Dominant spinal muscular atrophy with lower extremity predominance

Linkage to 14q32

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ABSTRACT

Objective: Spinal muscular atrophies (SMAs) are hereditary disorders characterized by weakness from degeneration of spinal motor neurons. Although most SMA cases with proximal weakness are recessively inherited, rare families with dominant inheritance have been reported. We aimed to clinically, pathologically, and genetically characterize a large North American family with an autosomal dominant proximal SMA.

Methods: Affected family members underwent clinical and electrophysiologic evaluation. Twenty family members were genotyped on high-density genome-wide SNP arrays and linkage analysis was performed.

Results: Ten affected individuals (ages 7–58 years) showed prominent quadriceps atrophy, moderate to severe weakness of quadriceps and hip abductors, and milder degrees of weakness in other leg muscles. Upper extremity strength and sensation was normal. Leg weakness was evident from early childhood and was static or very slowly progressive. Electrophysiology and muscle biopsies were consistent with chronic denervation. SNP-based linkage analysis showed a maximum 2-point lod score of 5.10 ($\theta = 0.00$) at rs17679127 on 14q32. A disease-associated haplotype spanning from 114 cM to the 14q telomere was identified. A single recombination narrowed the minimal genomic interval to Chr14: 100,220,765–106,368,585. No segregating copy number variations were found within the disease interval.

Conclusions: We describe a family with an early onset, autosomal dominant, proximal SMA with a distinctive phenotype: symptoms are limited to the legs and there is notable selectivity for the quadriceps. We demonstrate linkage to a 6.1-Mb interval on 14q32 and propose calling this disorder spinal muscular atrophy–lower extremity, dominant. *Neurology*® 2010;75:539–546

GLOSSARY

lod = logarithm of the odds; **SMA** = spinal muscular atrophy; **SMA-LED** = spinal muscular atrophy–lower extremity, dominant; **SNP** = single-nucleotide polymorphism.

Spinal muscular atrophies (SMAs) are hereditary disorders characterized by degeneration of spinal cord motor neurons. The majority of SMA cases show autosomal recessive inheritance and are caused by homozygous deletion or mutation of the *SMN1* gene on 5q (OMIM 253300, 253550, 253400, and 271150). Non-5q SMAs are rare, clinically diverse, and genetically heterogeneous.^{1,2} They are commonly classified by inheritance pattern and whether weakness involves predominantly distal or proximal musculature.

The non-5q SMAs with distal-predominant weakness show phenotypic overlap with the distal hereditary motor neuropathies. Recessive disorders in this category are caused by mutations in *IGHMBP2*,³ *PLEKHG5*,⁴ or show linkage to 9p21.1-p12⁵ or 11q.13.⁶ Dominant

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forms result from mutations in HSPB8,⁷ HSPB1,⁸ GARS,⁹ BSCL2,¹⁰ dynactin-1,¹¹ or show linkage to 7q34-q36¹² or 2q14.¹³

Other non-5q SMAs demonstrate proximal or diffuse weakness and demonstrate autosomal dominant inheritance. These include childhood autosomal dominant proximal SMA (OMIM 158600), SMA with late-onset Finkel type/ALS 8 (OMIM 182980/608627 caused by VAPB mutations¹⁴), scapuloperoneal SMA (OMIM 181405), and congenital benign SMA with contractures/congenital dominant SMA with lower limb predominance (OMIM 600175). These last 2 disorders were recently discovered to be allelic and caused by mutations in TRPV4 at 12q23-34.^{15,16}

In this study, we describe the clinical, pathologic, and genetic features of a large North American family with an autosomal dominant proximal SMA characterized by onset in early childhood, minimal progression, and an unusual pattern of selective proximal leg weakness. The gene for this disorder localizes to a 6.1 Mb interval on chromosome 14q32.

METHODS Medical histories and neurologic examinations were obtained from 25 family members (13 men and 12 women) spanning 4 generations of a North American family. Information on deceased or unavailable family members was obtained from relative interviews or genealogic records. A participant was considered to be affected when examination demonstrated proximal lower extremity weakness as assessed by a single senior neuromuscular specialist (M.A.-L.). Age at onset was considered to be the time when parents first noticed muscle atrophy, walking delay, or abnormal gait. Diagnostic EMG/nerve conduction studies were available and reviewed for 6 affected family members. All nerve conduction studies had been performed in our institutional electrodiagnostic laboratory using routine protocols and laboratory-specific normal values. EMGs were performed and interpreted by a senior clinical neurophysiologist (M.A.-L.). Five additional individuals (3 unaffected and 2 affected) consented to limited EMG of the quadriceps as part of this study. Slides from 2 muscle biopsies previously obtained for diagnostic purposes were reviewed. Linkage analysis was performed on 20 family members using single-nucleotide polymorphism (SNP) genotypes from Affymetrix Genome-wide Human SNP Arrays (version 5.0 or 6.0). All analyses assumed autosomal dominant inheritance with complete penetrance, a disease allele frequency of 0.01%, no phenocopies, and Affymetrix "Caucasian" allele frequencies. Two-point logarithms of the odds (lod) scores were calculated by FastLink V4.1,¹⁷ while parametric multipoint lod scores and haplotypes were generated with GeneHunter V2.1r5.¹⁸ Both software packages were accessed through easyLINKAGE Plus v. 5.08.¹⁹ SNP genotype calling and copy number analysis utilized Partek Genomics Suite v6.4 (Partek Inc., St. Louis, MO). Copy number changes were detected using a genomic segmentation algorithm requiring a minimum of 10

consecutive probes with copy number ≥ 2.5 or ≤ 1.5 . Baseline copy numbers were derived from International HapMap samples. SNP numbers and genomic locations reference NCBI Build 36.1 (March 2006).

Standard protocol approvals, registrations, and patient consents. This study received approval from the Washington University Human Studies Committee Institutional Review Board for experiments using human subjects. We obtained written informed consent from all subjects (or guardians of subjects) participating in the study.

RESULTS Clinical features. A partial pedigree of the studied North American family is presented in figure 1. Although participants' genders have been removed for anonymity, 5 instances of father-to-son transmission were observed, supporting an autosomal dominant mode of inheritance. Penetrance was high in the complete pedigree (not shown), with 45% (29 of 65) of at-risk individuals known to be affected by family report or examination. Clinical data from the 10 affected participants (6 men, 4 women) who were directly evaluated are presented in the table. The age at onset, pattern of weakness, and disease course were consistent across all individuals. Therefore, the proband's case history illustrates the phenotype. IV-13 was the product of a normal pregnancy and delivery, but in infancy his mother noted underdeveloped leg muscles. He did not walk until 18 months of age and his running was always slow. He could never climb stairs without the assistance of a railing, but managed a career involving upper extremity manual labor. His leg weakness did not progress even into the fifth decade, when he developed increased leg fatigue and pain. On examination at age 49, neurologic abnormalities were limited to lower extremity weakness and atrophy. No fasciculations were observed. Symmetric wasting was most prominent in the quadriceps, but involved distal leg muscles as well (figure 2A). Mild pes cavus deformity was present but there were no contractures. Quadriceps weakness was severe, with more moderate involvement of hip abduction. Other muscles, including knee flexors, distal leg, face, neck, and upper extremity muscles showed normal strength. Sensation was normal to all modalities. Patellar tendon reflexes were depressed, but all others were normal. His gait was waddling with excessive lumbar lordosis. Re-examination 4 years later found no significant decline in measured strength.

Sensory nerve conduction studies showed normal upper and lower extremity conduction velocities and amplitudes. Motor nerve conduction studies of the upper and lower extremities were normal except for small extensor digitorum brevis amplitudes. EMG showed large-amplitude (4–20 mV) and long-duration motor unit potentials in most leg muscles (figure 2B). Neurogenic recruitment patterns were

Figure 1 Spinal muscular atrophy–lower extremity, dominant pedigree and haplotype analysis

Gender and birth order have been deidentified to protect family privacy. Filled diamonds denote affected individuals while open diamonds represent unaffected individuals. A slash indicates deceased individuals. Generations are labeled with roman numerals while individuals are identified by numeral. The disease-associated haplotype is shaded in gray. The proband is marked with a large arrow. The small arrow and arrowhead mark recombination events that narrow the overall locus. Inferred haplotypes are indicated in italics. Eleven descendants of IV-1 are affected by family reports but were not available for study.

present in all leg muscles, but the severity was variable and paralleled the degree of muscle weakness. Although the first dorsal interosseous was normal in

bulk and strength, EMG showed large-amplitude motor unit potentials but normal recruitment. EMG of the proximal arm and lumbar paraspinal muscles

Table Clinical characteristics of spinal muscular atrophy–lower extremity, dominant

Patient no.	Age, y		Weak muscles, ^a MRC score	Reflexes: knee, ankle ^b	Pes cavus	EMG
	Onset	Examination				
IV-10	<1	50	KE 0, HF 4	0, 2	No	NA
IV-11	<1	46	KE 3, ADF 4	0, 0	No	Neurogenic
IV-13	<1	49	KE 2, HA 4	1, 2	Yes	Neurogenic
IV-3	7	58	KE 3	1, 2	Yes	Neurogenic
IV-4	6	55	KE 3, HA 4	1, 2	No	Neurogenic
IV-8	<1	53	KE 3, HF 4, KF 4	0, 2	No	Neurogenic
V-4	<2	33	KE 3, HA 4	NA	Yes	Neurogenic
V-5	4	24	KE 4	1, 2	Yes	Neurogenic
V-6	<1	24	KE 2, HF 4, KF 4, ADF 4	NA	Yes	Neurogenic
VI-1	<1	7	NA	0, 2	No	NA

Abbreviations: ADF = ankle dorsiflexion; HA = hip abduction; HF = hip flexion; KE = knee extension; KF = knee flexion; NA = not assessed or available; NCS = nerve conduction studies.

^a Muscles are only listed if Medical Research Council (MRC) score was <5. MRC strength scoring: 5 = normal strength, 4 = weak, 3 = full range against gravity, 2 = full range with gravity removed, 1 = visible contraction.

^b Reflex scoring: 2 = normal, 1 = reduced, 0 = absent.

was normal. No spontaneous activity was found in any muscle.

As with the proband, most affected individuals were recognized in the first 2 years of life. Three individuals were detected somewhat later in childhood (ages 4–7 years). IV-3 underwent heel cord release surgery before the age of 10. The indication for this release is unknown, but there was no history of toe walking in IV-3, nor in any other affected individual. None of the 10 participants examined had arthrogryposis or contractures, but 5 individuals had mild pes cavus. Prior diagnoses for affected family members include poliomyelitis (IV-4 and IV-5), limb girdle muscular dystrophy (V-4, IV-8), and congenital myopathy (V-6). The quadriceps muscle was most severely affected in all individuals, but the degree of weakness in other leg muscles varied. No patients had detectable arm or neck weakness. Leg weakness was static or only slowly progressive, with the oldest individual walking unassisted at age 58.

Nerve conduction studies in an additional 5 affected family members (IV-8, IV-10, V-4, V-5, and V-6) showed normal sural sensory responses. In the 3 younger patients (V-4, V-5, and V-6), the tibial and peroneal motor studies were also normal. In the 2 older patients, tibial and peroneal motor studies were normal except for a single small compound muscle action potential amplitude in each (extensor digitorum brevis in IV-8 and abductor hallucis in IV-10). EMG of all 5 individuals showed chronic denervation in both proximal and distal leg muscles, but in all cases the quadriceps showed the most severely reduced recruitment. Limited EMG of the quadriceps in 2 additional affected individ-

uals (IV-3 and IV-4) also showed severe neurogenic changes. Upper limb EMG was available for V-6 only, showing no abnormalities in the deltoid and first dorsal interosseous. Quadriceps EMG in 3 clinically unaffected individuals (IV-6, V-1, and V-2) was normal.

Quadriceps biopsies were available for 2 participants (IV-8 and V-4). IV-8 (age 26) had chronic partial denervation (figure 2, C and D), type II muscle fiber predominance, and inflammatory cell foci surrounding several perimysial blood vessels. V-4 (age 2) had end-stage muscle with atrophic fibers and type II muscle fiber predominance, but no inflammation (not shown).

Genetic studies. Genome-wide linkage analysis identified SNPs on chromosomes 3, 9, and 14 with 2-point lod scores >3.0 (figure 3A). Fine mapping of these 3 regions using additional SNPs identified a maximum 2-point lod score of 5.10 ($\theta = 0.00$) on 14q32 at SNP rs17679127. An additional 33 SNPs in the region had 2-point lod scores >3.0 ($\theta = 0.00$) (figure 3B). Linkage to 14q32 was further supported by multipoint parametric LOD scores of 3.00 over the 6.4-Mb (16 cM) interval between rs2615453 and rs10143250 (figure 3C). A disease-associated haplotype from 114 cM through the telomere at 14q (rs734313 to rs8011590) was shared by all affected members of the family (figure 1). No unaffected individuals carried the at-risk haplotype. A recombination between rs11620937 and rs1981266 in individual IV-7 narrowed the centromeric boundary to 126 cM. No telomeric recombinations were observed, leaving a minimal genomic interval of 6.1 Mb

(A) Leg atrophy in the proband (IV-13) was most pronounced in quadriceps, but also present in muscles of the lower leg. (B) Neurogenic giant motor unit potentials on EMG of the quadriceps in the proband (IV-13). (C) Hematoxylin-eosin-stained frozen section of the vastus medialis muscle (patient IV-8). Changes include internal nuclei, fiber splitting, muscle fiber hypertrophy, and atrophy. Small muscle fibers are angular (black arrow). (D) In another region, cellular infiltrate surrounds a perimysial vessel (white arrowhead). Bar = 30 μ m.

(Chr14:100,220,765–106,368,585). Because high-density SNP arrays were used for genotyping, we employed a genomic segmentation algorithm to assess copy number variation across chromosome 14. No segregating duplications or deletions were found.

Fine mapping of 3q27 showed only a single SNP with lod score of 3.00 ($\theta = 0.00$), while 7 SNPs with lod scores >3.00 were identified at 9q34 (maximal lod score 3.09, $\theta = 0.00$) (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). However, these loci were excluded after regional multipoint lod scores were negative (figure e-2) and no disease-associated haplotypes could be reconstructed.

DISCUSSION We identified a large North American family with dominantly inherited proximal lower extremity weakness. All affected individuals were recognized in childhood and showed the same pattern of proximal leg weakness with a striking predilection

for the quadriceps. The clinical histories we obtained suggest static or very slowly progressive weakness, but our follow-up has been too brief to objectively document this feature.

The EMG findings and myopathology were consistent with a chronic neurogenic etiology, but could not distinguish between loss of anterior horn cells and degeneration of motor axons. On clinical grounds, however, the absence of length-dependent weakness in this family argues against a motor neuropathy and the overall phenotype meets diagnostic criteria for a SMA.²⁰ In further support of classification as a SMA, other families with similar early-onset, proximal neurogenic weakness have historically been considered to have SMA and categorized as childhood/juvenile proximal SMA,²¹ autosomal dominant SMA III,²² or proximal hereditary motor neuronopathy type IV.²³ Therefore, we propose calling this disease spinal muscular atrophy–lower ex-

Figure 3 Linkage analysis of the spinal muscular atrophy–lower extremity, dominant pedigree

(A) Two-point linkage analysis of single-nucleotide polymorphism (SNP) markers spaced every 0.05 cM was performed, showing SNPs with logarithm of the odds (lod) scores >3.00 on chromosomes 3, 9, and 14. (B) Two-point linkage analysis with all Affymetrix GenomeWide 5.0 SNPs on distal 14q showed additional SNPs with significant lod scores. (C) Multipoint linkage analysis using SNPs spaced at 1-cM intervals (and increased around potential recombination sites) across distal 14q.

tremity, dominant (SMA-LED) to reflect its likely site of pathology, notable quadriceps involvement, and inheritance pattern.

The SMA-LED phenotype is unusual and can be distinguished from most other reported cases of autosomal dominant proximal SMA²⁴ by the absence of clinically apparent upper extremity involvement. None of the participating SMA-LED family members had detectable upper extremity weakness or atrophy on examination. The proband showed mild, subclinical, chronic denervation in the hand, but his child did not. This finding suggests that upper extremity involvement is related to length of disease or that there is intrafamilial variability. Because upper limb EMG was only available for these 2 family

members, we could not distinguish between these 2 possibilities. Lower extremity predominance has been described in several other dominant SMA families,^{25–27} including the one family with a mutation in TRPV4 on 12q23–q24.^{15,16,28,29} However, in contrast to SMA-LED, these pedigrees showed more prominent distal leg weakness, high rates of arthrogryposis, and congenital onset. Although the features of SMA-LED are different from most other autosomal dominant SMAs, we cannot exclude the possibility that SMA-LED represents one end of a spectrum shared with these other families. The SMA-LED phenotype most closely resembles 3 previously described small families,^{27,30,31} matching their age at onset, proximal lower extremity predominance, and

mild or absent progression. However, these case descriptions did not include enough clinical information to judge whether pronounced quadriceps involvement was present.

The SMA-LED quadriceps biopsies we analyzed were consistent with chronic denervation. In contrast to the type I muscle fiber predominance typically found in autosomal dominant proximal SMA,²⁷ both SMA-LED biopsies showed prominent type II muscle fiber predominance. Similar type II predominance has been reported in one other family.²⁸ The degree of fiber type predominance we have observed could originate from several potential mechanisms. First, successive rounds of denervation with reinnervation could produce what amounts to severe fiber type grouping. Alternatively, the SMA-LED pathologic process could selectively spare type II motor units or specifically target type I motor units. Finally, some authors have hypothesized that the absence of fiber type grouping, the onset of symptoms in utero or in early infancy, a lack of ongoing denervation, and static or minimally progressive weakness all argue for a defect of motor neuron embryogenesis rather than for motor neuron degeneration.²⁷ In this family, the presence of giant motor units on EMG is most consistent with successive rounds of denervation and reinnervation. We also found perivascular inflammation in one muscle biopsy. This inflammation is of uncertain significance. Perivascular mononuclear cell inflammation is a frequent finding in some hereditary neuromuscular disorders, including fascioscapulohumeral dystrophy³² and the dysferlinopathies,³³ but to our knowledge, has not been reported for any SMA. Additional pathologic studies are needed to clarify whether inflammation is a consistent finding in SMA-LED.

By genetic linkage studies we have identified the locus for SMA-LED on 14q32. SMA-LED is the first dominantly inherited SMA to show linkage to this region. Interestingly, a recessively inherited, severe SMA that is accompanied by pontocerebellar hypoplasia (SMA-PCH1 OMIM 607596) also localizes to 14q32. Null mutations in *vaccinia-related kinase 1* (*VRK1*) were recently identified as the causative genetic defect.³⁴ Although the *VRK1* gene is nearby, it is 3.6 Mb outside the minimal genomic interval for SMA-LED. According to the UCSC database, the genomic region we have identified spans 6.1 Mb and contains 73 known or predicted genes. Identification of the causative gene mutation in SMA-LED will have important implications for the pathogenesis of motor neuron diseases.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. M.B. Harms.

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DISCLOSURE

Dr. Harms, Dr. Allred, Dr. Gardner, and Dr. Fernandes Filho report no disclosures. Dr. Florence serves on a scientific advisory board for Prosensa; serves on the editorial board of *Neuromuscular Disorders*; and serves as a consultant for PTC Therapeutics, Inc. and Acceleron Pharma. Dr. Pestronk serves on the scientific advisory board of the Myositis Association; has served on a speakers' bureau for and received speaker honoraria from Athena Diagnostics, Inc.; owns stock in Johnson & Johnson; is director of the Washington University Neuromuscular Clinical Laboratory which performs antibody testing and muscle and nerve pathology analysis, procedures for which the Washington University Neurology Department bills; may accrue revenue on patents re: TS-HDS antibody, GALOP antibody, GM1 ganglioside antibody, and Sulfatide antibody; has received license fee payments from Athena Diagnostics, Inc. for patents re: antibody testing; and receives/has received research support from Genzyme Corporation, Inmed Inc., Knopp Neurosciences Inc., Prosensa, Isis Pharmaceuticals, Inc., sanofi-aventis, the NIH (5R01NS04326407 [site PI]), CINRG Children's Hospital Washington DC, and from the Muscular Dystrophy Association. Dr. Al-Lozi and Dr. Baloh report no disclosures.

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