Prevalence study of genetically defined skeletal muscle channelopathies in England

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ABSTRACT

Objectives: To obtain minimum point prevalence rates for the skeletal muscle channelopathies and to evaluate the frequency distribution of mutations associated with these disorders.

Methods: Analysis of demographic, clinical, electrophysiologic, and genetic data of all patients assessed at our national specialist channelopathy service. Only patients living in the United Kingdom with a genetically defined diagnosis of nondystrophic myotonia or periodic paralysis were eligible for the study. Prevalence rates were estimated for England, December 2011.

Results: A total of 665 patients fulfilled the inclusion criteria, of which 593 were living in England, giving a minimum point prevalence of 1.12/100,000 (95% confidence interval [CI] 1.03–1.21). Disease-specific prevalence figures were as follows: myotonia congenita 0.52/100,000 (95% CI 0.46–0.59), paramyotonia congenita 0.17/100,000 (95% CI 0.13–0.20), sodium channel myotonias 0.06/100,000 (95% CI 0.04–0.08), hyperkalemic periodic paralysis 0.17/100,000 (95% CI 0.13–0.20), hypokalemic periodic paralysis 0.13/100,000 (95% CI 0.10–0.17), and Andersen-Tawil syndrome (ATS) 0.08/100,000 (95% CI 0.05–0.10). In the whole sample (665 patients), 15 out of 104 different *CLCN1* mutations accounted for 60% of all patients with myotonia congenita, 11 out of 22 *SCN4A* mutations for 86% of paramyotonia congenita/sodium channel myotonia pedigrees, and 3 out of 17 *KCNJ2* mutations for 42% of ATS pedigrees.

Conclusion: We describe for the first time the overall prevalence of genetically defined skeletal muscle channelopathies in England. Despite the large variety of mutations observed in patients with nondystrophic myotonia and ATS, a limited number accounted for a large proportion of cases. *Neurology*® 2013;80:1472–1475

GLOSSARY

ATS = Andersen-Tawil syndrome; **CACNA1S** = calcium channel, voltage-dependent, L type, α 1S subunit gene; **CI** = confidence interval; **CLCN1** = chloride channel, voltage-sensitive 1 gene; **HyperPP** = hyperkalemic periodic paralysis; **HypoPP** = hypokalemic periodic paralysis; **KCNJ2** = potassium inwardly rectifying channel, subfamily J, member 2 gene; **MC** = myotonia congenita; **NDM** = nondystrophic myotonias; **PMC** = paramyotonia congenita; **PP** = periodic paralysis; **SCM** = sodium channel myotonias; **SCN4A** = sodium channel, voltage-gated, type 4, α subunit gene.

Nondystrophic myotonias (NDM) and periodic paralysis (PP) comprise a heterogeneous group of skeletal muscle disorders caused by mutations in genes encoding ion channels.^{e1} NDM include myotonia congenita (MC), paramyotonia congenita (PMC), and the sodium channel myotonias (SCM). PP encompass hypokalemic periodic paralysis (HypoPP), hyperkalemic periodic paralysis (HyperPP), and Andersen-Tawil syndrome (ATS). These are autosomal dominant disorders except for MC, which is inherited in either a dominant or recessive manner.^{e1}

Although significant progress in the clinical, electrophysiologic, and genetic characterization of the skeletal muscle channelopathies has taken place in the past 2 decades, their actual prevalence remains incompletely evaluated. Previous estimates range from 1 to 10/100,000^{e2}; however, few studies have specifically addressed this issue and most of them predate genetic diagnosis (table e-1 on the *Neurology*® Web site at www.neurology.org). To obtain more accurate prevalence data, we undertook analysis of all patients with NDM and PP assessed at the UK

Supplemental data at
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national referral center for skeletal muscle channelopathies. The frequency distribution of mutations in this patient population was also evaluated.

METHODS Patients. This study covered all patients with suspected NDM or PP referred to our national channelopathy service for specialist clinical or genetic assessment between 1997 and 2011. Demographic, clinical, electrophysiologic, and genetic data from these patients were prospectively collected in a database from which the study sample was drawn. Inclusion criteria were individuals 1) of any age, 2) living in the United Kingdom, 3) with clinical and electrophysiologic features consistent with NDM or PP,^{c1} and 4) with confirmed mutations in genes encoding the skeletal muscle chloride (*CLCN1*), sodium (*SCN4A*), calcium (*CACNA1S*), or potassium (*KCNJ2*) channel. Alternative causes, such as thyrotoxic PP or myotonic dystrophy, were ruled out when indicated.

Electrophysiologic tests were performed as reported previously.^{c3,c4} The algorithm and methods for DNA sequencing have been described in detail elsewhere.^{c1,c5-c8} Briefly, sequencing of the entire coding region of *CLCN1* or *KCNJ2* was performed in patients with suspected MC or ATS, respectively. Those with other forms of NDM or PP underwent sequence analysis of commonly mutated *SCN4A* or *CACNA1S* exons and, if negative, of the remaining coding regions.^{c1}

Data analysis. England was selected as the geographical area for the prevalence analysis, with a total population of 53,012,500 according to the 2011 Census for England and Wales (<http://www.ons.gov.uk>). December 31, 2011 was chosen as the prevalence day. Minimum point prevalence rates were calculated as the number of patients in the study area on the prevalence day divided by the total number of at-risk individuals (England population). Rates were expressed as cases/100,000 and 95% confidence intervals (CI) were calculated using the method proposed by Schoenberg, based on the Poisson distribution.^{c9}

The frequency of mutations in each gene was also determined. For this analysis, all patients from any UK location were included. Descriptive statistics were performed using IBM SPSS Statistics v20.

Standard protocol approvals, registration, and patient consents. The study had ethical approval from the NHNN/ION Joint Research Ethics Committee. All patients gave written informed consent for genetic testing.

RESULTS From a total of 722 patients with clinical and electrophysiologic features suggestive of NDM or PP, 665 patients (92%) from 453 apparently unrelated pedigrees fulfilled the inclusion criteria. Of these, 593 (89%) were living in England on the prevalence day, giving a minimum point prevalence of skeletal muscle channelopathies of 1.12/100,000 (95% CI 1.03–1.21). Disease-specific demographic characteristics and prevalence figures are shown in table 1.

Nondystrophic myotonias. From a total of 321 patients with MC, 168 had a positive family history. Of these, 99 patients (59%) from 50 pedigrees were classified as dominant MC and 69 patients (41%) from 49 pedigrees as recessive MC, based on the inheritance pattern and genotype. Of the remaining 153 patients, 5 were sporadic cases and 148 had an uncertain family history (table 1). A total of 104 different *CLCN1* mutations were detected, of which 65 were confined to 60 unique pedigrees (private mutations). Of the nonprivate mutations, 15 were found in 83% of all patients with MC (table 2) and accounted for 60% of them (85% of heterozygous, 32% of compound heterozygous, 20% of homozygous) (table e-2, e-3, and e-4; figure e-1A).

Table 1 Demographic characteristics and minimum point prevalence rates

	Patients (pedigrees)	Age, y, mean ± SD ^a	Male/female ratio	Patients from England, n (%)	Prevalence rate (×10 ⁻⁵), (95% CI)
NDM	449 (322)	38.0 ± 17.5	1.57	395 (88)	0.75 (0.67–0.82)
MC	321 (252)	39.0 ± 16.3	1.97	277 (86)	0.52 (0.46–0.59)
AD MC	99 (50)	40.8 ± 17.3	1.30	73 (74)	0.14 (0.11–0.17)
AR MC	69 (49)	33.5 ± 17.7	2.00	63 (91)	0.12 (0.09–0.15)
Other ^b	153 (153)	40.2 ± 14.5	2.64	141 (92)	0.27 (0.22–0.31)
PMC ^{c,d}	96 (56)	35.1 ± 19.5	0.88	88 (92)	0.17 (0.13–0.20)
SCM	32 (14)	37.7 ± 21.3	1.00	30 (94)	0.06 (0.04–0.08)
PP	216 (131)	39.1 ± 18.3	2.27	198 (92)	0.37 (0.32–0.43)
HypoPP	95 (59)	36.6 ± 18.1	3.52	88 (93)	0.17 (0.13–0.20)
HyperPP	77 (48)	40.2 ± 19.3	2.08	70 (91)	0.13 (0.10–0.17)
ATS	44 (24)	42.7 ± 16.2	1.20	40 (91)	0.08 (0.05–0.10)

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; ATS = Andersen-Tawil syndrome; CI = confidence interval; HyperPP = hyperkalemic periodic paralysis; HypoPP = hypokalemic periodic paralysis; MC = myotonia congenita; NDM = nondystrophic myotonias; PMC = paramyotonia congenita; PP = periodic paralysis; SCM = sodium channel myotonias.

^aAt the time of the prevalence day.

^bSporadic cases and patients with uncertain family history of MC.

^cThree patients from 3 pedigrees had overlapping features with SCM.

^dTwo patients with p.Arg1448Cys and one with p.Ile693Thr also had episodes of paralysis.

Table 2 Frequency of common mutations in patients with chloride channelopathies^a

CLCN1 mutation	All patients with MC, n (%) (n = 321)	Patients with positive family history	
		AD MC, n (%) (n = 99)	AR MC, n (%) (n = 69)
p.Gly230Glu	58 (18)	34 (34)	1 (1)
p.Gly285Glu	31 (10)	0	10 (14)
p.Trp303Arg	29 (9)	21 (21)	0
c.180+3A>T (splice site)	25 (8)	1 (1) ^b	16 (23)
p.Arg894X	18 (6)	2 (2)	5 (7)
p.Ala313Thr	15 (5)	8 (8)	0
c.1437_1450del	15 (5)	1 (1) ^c	2 (3)
p.Phe297Ser	13 (4)	9 (9)	0
p.Phe413Cys	13 (4)	0	4 (6)
p.Phe307Ser	11 (3)	7 (7)	1 (1)
p.Phe167Leu	8 (2)	1 (1)	2 (3)
p.Met485Val	8 (2)	1 (1) ^d	3 (4)
p.Ala313Val	7 (2)	5 (5)	0
p.Phe306Leu	7 (2)	5 (5)	0
p.Val327Ile	7 (2)	0	2 (3)

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; CLCN1 = chloride channel, voltage-sensitive 1 gene; MC = myotonia congenita.

^aNonprivate mutations present in >2 pedigrees and ≥2% of all patients with MC.

^bCompound heterozygous with the dominant mutation p.Arg894X.

^cCompound heterozygous with the dominant mutation p.Phe307Ser.

^dCompound heterozygous with the dominant mutation p.Gly230Glu.

Ninety-six patients had a diagnosis of PMC and 32 of SCM based on clinical and electrophysiologic features. Three of the patients with PMC displayed overlapping features with SCM. Overall, of the 22 different *SCN4A* mutations detected in patients with PMC and SCM, 11 were present in 86% of all pedigrees and 11 were private mutations (table 3; figure e-1B). Two patients with PMC from the same pedigree had both one *SCN4A* mutation and a sequence variant of unknown clinical significance (table e-4).

Periodic paralyses. Ninety-five patients had a diagnosis of HypoPP and 77 of HyperPP. In patients with HypoPP, a total of 5 different *CACNA1S* and 9 *SCN4A* mutations were detected. Of these mutations, 6 accounted for 86% of pedigrees. Six different *SCN4A* mutations were found in patients with HyperPP, of which 3 accounted for 94% of pedigrees (table 3; figure e-2B and e-2C).

Forty-four patients with ATS were identified. All had episodes of weakness with or without other features of the disorder (cardiac arrhythmias and distinctive physical features). Seventeen different *KCNJ2* mutations were detected: 3 were present in 42% of pedigrees and the remaining 14 were private mutations (table 3).

DISCUSSION We have performed a comprehensive analysis of a large series of patients with genetically defined

skeletal muscle channelopathies, and documented for the first time the overall frequency of these disorders in England. Our data revealed a minimum prevalence of 1.12/100,000. This figure is comparable to that of other rare neuromuscular disorders such as Pompe disease or Lambert-Eaton myasthenic syndrome (1.5 and 1/100,000, respectively) (<http://www.orpha.net>).

No previous data are available on the prevalence of SCM, HyperPP, and ATS, for which we found rates ≤0.13/100,000. The figures for MC, PMC, and HypoPP were similar to that observed in other areas (table e-1). Other studies have reported significantly higher rates; however, most of them predate genetic testing, were restricted to pediatric cases, or were performed in areas with an unusually high population frequency of mutations due to founder effects and geographical factors (e.g., Northern Scandinavia or Ravensberg Land, Germany).¹⁻⁴ This precludes direct comparison with our data. On the other hand, we cannot dismiss the possibility of incomplete case ascertainment in our study. This had a service-based epidemiologic design, so only affected individuals seeking medical attention who were referred to our center were identified. Since 8% of these patients still remain genetically undefined, the use of strict inclusion criteria may also have eliminated true cases from the study sample. These criteria, however, ensure a reliable estimate of the minimum prevalence.

The spectrum and frequency of genetic alterations observed in patients with NDM and PP were similar to those reported in the literature.⁵⁻¹⁰ A large variety of mutations were found in patients with NDM and ATS, yet only a limited number accounted for a significant proportion of cases: 15 *CLCN1* mutations accounted for 60% of all patients with MC, 11 *SCN4A* mutations for 86% of PMC and SCM pedigrees, and 3 *KCNJ2* mutations for 42% of ATS pedigrees. This suggests that, in the diagnosis of NDM and ATS, a panel of common mutations could be tested initially if a targeted mutation analysis approach is used. Given the high number of private mutations, however, whole-gene sequence analysis would be advisable in patients with suspected MC and ATS.

While previous studies have suggested a predominance of recessive over dominant MC,^{2,4,10} we found similar percentages of dominant and recessive pedigrees. Studies in areas with high prevalence of MC (e.g., Northern Scandinavia) have shown that more than 85% of affected individuals are compound heterozygous or homozygous for *CLCN1* mutations, suggesting recessive inheritance in most cases, even in families with apparent dominant transmission. This may be explained by the high carrier frequency of certain mutations in those areas.^{3,4} In our study, most patients with a dominant family history were heterozygous, supporting a true dominant inheritance.

This study indicates a minimum prevalence of skeletal muscle channelopathies in England of 1.12/100,000.

Table 3 Frequency of common mutations in patients with sodium, calcium, and potassium channelopathies^a

	Patients, n (%)	Pedigrees, n (%)
PMC, SCM		
SCN4A mutations	128 (100)	70 (100)
p.Thr1313Met	22 (17)	15 (21)
p.Arg1448Cys/His/Leu	28 (22)	13 (19)
p.Val1589Met	27 (21)	11 (16)
p.Gly1306Ala ^b /Glu/Val	17 (13)	9 (13)
p.Leu1436Pro ^b	7 (5)	6 (9)
p.Ile693Thr	6 (5)	4 (6)
p.Val1293Ile	3 (2)	2 (3)
HypoPP		
CACNA1S mutations	78 (82)	47 (80)
p.Arg528His	34 (36)	24 (41)
p.Arg1239His	39 (41)	19 (32)
p.Arg1239Gly	3 (3)	2 (3)
SCN4A mutations	17 (18)	12 (20)
p.Arg1135His	4 (4)	2 (3)
p.Arg672His/Ser	4 (2)	4 (7)
HyperPP		
SCN4A mutations	77 (100)	48 (100)
p.Thr704Met	53 (69)	32 (67)
p.Met1592Val	14 (18)	11 (23)
p.Arg675Gly	5 (7)	2 (4)
ATS		
KCNJ2 mutations	44 (100)	24 (100)
p.Arg218Trp	9 (20)	4 (17)
p.Arg67Trp	6 (14)	4 (17)
p.Arg82Gln	4 (9)	2 (8)

Abbreviations: ATS = Andersen-Tawil syndrome; CACNA1S = calcium channel, voltage-dependent, L type, α 1S subunit gene; HyperPP = hyperkalemic periodic paralysis; HypoPP = hypokalemic periodic paralysis; KCNJ2 = potassium inwardly rectifying channel, subfamily J, member 2 gene; PMC = paramyotonia congenita; SCM = sodium channel myotonias; SCN4A = sodium channel, voltage-gated, type 4, α subunit gene.

^aNonprivate mutations present in all patients with PMC, SCM, HypoPP, HyperPP, and ATS.

^bSCN4A mutations associated with an overlapping PMC/SCM phenotype.

Despite the large variety of mutations observed in patients with NDM and ATS, a limited number accounted for a large proportion of cases in the UK patient population. We believe that these findings can inform the design of health care services and diagnostic algorithms for patients with these disabling disorders.

AUTHOR CONTRIBUTIONS

A. Horga contributed to study concept and design, acquisition, analysis, and interpretation of data, statistical analysis, writing the first draft of the manuscript, and making subsequent revisions. D.L. Raja Rayan contributed to study concept and design, acquisition, analysis, and interpretation of data, and writing and revising the manuscript. R. Sud, J.A. Burge, M.B. Davis, and A. Haworth contributed to acquisition and interpretation of data and revising the manuscript. E. Matthews, D. Fialho, S.C.M. Durran, and S. Portaro contributed to acquisition of data and revising the manuscript. M.G. Hanna contributed

to study concept and design, study supervision, acquisition, analysis, and interpretation of data, and writing and revising the manuscript.

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