Am. J. Hum. Genet. 65:1104–1113, 1999

A Novel Syndrome of Episodic Muscle Weakness Maps to Xp22.3

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Summary

We describe a family with a novel disorder characterized by episodic muscle weakness and X-linked inheritance. Eight males in three generations demonstrate the characteristic features of the disorder. Episodes of severe muscle weakness are typically precipitated by febrile illness and affect the facial and extraocular musculature, as well as the trunk and limbs, and resolve spontaneously over a period of weeks to months. Younger members of the family are normal between episodes but during relapses show generalized weakness, ptosis, and fluctuations in strength. In some cases, fatigability can be demonstrated. The proband has late-onset chronic weakness and fatigability. The clinical phenotype has features suggestive both of the congenital myasthenic syndromes and of ion-channel disorders such as the periodic paralyses. We have localized the responsible gene to chromosome Xp22.3, with a maximum two-point LOD score of 4.52 at a recombination fraction of .0, between *OACA2* and *DXS9985*.

Introduction

Episodic symptomatology as a clinical phenomenon is seen in a number of neurogenetic diseases, including the congenital myasthenic syndromes, periodic paralyses, myotonias, and episodic ataxias. The congenital myasthenic syndromes are a group of genetically determined, nonautoimmune disorders affecting the neuromuscular junction (reviewed by Engel [1994] and Middleton [1998]). The cardinal features of the congenital myasthenic syndromes include fatigue-induced weakness, absence of acetylcholine-receptor antibodies, and neurophysiological evidence of a defect in neuromuscular transmission. Onset is usually in infancy or early childhood, and response to anticholinesterase therapy is variable. The periodic paralyses are skeletal myopathies in which disordered sarcolemmal ion-channel function causes periods of temporary muscle weakness. Weakness occurs in response to environmental stressors, exercise, and either potassium loading or depletion. There is wide variation in the frequency of relapses. Patients can be completely asymptomatic between episodes, or they may complain of cramping and muscle stiffness (Rudel and Lehmann-Horn 1998). Within each of these groups of disorders, there is considerable genetic and clinical heterogeneity. However, none of the disorders identified, to date, are X linked. In most instances, the pathophysiology of episodic symptomatology is only poorly understood.

We report a family with the clinical and pathological features of a new syndrome of episodic muscle weakness. Eight males in generations II and IV demonstrate the typical features of the disorder, consistent with X-linked inheritance. Muscle biopsy in the index case demonstrates dilatation and focal proliferation of the sarcoplasmic reticulum. We have mapped the disease locus to Xp22.3. The clinical phenotype overlaps both with the familial myasthenic syndromes and with channelopathies, such as the periodic paralyses. However, other features of this disorder, such as the severity of exacerbations, the complete remission of symptoms and signs between episodes, the X-linked pattern of inheritance, and the atypical manifestations in some members of the kindred, suggest that this syndrome represents the first member of a novel subgroup of the episodic disorders.

Subjects and Methods

This study was approved by the Research Ethics Committee of the New Children's Hospital, Sydney (approval no. 98028), and was conducted in accordance with institutional guidelines. A multigenerational, nonconsan-

Received April 29, 1999; accepted for publication August 9, 1999; electronically published September 9, 1999.

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0002-9297/1999/6504-0021$02.00

guineous Australian family of European origin was identified for this study (fig. 1). Informed consent was obtained from all adult participants prior to physical examination and sample collection. In addition to written parental consent, a verbal agreement to participate was obtained from all subjects of age <16 years. Neurological examination of 34 members in generations II–IV was performed by K.N. and M.R.

Genotyping

DNA samples were collected from 37 individuals, including 8 affected and 8 unaffected males in generations II and IV, obligate carrier females in generation III, and their partners. Genomic DNA was prepared from peripheral blood leukocytes in duplicate 9-ml blood samples by following the procedure of Miller et al. (1988). DNA was quantitated by UV spectroscopy, diluted to a standard concentration of 100μg/ml with 1 × Tris-EDTA, and stored at −20°C for analysis.

Eighteen microsatellite markers from the PE Biosystems X-Chromosome Linkage Set were used in an initial screen for linkage (Australian Genome Research Facility). The average PIC of the marker set is ~.78, with an average map resolution of ~10.8 cM. For the refinement of the candidate area on distal Xp, we analyzed nine other fully or partially informative simple tandem-repeat polymorphisms (STRPs) between *DXS1060* and *DXS1226*. The STRPs used in the fine-mapping study were determined principally from the physical maps of distal Xp, constructed by the Baylor Genome Sequencing Center and Telethon Institute of Genetics and Medicine, Milan (Ferrero et al. 1995; Cox et al. 1998). The order and genetic distances of markers were determined from the map of chromosome X, developed by the Marshfield Center for Medical Genetics and by the Whitehead Institute for Biomedical Research/MIT Center for Genome Research (fig. 2). Markers without published genetic distances were assigned approximate genetic distances on the basis of their physical map position.

Oligonucleotide-primer sequences were determined from the Integrated X-Chromosome Database and from the publications of Ferrero et al. (1995) and Cox et al. (1998). For all STRP loci, the forward primer in each pair was HEX-labeled to enable fluorescent detection. Primers were synthesized by Life Technologies.

PCR amplifications were performed in 15-μl vols containing 50 ng genomic DNA, 200 μM dNTPs, 5 pmol each of forward and reverse primer, 0.5 U Ampli*Taq* Gold DNA polymerase (PE Biosystems), and 1 × PCR buffer II (PE Biosystems) with 1.25 mM Mg^{++}. PCR cycle conditions were as follows: initial denaturation for 9 min at 95°C, followed by 30 cycles of 95°C for 0.5 min, 55°C for 0.5 min, and 72°C for 1 min, with a final extension for 5 min at 72°C. PCR products were separated by gel electrophoresis in 6% Gene-Page Plus (Amresco) denaturing acrylamide-matrix gels. STRP alleles were resolved on a Corbett Research GS.2000 Fluorescent DNA Fragment Analyzer. Alleles were independently scored by two individuals.

Linkage Analysis

Two-point and multipoint linkage analyses were performed with the LINKAGE computer packages (Lathrop et al. 1984). Linkage analyses assumed X-linked recessive inheritance and a fully penetrant disorder without phenocopies. Equal allele frequencies were assigned to STRP loci, since all transmitting individuals were fully typed.

Results

Clinical Findings

Eight males in three generations demonstrated the typical features of this disorder, with episodes of muscle weakness precipitated by viral illness. There is no male-to-male transmission, and obligate female carriers have no episodes of weakness, consistent with X-linked recessive inheritance (fig. 1).

Characteristics of episodic weakness.—A typical member of this family is patient IV-27. He was unaffected until age 25 mo, at which time he developed ptosis and weakness after an episode of gastroenteritis. Within 48 h, he was unable to walk. Clinical improvement occurred over a period of 3 wk, with occasional fluctuations in strength. There was no response to a neostigmine test. Nerve conduction studies and electromyography (EMG) were normal. No medications were given, and he has demonstrated slight weakness over a subsequent period of 12 mo.

The clinical history is similar in five other members of generation IV. The first episode of weakness occurred at age 6 mo–8 years. Three of the eight patients experienced a single episode of weakness, whereas one had >10 discrete episodes. In each of the eight affected family members, viral illness (seven patients) or halothane anaesthesia (one patient) precipitated the initial presentation and subsequent relapses. Weakness has persisted for variable periods, with the initial episode lasting for as long as 8 mo; subsequent relapses tend to be shorter. The clinical features are summarized in table 1.

Symptom severity varied widely between episodes and among patients. The initial episode tended to be more severe in those with a younger age at onset. When weakness was relatively mild, it was localized to the proximal musculature. In three patients, episodes of weakness were so severe that loss of head control was associated with inability to walk or to raise the arms against gravity. During such episodes, the reflexes were depressed

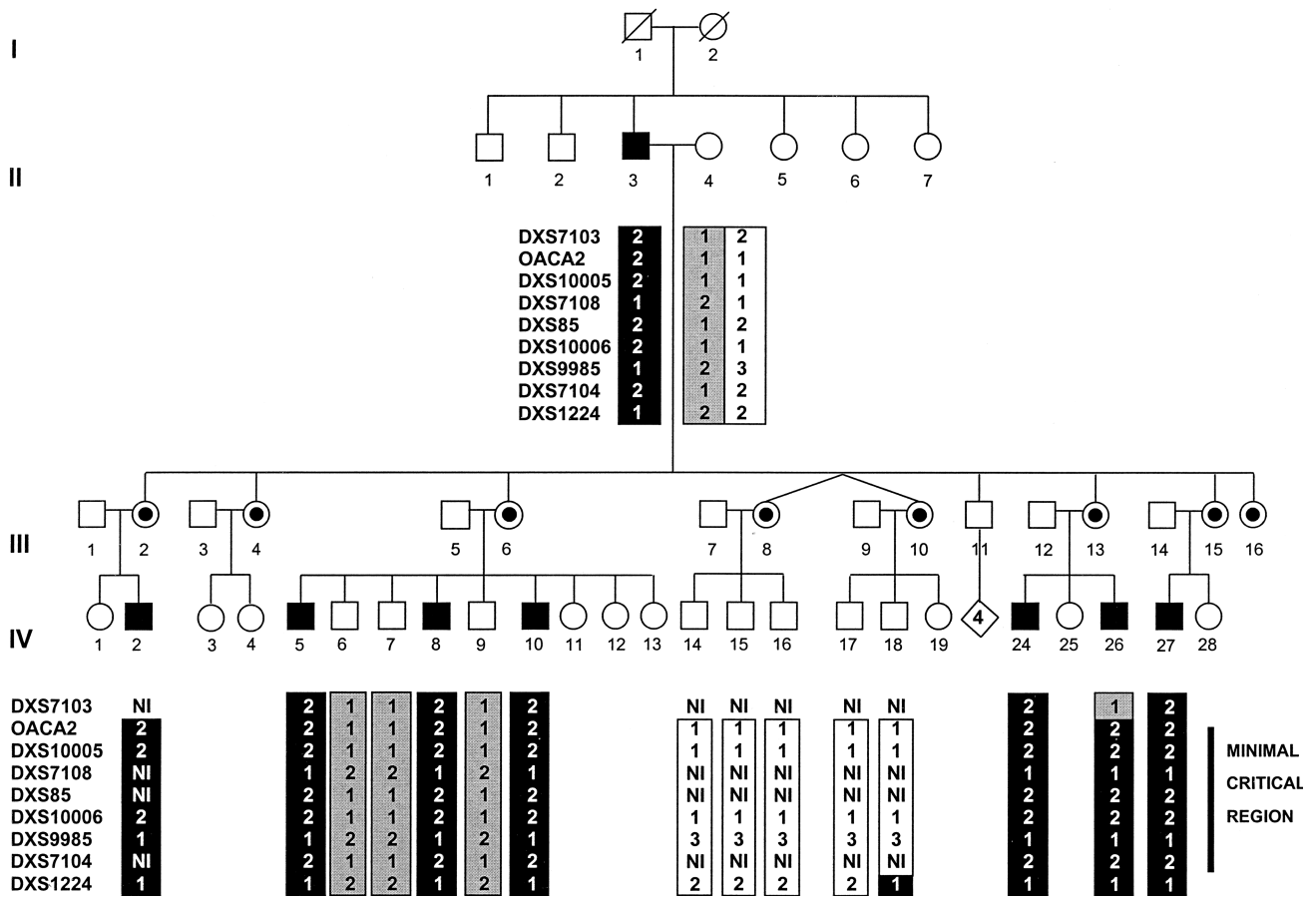

Figure 1 Pedigree structure and partial X-chromosome haplotypes in the region Xp22.3 for the family with X-linked episodic muscle weakness. The haplotype shared by affected family members is denoted by a blackened box. The grandmaternal haplotypes are denoted by white and gray-shaded boxes. The order of STRP is from telomere (top) to centromere (bottom). Individuals IV-18 and IV-26 show maternally derived recombinations.

or absent, although they usually returned between exacerbations.

All patients had ptosis during at least one episode, and two of eight patients had intermittent strabismus during exacerbations. Three had bulbar weakness, although none required gavage feeds or parenteral nutrition. No patient required mechanical ventilation or showed any evidence of significant respiratory compromise, even with the most severe exacerbations. Fatigability was evident in three patients. Clearly distinguishable from fatigability were momentary fluctuations in muscle strength and ptosis, unrelated to effort or exercise, which were seen in five of eight patients.

Additional phenotypic features.—Both patient IV-2 and patient IV-24 reported myalgia and cramps precipitated by minimal exercise. At age 4 years patient IV-24 developed episodic dystonia, which frequently was associated with exercise although not with cold. Basal-ganglia calcification was seen on neuroimaging, although cerebrospinal fluid (CSF) protein and lactate and mitochondrial enzyme analysis on muscle biopsy were normal. The patient continues to have episodic dystonia, sometimes associated with tremor, which has proved refractory to therapy with levodopa and benzhexol. Two patients also experienced transient episodes of dystonic posturing, either precipitated by exercise (patient IV-2) or during the initial episode of weakness (patient IV-8). These episodes resolved spontaneously. No patient had myotonia at any time. Patient IV-5 also has an intermittent tremor that is increased by anxiety. Interestingly, three of the obligate female carriers in this family have a history of essential tremor, increased by stress and not relieved by alcohol.

Clinical course.—Seven of the eight affected males are age <18 years. At last review, five of the seven affected males in generation IV were in periods of remission (18 mo–9 years). Patient IV-27 is in a phase of continuing recovery from his initial episode, whereas patient IV-24 has had normal strength for 5 years but has intermittent dystonia.

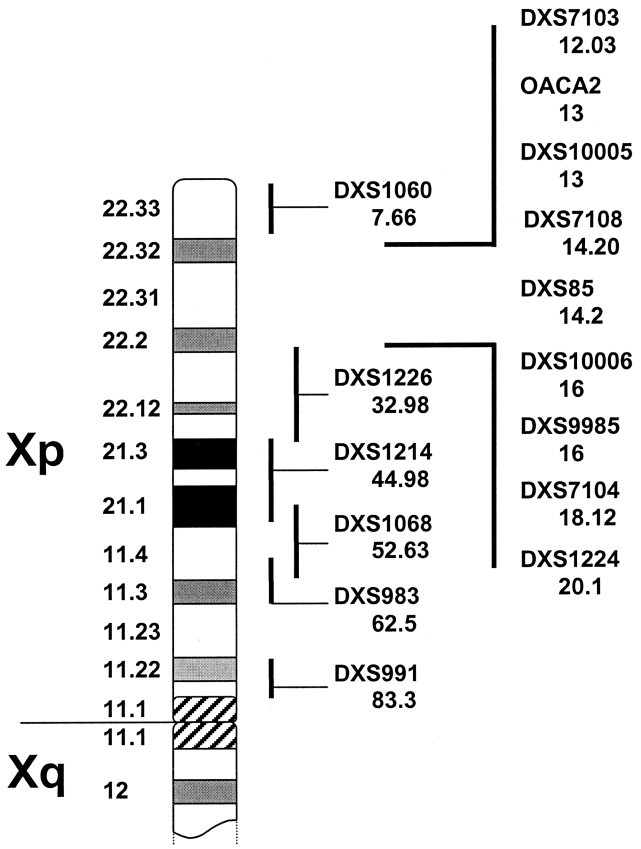

Figure 2 Ideogram of the short arm of the X chromosome, with STRP genetic distances. Intermarker distances were obtained from public databases or, when unknown, have been assigned on the basis of physical-mapping data and known genetic distances for flanking markers.

The index case, patient II-3, is now 69 years old. At age 7 years he developed severe flaccid paralysis after a febrile illness, which was diagnosed as poliomyelitis. He recovered fully over a period of 6–12 mo. After this, he experienced >10 episodes of lower-limb weakness at age <25 years. At age 25–53 years, he was relatively asymptomatic, apart from intermittent ptosis and mild dysphagia. Since that time, he has experienced continuing clinical deterioration, with progressive weakness and fatigability. He also has a late-onset axonal neuropathy and episodes of agitated depression.

Clinical Investigations

Muscle histology and ultrastructure.—The index patient underwent muscle biopsy at age 69 years, at a time when the patient demonstrated chronic weakness. Light microscopy revealed nonspecific changes with widened interfibrillary spaces. On electron microscopy, there was dilatation of the sarcoplasmic reticulum (fig. 3), with focal areas of proliferation. There were large spaces between the myofibers and within the subsarcolemmal regions, which likely represent increased glycogen deposits. The mitochondrial appearance was normal. A muscle biopsy in patient IV-24 (performed during an episode of weakness) revealed type 2B fiber atrophy with occasional lymphocytic infiltrates. The significance of these changes is not known. Muscle biochemistry and respiratory-chain–enzyme analysis were normal. Muscle was not available for electron microscopy.

Neurophysiology.—Neurophysiological studies (nerve conduction studies and EMG) in affected members of this family have not demonstrated a diagnostic pattern of abnormal findings. The proband developed symptoms associated with an axonal neuropathy, in his 6th decade. Conduction studies at age 69 years revealed mild slowing of nerve conduction and significantly decreased CMAP (compound muscle action potential) and SNAP (sensory nerve action potential) amplitudes. Results of repetitive nerve stimulation were normal. Standard EMG showed some loss of motor-unit density but no myotonia or active denervation, whereas single-fiber electromyography, with increased jitter and some blocking, was suggestive of chronic denervation/reinnervation. The changes seen were not typical either of the channelopathies or of the congenital myasthenic syndromes, although the single-fiber EMG was potentially consistent with myasthenia. In affected members of generation IV, nerve conduction studies were normal in one patient, nonspecific abnormalities on EMG were seen in one of two patients, and repetitive nerve stimulation of limb muscles was normal in three of three patients. EMG of the facial musculature was not performed.

Assays for antibodies to the acetylcholine receptor were negative in three of three patients. Neostigmine tests were performed in five of eight patients. These were unequivocally positive in two, equivocal in two, and negative in one patient. Three patients received anticholinesterase therapy during episodes of weakness with sustained response; however, the weakness resolved spontaneously in patients not receiving therapy. The proband was given regular pyridostigmine (500 mg/d) from age 60 years and reported subjective improvement in his chronic weakness. However, pyridostigmine was recently withdrawn without adverse effect or change in his level of function.

Additional investigations.—Neuroimaging was performed in two patients and was normal in one. Patient IV-24 had basal-ganglia calcification on brain computed tomography (CT) scan. This finding was confirmed on magnetic resonance imaging, which showed hyperintensity of the putamina and caudate nuclei bilaterally on T2-weighted images. CSF and serum studies for mitochondrial and inherited metabolic disorders were normal in this patient and in one other. Investigations performed in a minority of patients, which were normal in

Table 1

Summary of Clinical Data

Patient	Age at Onset (Years)	Current Age (Years)	Episodes of Weakness	Precipitant for Episode(s)	Duration of Episode(s)	Course
II-3	7	69	>10	Viral illness; subsequent precipitants less clear	Initial episode >6 mo	Fatigability worsening with increased age; increasing weakness
IV-2	8	11	1	Tonsillectomy	Initial episode >1 mo	Asymptomatic for 2 years
IV-5	2.2	18	5	Viral illnesses and gastroenteritis	Initial episode >8 mo; subsequent episodes shorter	Asymptomatic for 9 years
IV-8	1.5	12	3	Viral illnesses on each occasion	Initial episode 4 mo; subsequent episodes shorter	Asymptomatic for 6 years
IV-10	1.1	9	4	Viral illness on one occasion	Initial episode 3 wk; other episodes <24 h	Asymptomatic for 7 years
IV-24	.5	9	1	Viral illness	Episodic ptosis; fatigable; spontaneously resolving after 3–4 d	Development of dystonia
IV-26	.9	5	>5	Viral illnesses	Initially ⩽2 wk; subsequent episodes shorter	Asymptomatic for 18 mo
IV-27	2.1	3	1	Gastroenteritis	3 wk	Remains slightly weak 12 mo after initial episode

each instance, included measurement of serum creatine kinase and electrolytes during episodes of weakness (in three patients), CT scan of the mediastinum (in two patients), and CSF protein and biochemical analysis (in two patients). In the index case, a screen for causes of late-onset axonal neuropathies (including serum and urine protein electrophoresis, immunoglobulin levels, urine heavy metal, and porphyrin screening) was negative.

Linkage Analysis

The mode of inheritance of the disorder in this family is most consistent with a single, fully penetrant X-linked recessive gene. As an initial step toward identifying the molecular basis of this disorder, we undertook linkage analysis of the X chromosome. The initial linkage studies were conducted at a map resolution of ~10 cM and demonstrated linkage to distal Xp. We therefore tested nine other STRPs between *DXS1060* and *DXS1226,* narrowing the genetic interval containing the putative locus to a region within chromosome band Xp22.3 (fig. 2). The maximum two-point LOD score of 4.52 was obtained between *OACA2* and *DXS9985,* at a recombination fraction (θ) of .0, consistent with significant linkage (table 2). The LOD score is reduced at *DXS7108, DXS85,* and *DXS7104,* because of the reduced informativeness of these markers. The Human Gene Nomenclature Committee has approved the use of the gene symbol *EMWX* (episodic muscle weakness, X-linked) for the gene encoding this disorder.

A centromeric crossover event was identified in the ~1-Mb region between the markers *DXS1224* and *DXS9985* in individual IV-18 (fig. 1). A telomeric crossover was identified in the ~200-kb region between the markers *DXS7103* and *OACA2* in individual IV-26. The position of these recombination events allows us to assign the interval for the *EMWX* locus to the ~2.8-Mb region between *DXS1224* and *DXS7103* (on the basis of the physical map of the region produced by Cox et al. [1998] and the current release of the distal Xp map produced by the Baylor Human Genome Center). Additional informative STRPs are currently being sought in the interval between *DXS9985* and *DXS1224,* to further reduce the size of the critical region.

Discussion

We have reported a novel syndrome of episodic weakness linked to Xp22.3. Although this disorder overlaps clinically with both the channelopathies and the congenital myasthenic syndromes, the temporal pattern of the disorder, the severity of exacerbations, and the X-linked mode of inheritance distinguish it from other known episodic syndromes.

The episodic nature of the weakness in this family is similar to that seen in disorders of ion-channel function, such as the periodic paralyses, nondystrophic myotonias, and episodic dyskinesias (table 3). These disorders have a similar pathophysiological basis, with dysfunction of ion-permeable transmembrane channels, resulting in abnormalities of sodium-, potassium-, or chloride-ion transport and altered neuromuscular transmission (Rudel and Lehmann-Horn 1998). Common clinical features include onset in the 1st decade of life, relatively rapid fluctuations in clinical status, and precipitation of episodes by environmental or other stimuli. Patients may be symptomatic only on exertion, when cold, or after ingestion of potassium, coffee, or alcohol. Diagnosis

is given on the basis of the clinical phenotype and characteristic neurophysiological findings of myotonia or electrical inexcitability. A variable response to membrane-stabilizing agents is seen (Hudson et al. 1995; Bulmand 1997). There is considerable genetic and clinical heterogeneity within this group of disorders. The mode of inheritance is either autosomal dominant or autosomal recessive; X-linked inheritance has not been identified in any channelopathy, to date.

Fluctuations in muscle strength, fatigability, ptosis, and response to anticholinesterases in some members of the family raise the diagnostic possibility of a congenital myasthenic syndrome (table 4). These syndromes are due to altered neuromuscular transmission secondary to abnormalities of acetylcholine-receptor subunits, or to synthesis, transport, or metabolism of acetylcholine. Inheritance is usually autosomal recessive, apart from the slow-channel syndromes, which are inherited in an autosomal dominant fashion (Engel 1994; Middleton 1998). Patients with congenital myasthenic syndromes usually have both an abnormal decremental response to repetitive nerve stimulation of affected muscles and increased jitter on single-fiber EMG. However, these studies may be normal in interictal periods in patients with a defect in acetylcholine resynthesis or packaging (see below). Fatigue-induced muscle weakness usually responds to anticholinesterase therapy, with the exception of patients with the slow-channel syndrome or endplate-cholinesterase deficiency (Engel 1994).

The temporal pattern of weakness seen in this family is unique. The severity and speed of onset of weakness are similar to those of the channelopathies, suggesting that the underlying pathophysiology may be dysfunction of ion-permeable transmembrane channels (table 4). In the periodic paralyses, weakness may develop over minutes to hours but does not usually persist for more than a few days, as opposed to the weeks-to-months–long period of weakness seen in several of the patients described above. The proband developed progressive chronic weakness and fatigability in his 5th decade, after 25 years of being relatively symptom free. A similar disease course has been described in the subset of patients with periodic paralysis in whom a progressive myopathy develops in middle age (Bradley et al. 1990; Links et al. 1990).

Episodic symptomatology is unusual in the congenital myasthenic syndromes, apart from the rare autosomal recessive disorder known as "familial infantile myasthenia," which is the result of a presynaptic defect in acetylcholine resynthesis or packaging (Mora et al. 1987; Matthes et al. 1991; Engel 1994). Onset is usually at birth or in infancy, with fluctuating ptosis and feeding difficulties. Exacerbations of severe weakness and respiratory insufficiency occur during infancy and childhood and are precipitated by fever, excitement, or vomiting. The exacerbations become less frequent with increased age, and patients may experience only fatigability on exertion. Other patients develop mild-to-moderate weakness of cranial, limb, and respiratory muscles at rest (Mora et al. 1987; Engel 1994).

The muscle biopsy of the index case demonstrated dilatation and focal proliferation of the sarcoplasmic reticulum on electron microscopy, although frank vacuolation was not evident on light microscopy. The ultrastructural morphology has features in common with the vacuolar myopathy associated with the periodic paralyses (Rudel and Lehmann-Horn 1998) and with sarcotubular myopathy. The latter disorder was described in a single case report of two brothers from a Hutterite family with a nonprogressive congenital myopathy and myopathic changes on EMG (Jerusalem et al. 1973). Their subsequent clinical course has not been reported, but the muscular weakness was not thought to be episodic.

The linkage results obtained in this family have narrowed the critical interval to that between *DXS7103* and *DXS1224,* a genomic region of ~2.8 Mb. The LOD score of 4.52, obtained for the fully informative STRPs between *OACA2* and *DXS9985,* significantly exceeds the threshold for linkage on the X chromosome, which is conventionally cited as a LOD score of 2.

Within the critical interval, as currently defined, are several positional candidate genes. The chloride-channel IV gene (*CLCN4*) and Apical protein, *Xenopus laevis*–like gene (*APXL*) were identified as part of the Baylor Human Genome Center's genome-sequencing project (Ferrero et al. 1995). No genetic diseases have been associated with mutations in *CLCN4* or *APXL,* to date. *CLCN4* is a voltage-gated chloride channel that has been shown to be particularly abundant in skeletal and cardiac muscle and is also expressed in the brain, an expression pattern that is consistent with the symptomatology of this family (Van Slegtenhorst et al. 1994). No mutation has been identified in *CLCN4* in this family by DNA sequencing of all coding exons (Genbank);

Table 2

Two-Point LOD Scores for Polymorphic Markers on the X Chromosome

Marker Locus (cM)	LOD Score at θ =							
	.0	.001	.01	.05	.1	.2	.3	.4
DXS7103 (12.03)	$-\infty$	−.29	.67	1.23	1.34	1.23	.95	0.54
OACA2 (13)	4.52	4.51	4.45	4.18	3.83	3.06	2.19	1.19
DXS10005 (13)	4.52	4.51	4.45	4.18	3.83	3.06	2.19	1.19
DXS7108 (14.20)	2.71	2.71	2.67	2.51	2.30	1.84	1.32	.71
DXS85 (14.2)	2.71	2.71	2.67	2.51	2.30	1.84	1.32	.71
DXS10006 (16)	4.52	4.51	4.45	4.18	3.83	3.06	2.19	1.19
DXS9985 (16)	4.52	4.51	4.45	4.18	3.83	3.06	2.19	1.19
DXS7104 (18.12)	2.71	2.71	2.67	2.51	2.30	1.84	1.32	.71
DXS1224 (20.1)	$-\infty$	1.51	2.45	2.90	2.87	2.46	1.82	1.01

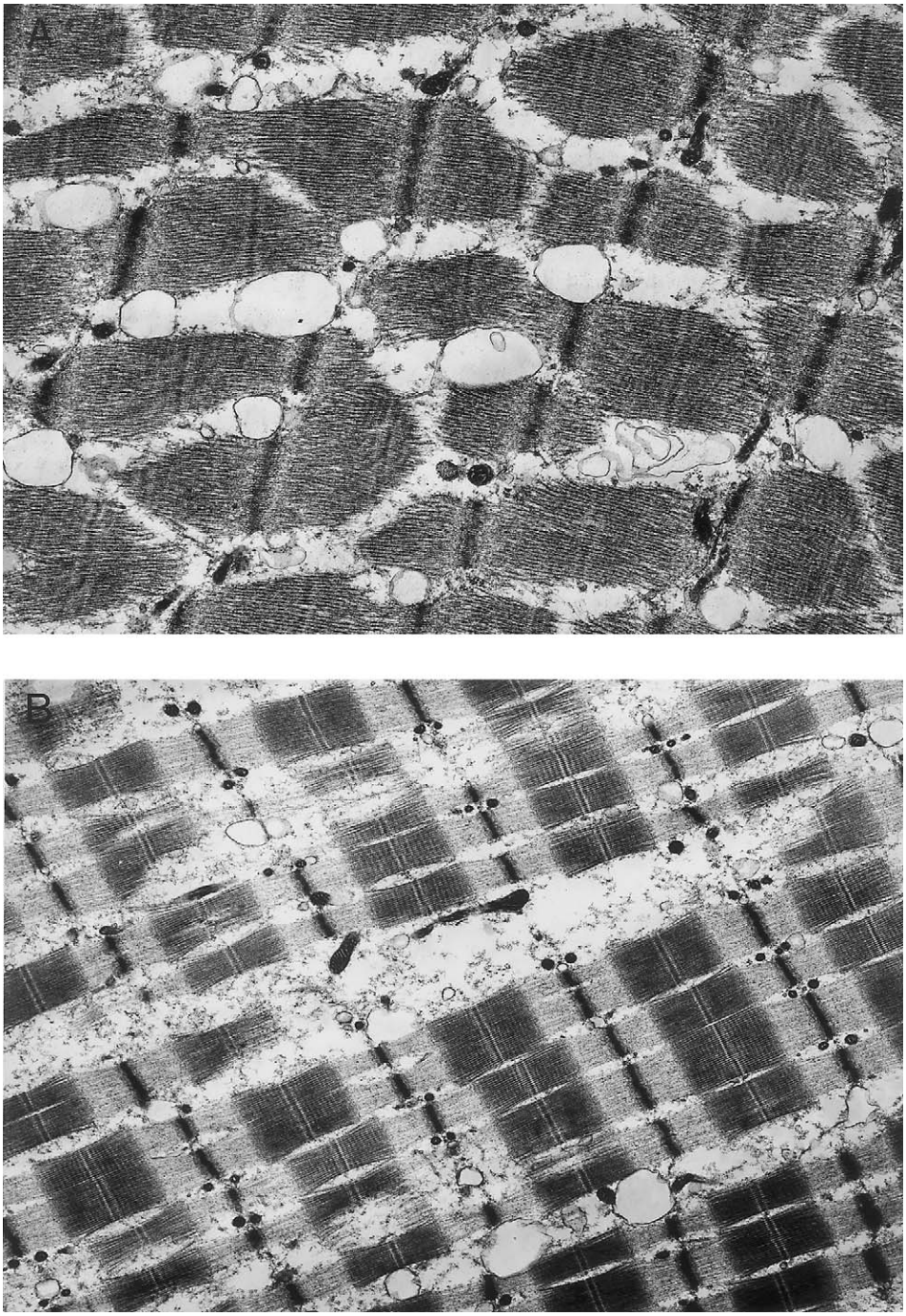

Figure 3 Electron microscopy of a quadriceps-muscle biopsy from individual II-3. The ultrastructural appearance shows dilation of the sarcoplasmic reticulum, with widened intermyofibrillar spaces.

however, the investigation of large-scale genomic rearrangements is still in progress. The *APXL* gene encodes a protein with a PDZ domain homologous to those of sodium-channel–binding proteins. (The name PDZ derives from the names of the three proteins that contain these motifs: the mammalian postsynaptic density protein, PSD95; the Drosophila disc large tumor suppressor, DlgA; and the mammalian tight junction protein, Z01.) *APXL* also has a domain with significant identity to the amiloride-sensitive sodium-channel–interacting protein APX of *Xenopus laevis* (Schiaffino et al. 1995). Although there is no evidence that *APXL* is expressed at significant levels in skeletal muscle, mutations in sodium-ion channels are well-described causes of muscle weak-

Table 3

Genetic Episodic Disorders

Disorder	Locus	Gene	Protein Product
Periodic paralyses/myotonias:			
Sodium-channel disorders:[a]			
Hyperkalaemic periodic paralysis, paramyotonia congenita, myotonia fluctuans, permanent myotonia, atypical (acetazolamide-responsive) myotonia[b]	17q23-q25	*SCN4A*	Skeletal-muscle sodium-channel α subunit
Calcium-channel disorders:[c]			
Hypokalaemic periodic paralysis	1q31-q32	*CACNL1A3*	α_{1S} Subunit of dihydropyridine receptor
Familial hemiplegic migraine, spinocerebellar ataxia type 6 (EA2)	19p13	*CACNL1A4*	α_{1A} Subunit of P/Q-type calcium channel
Malignant hyperthermia	19q13.1	*RYR1*	Skeletal-muscle–ryanodine receptor
	7q21-q22	*CACNL2A*	α_{2}–δ subunit of voltage-gated calcium channel
Chloride-channel disorders:[d]			
Thomsen's myotonia congenita, Becker's myotonia congenita	7q35	*CLC1*	Skeletal-muscle chloride channel
Startle disease (hyperekplexia)	5q32	Glyα1	Glycine receptor α_1 subunit (chloride channel)
Potassium-channel disorders:			
Episodic ataxia/myokymia (EA1)[d]	12p13	*KCNA1*	Voltage-gated potassium channel
Paroxysmal choreoathetosis/spasticity[e]	1p		
Familial paroxysmal dyskinesias:[f]			
Paroxysmal nonkinesigenic dyskinesia	2q33-q35	*SLC2C*	? Ion-channel gene
Familial kinesigenic dyskinesia, paroxysmal exertional dyskinesia, paroxysmal hypnogenic dyskinesia, nocturnal paroxysmal dystonia			
Episodic ataxias:			
Periodic vestibulocerebellar ataxia[g]	19p		
Acetazolamide-responsive hereditary paroxysmal cerebellar ataxia[h]	19p		
Long QT syndrome:[i]			
Long QT syndrome 1	11p15.5	*KVLQT1*	Cardiac-potassium channel
Long QT syndrome 2	7q35-q36	*HERG*	Cardiac-potassium channel
Long QT syndrome 3	3p21-p24	*SCN5A*	Cardiac-sodium channel
Long QT syndrome 4	4q25-q27		
Long QT syndrome 5	21q22	*MinK*	
Miscellaneous:			
Hereditary thermosensitive neuropathy[j](autosomal dominant)			

[a] From Ptacek et al. 1993.
[b] From Rudel et al. 1993.
[c] From Greenberg 1997.
[d] From Rudel and Lehmann-Horn 1998.
[e] From Auburger et al. 1996.
[f] From Fink et al. 1996 and Fouad et al. 1996.
[g] From Damji et al. 1996.
[h] From Vahedi et al. 1995 and Von Brederlow 1995.
[i] From Wang 1996.
[j] From Magy et al. 1997.

Table 4

Comparison of Clinical Characteristics of the Myasthenic Syndromes, Channelopathies, and X-Linked Episodic Weakness

Clinical Feature(s)	Congenital Myasthenic Syndromes	Periodic Paralyses	X-Linked Episodic Weakness
Ophthalmoplegia and ptosis	+	−	+
Complete recovery between episodes	−	+	+
Exacerbations with illness	+	−	+
Environmental precipitants	−	+	+
Fatigability	+	−	+
Bulbar involvement	+	−	+
Respiratory muscle involvement	+	−	−
Myalgia, cramps	−	+	+
Dystonia	−	+	+
Tremor	−	+	+
Neuropathy	−	−	+
Response to anticholinesterases	±	−	±
Decrement on repetitive nerve stimulation	+	−	−

NOTE.— "+" indicates presence; "−" indicates absence; and "±" indicates variability.

ness (table 3). Other genes within the region include those responsible for oculo-cutaneous albinism type 1 (MIM 300500); the WD-40 repeat–containing gene *TBL1,* associated with late-onset sensorineural deafness (Bassi et al. 1999); microphthalmia with linear skin-defects syndrome (MIM 309801); Opitz G/BBB syndrome, associated with midline abnormalities, such as cleft lip, laryngeal cleft, heart defects, hypospadias, and agenesis of the corpus callosum (MIM 300000); amelogenesis imperfecta (MIM 301200); and phosphoribosylpyrophosphate synthetase II, which causes a Lesch-Nyhan–like syndrome (MIM 311860).

The identification of additional families with X-linked episodic weakness will permit the further assessment of candidate *EMWX* genes. Further characterization of the underlying genetic defect will clarify questions of nosology and, it is hoped, give insights into the etiology and pathogenesis of inherited episodic muscle syndromes.

Acknowledgments

The authors would like to thank the members of the family described in this report, for their enthusiastic cooperation and support. We thank Dr. Alex Kan, Department of Anatomical Pathology, The New Children's Hospital, for interpretation of muscle electron microscopy. We acknowledge and thank Anh Tran, George Elakis, Alexander Delvendahl, and Dr. Nan Yang for undertaking DNA extraction, SSCP analysis of *CLCN4,* and preparation and sequencing of the *CLCN4* mRNA. The initial genotyping was performed at the Australian Genome Research Facility, Melbourne. This study has been funded by a grant from the Muscular Dystrophy Association of New South Wales and by the Children's Hospital Fund. Infrastructure support from the South Eastern Area Laboratory Services (to P.T. and M.B.) is gratefully acknowledged.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Australian Genome Research Facility, http://www.agrf.org.au/ (for microsatellite typing with the PE Biosystems Linkage Set)

Baylor Genome Sequencing Center, http://www.hgsc.bcm.tmc.edu/ (for physical map of Xp22)

Genbank, http://www.ncbi.nlm.nih.gov/Web/Genbank/ (for genomic DNA sequences of *CLCN4*)

Marshfield Center for Medical Genetics, http://www.marshmed.org/genetics/ (for the order and genetic distances of STRP loci in Xp22.3)

Max Planck Institute of Molecular Genetics, http://www.mpimg-berlin-dahlem.mpg.de/ (for the integrated X-chromosome–database oligonucleotide primer sequences)

Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/Omim (for oculo-cutaneous albinism type 1 [MIM 300500], microphthalmia with linear skin-defects syndrome [MIM 309801], Opitz G/BBB syndrome [MIM 300000], amelogenesis imperfecta [MIM 301200], and phosphoribosylpyrophosphate synthetase II [MIM 311860])

Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www-genome.wi.mit.edu/ (for order and genetic distances of STRP loci in Xp22.3)

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