel of the sarcoplasmic reticulum (ryanodine receptor, RYD1) (McCarthy et al. 1990; MacLennan et al. 1990; Gillard et al. 1991; Hogan et al. 1992). Genetic heterogeneity was demonstrated with the identification of two other loci, one on chromosome 17q22–23 (Levitt et al. 1992; Olckers et al. 1992), and one that does not map either to 19q or 17q (Sudbrak et al. 1993; Iles et al. 1993). The fact that muscle disorders caused by different defective genes exhibit the same phenotype suggests that the products of the implicated genes may cooperate in a still undetermined manner to result in an appropriate muscle contraction. The identification of these genes through studies of families presenting ion channelopathies may lead to a better basic understanding of the interaction between ion channels or with the genes regulating their function.

Acknowledgements We thank Prof. Michel Fardeau, Olivier Lyon-Caen, and Yves Agid, and Dr. Nicole Baumann for their support. We thank Sophie Marc and the Généthon Laboratory for their help, as well as Dr. Dominique Récan (Banque de cellules, Hôpital Cochin, Paris). The financial support of AFM (Association Française contre les Myopathies), GREG (Groupe d'Etudes et de Recherches sur les Génomes), and AP-HP (Assistance-Publique-Hôpitaux de Paris) as well as the help of families and physicians are gratefully acknowledged. E.P., A.E., J.V.S. and P.L. received fellowships from the "Ministère de la Recherche", AP-HP, INSERM and AFM respectively. We thank Dr. Marc Del Bigio for English revision.

References

Abdalla JA, Casley WL, Cousin KH, Hudson AJ, Murphy EJ, Cornelis FC, Hashimoto L, Ebers GC (1992) Linkage of Thomsen disease to the T-cell-receptor beta (TCRB) locus on chromosome 7q35. Am J Hum Genet 51:579–584

Barchi RL (1992) Sodium channel gene defects in the periodic paralysis. Curr Op Neurobiol 2:631–637

Buruna OJS, Schipperheyn JJ (1979) Periodic paralysis. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 41. North Holland Publishing Company, Amsterdam, New York, Oxford, pp 147–174

Casley WL, Allon M, Cousin HK, Ting SS, Crackower MA, Hashimoto L, Cornelis F, Beckmann JS, Hudson AM, Ebers GC (1992) Exclusion of linkage between hypokalemic periodic paralysis (Hokpp) and three candidate loci. Genomics 14: 493–494

Fontaine B (1993) Periodic paralysis, myotonia congenita and sarcolemnal ion channels: a success of the candidate gene aproach. Neuromusc Disord 3:101–107

Fontaine B, Khurana TS, Hoffman EP, Bruns GAP, Haines JL, Trofater JA, Hanson MP, Rich J, McFarlane H, Yasek DM, Romano D, Gusella JF, Brown RH Jr (1990) Hyperkalemic periodic paralysis and the adult muscle sodium channel α-subunit gene. Science 250:1000–1002

Fontaine B, Troffater J, Rouleau GA, Khurana TS, Haines J, Brown R, Gusella JF (1991) Different gene loci for hyperkalemic and hypokalemic periodic paralysis. Neuromusc Disord 1:235–238

Fontaine B, Vale Santos JM, Jurkat-Rott K, Reboul J, Plassart E, Rime CS, Elbaz A, Heine R, Guimaraes J, Weissenbach J, Baumann N, Fardeau M, Lehmann-Horn F (1994) Mapping of hypokalaemic periodic paralysis (HypoPP) to chromosome 1q31–q32 in three European families. Nature Genet 6:267–272

George AL Jr, Ledbetter DH, Kallen RG, Barchi RL (1991) Assignment of a human skeletal muscle sodium channel α-subunit gene (SCN4A) to 17q23.1–25.3. Genomics 9:555–556

George AL Jr, Crackower MA, Abdalla JA, Hudson AJ, Ebers GC (1993) Molecular basis of Thomsen's disease (autosomal dominant myotonia congenita). Nature Genet 3:305–309

Gillard EF, Otsu K, Fujii J, Khanna VK, De Leon S, Derdemezi J, Britt BA, Duff C, Worton R, MacLennan D (1991) A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of malignant hyperthermia. Genomics 11: 751–755

Gusella JF (1986) DNA polymorphism and human diseases. Annu Rev Biochem 55:831–854

Gyapay G, Morissette J, Vignal a, Dib C, Fizames C, Millasseau P, Marc S, Bernardi G, Lathrop M, Weissenbach J (1994) The 1993/94 Généthon human genetic linkage map. Nature Genet 7: 246–339

Hazan J, Dubay C, Pankowiak MP, Becuwe N, Weissenbach J (1992) A genetic linkage map of human chromosome 20 composed entirely of microsatellite markers. Genomics 12:183–189

Heine R, Pika U, Lehmann-Horn F (1993) A novel SCN4A mutation causing myotonia aggravated by cold and potassium. Hum Mol Genet 2:1349–1353

Hoffman EP, Wang J (1993) Duchenne-Becker muscular dystrophy and the nondystrophic myotonias. Arch Neurol 50:1227–1237

Hogan K, Couch F, Powers PA, Gregg RG (1992) A Cysteine-for-Arginine substitution (R614C) in the human skeletal muscle calcium release channel cosegregates with malignant hyperthermia. Anesth Analg 75:441–448

Iles DE, Segers B, Sengers RC, Monsieurs K, Heytens L, Halsall PJ, Hopkins PM, Ellis FR, Hall-Curran JL, Stewart AD, Wieringa B (1993) Genetic mapping of the β1 and γ subunits of the human skeletal muscle L-type voltage-dependent calcium channel on chromosome 17q and exclusion as candidate genes for malignant hyperthermia susceptibility. Hum Mol Genet 2: 863–868

Koch MC, Steinmeyer K, Lorenz C, Ricker K, Wolf F, Otto M, Zoll B, Lehmann-Horn F, Grzeschik K, Thomas J (1992) The skeletal muscle chloride channel in dominant and recessive human myotonia. Science 257:797–800

Koch MC, Ricker K, Otto M, Wolf F, Zoll B, Lorenz C, Steinmeyer K, Thomas J (1993) Evidence for genetic homogeneity in autosomal recessive generalized myotonia (Becker). J Med Genet 30:914–917

Lathrop GM, Lalouel JM, Julier C, Ott J (1985) Multilocus linkage analysis in humans: detection of linkage and estimation of recombination. Am J Hum Genet 37:482–498

Lehmann-Horn F, Küther G, Ricker K, Grafe P, Ballanyi K, Rüdel R (1987) Adynamia episodica hereditaria with myotonia: a non-inactivating sodium current and the effect of extra-cellular pH. Muscle Nerve 10:363–374

Lehmann-Horn F, Engel AG, Ricker K, Rüdel R (1993) Periodic paralysis and paramyotonia congenita. In: Engel AG, Franzini-Armstrong C (eds) Myology, 2nd edn. McGraw-Hill, New York, pp 1303–1334

Levitt RC, Olckers A, Meyers S, Fletcher JE, Rosenberg H, Isaacs H, Meyers DA (1992) Evidence for the localization of a malignant hyperthermia susceptibility locus (MSH2) to human chromosome 17q. Genomics 14:562–566

Links T, Zwarts MJ, Wilmink JT, Molenaar WM, Oosterhuis HJGH (1990) Permanent muscle weakness in familial hypokalemic periodic paralysis. Brain 113:1873–1889

McCarthy TV, Healy JM, Heffron JJ, Lehane M, Deufel T, Lehmann-Horn F, Farrall M, Jonhson K (1990) Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12–13.2. Nature 343:562–564

McClatchey AI, Troffater J, McKenna-Yasek D, Raskind W, Bird T, Pericak-Vance M, Gilchrist J, Arahata K, Radosavljevic D, Worthen HG, Van den Berg P, Haines JL, Gusella JF, Brown RH Jr (1992) Dinucleotide repeat polymorphisms at the SCN4A locus suggest allelic heterogeneity of hyperkalemic periodic paralysis and paramyotonia congenita. Am J Hum Genet 50:869–901

McKusick VA (1990) Mendelian inheritance in man. The Johns Hopkins University Press. Baltimore and London

MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Brit B, Worton R (1990) Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature 343:559–561

Olckers A, Meyers DA, Meyers S, Taylor EW, Fletcher JE, Rosenberg H, Isaacs H, Lewitt RC (1992) Adult muscle sodium channel α-subunit is a gene candidate for malignant hyperthermia susceptibility. Genomics 14:829–831

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore and London

Plassart E, Reboul J, Rime CS, Recan D, Millasseau P, Eymard B, Pelletier J, Thomas C, Chapon F, Desnuelle C, Confavreux C, Bady B, Martin J, Lenoir G, Serratrice G, Fardeau M, Fontaine B (1994) Mutations in the muscle sodium channel gene (SCN4A) in 13 French families with hyperkalemic periodic paralysis and paramyotonia congenita: phenotype to genotype correlations and demonstration of the predominance of two mutations. Eur J Hum Genet 2:110–124

Ptacek LJ, Johnson KJ, Griggs RC (1993) Genetics and physiology of the myotonic muscle disorders. N Engl J Med 328:482–489

Rüdel R, Ricker K (1985) The primary periodic paralysis. TINS 8: 467–470

Rüdel R, Ricker K, Lehman-Horn F (1993) Genotype-phenotype correlations in human skeletal muscle sodium channel diseases. Arch Neurol 50:1241–1248

Sudbrak R, Golla A, Hogan K, Powers P, Gregg R, Du Chesne I, Lehmann-Horn F, Deufel T (1993) Exclusion of malignant hyperthermia susceptibility (MHS) from a putative MHS2 locus on chromosome 17q and of the α1, β1, and γ subunits of the dihydropyridine receptor calcium channel as candidates for the molecular defect. Hum Mol Genet 2:857–862

Wang J, Zhou J, Todorovic SM, Feero WG, Barany F, Conwit R, Hausmanowa-Petrusewicz I, Fidzianska A, Arahata K, Wessel HB, Sillen A, Marks HG, Hartlage P, Galloway G, Ricker K, Lehmann-Horn F, Hayakawa H, Hoffman EP (1993) Molecular genetic and genetic correlations in sodium channelopathies: lack of founder effect and evidence for a second gene. Am J Hum Genet 52:1074–1084

Weissenbach J, Gyapay G, Dib C, Vignal A, Morisette J, Millasseau P, Vaysseix G, Lathrop M (1992) Second generation linkage map of the human genome. Nature 359:794–801