Am. J. Hum. Genet. 59:872–878, 1996

Limb-Girdle Muscular Dystrophy and Miyoshi Myopathy in an Aboriginal Canadian Kindred Map to *LGMD2B* and Segregate with the Same Haplotype

Tracey Weiler,[1] Cheryl R. Greenberg,[2,4] Edward Nylen,[1] William Halliday,[3], Kenneth Morgan,[6] Douglas Eggertson,[5] and Klaus Wrogemann[1,2]

Departments of [1]Biochemistry and Molecular Biology, [2]Human Genetics, [3]Pathology, and [4]Pediatrics and Child Health, University of Manitoba, and [5]Department of Internal Medicine, St. Boniface General Hospital, Winnipeg; and [6]Departments of Human Genetics and Medicine, McGill University, and Montreal General Hospital Research Institute, Montreal

Summary

We report the results of our investigations of a large, inbred, aboriginal Canadian kindred with nine muscular dystrophy patients. The ancestry of all but two of the carrier parents could be traced to a founder couple, seven generations back. Seven patients presented with proximal myopathy consistent with limb girdle–type muscular dystrophy (LGMD), whereas two patients manifested predominantly distal wasting and weakness consistent with Miyoshi myopathy (distal autosomal recessive muscular dystrophy) (MM). Age at onset of symptoms, degree of creatine kinase elevation, and muscle histology were similar in both phenotypes. Segregation of LGMD/MM is consistent with autosomal recessive inheritance, and the putative locus is significantly linked (LOD scores >3.0) to six marker loci that span the region of the *LGMD2B* locus on chromosome 2p. Our initial hypothesis that the affected patients would all be homozygous by descent for microsatellite markers surrounding the disease locus was rejected. Rather, two different core haplotypes, encompassing a 4-cM region spanned by *D2S291-D2S145-D2S286,* segregated with the disease, indicating that there are two mutant alleles of independent origin in this kindred. There was no association, however, between the two different haplotypes and clinical variability; they do not distinguish between the LGMD and MM phenotypes. Thus, we conclude that LGMD and MM in our population are caused by the same mutation in *LGMD2B* and that additional factors, both genetic and nongenetic, must contribute to the clinical phenotype.

Received February 8, 1996; accepted for publication July 1, 1996.

Address for correspondence and reprints: Dr. Klaus Wrogemann, Department of Biochemistry and Molecular Biology, University of Manitoba, 770 Bannatyne Avenue, Winnepeg, Manitoba, R3E OW3 Canada. E-mail: wrogemn@bldghsc.lan1.umanitoba.ca

0002-9297/96/5904-0018$02.00

Introduction

The limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of disorders with variable inheritance patterns, ages at onset, rates of progression, and patterns of muscle involvement, although muscles of the shoulder and pelvic girdles are primarily involved (Brooke 1986; Bushby 1995; Yamanouchi et al. 1995). The clinical spectrum is broad, and a clearer classification is now beginning to emerge, with the identification of multiple loci for this group of muscular dystrophies. Thus far, one autosomal dominant locus has been identified and mapped to chromosome 5q31-q33 (Speer et al. 1992; Yamaoka et al. 1994), and another has been inferred to exist, by exclusion of linkage (Speer et al. 1993, 1995). Five loci for autosomal recessive forms of LGMD have also been mapped: *LGMD2A* to chromosome 15q15.1-q15.3 (Allamand et al. 1995), with the gene identified as *CANP3*, encoding a calcium-activated neutral protease (Richard et al. 1995); *LGMD2B* to chromosome 2p13.3 (Passos-Bueno et al. 1995); *LGMD2C* to chromosome 13q12 (Ben-Othmane et al. 1992, 1995), with the gene product identified as γ-sarcoglycan (A4,35DAG [Noguchi et al. 1995]); *LGMD2D* to chromosome 17q12-q21.33 (Roberds et al. 1994), with the gene product identified as α-sarcoglycan (adhalin); and *LGMD2E* to chromosome 4q12 (Bönnemann et al. 1995), with the gene product identified as β-sarcoglycan (Lim et al. 1995). In addition, a form of distal myopathy (Miyoshi myopathy [MM]) recently has been mapped to chromosome region 2p12-p14, and it has been suggested that MM may be an allelic variant of LGMD2B (Bejaoui et al. 1995).

Clinically, these various forms of LGMD have not been distinguishable (Bushby 1995; Bushby and Beckmann 1995; Yamanouchi et al. 1995), and therefore linkage studies of unrelated families may encounter genetic heterogeneity. It is thus useful to study large, consanguineous pedigrees and families from isolated populations (Lander and Botstein 1986; Hästbacka et al. 1992), to minimize genetic heterogeneity. We identified a large aboriginal Canadian kindred with nine affected

individuals who presented with autosomal recessive LGMD. Some of the patients were inbred, and our initial hypothesis was that they would be homozygous by descent for the chromosomal region harboring the disease-causing mutation. This has turned out not to be the case, and we report here that the candidate locus in this pedigree is linked to the *LGMD2B* locus with two distinct phenotypes, one a classical LGMD and the other MM.

Subjects and Methods

Patients and Pedigree

A large aboriginal kindred with nine patients exhibiting autosomal recessive LGMD or MM was identified in the province of Manitoba. Multiple sources of ascertainment were utilized to verify genealogical information and to construct a detailed pedigree (fig. 1). These included an extensive review of Anglican and Catholic diocese records dating back to 1860, interviews with the families and elders of the Sagkeeng First Nation, interview with the Grand Chief of Manitoba First Nations and review of his genealogical documents, and review of the records of both the Archives of the Government of Manitoba and the Hudson's Bay Company of Canada. Several consanguineous matings were identified, with one or both parents of every affected individual confirmed as a descendant of one founder couple, seven generations back. The pedigree as illustrated has been modified for reasons of confidentiality.

The affected individuals and some of their close relatives were interviewed and examined by C.R.G. and/or D.E. After informed consent was obtained, patients and extended-family members underwent a neuromuscular examination, and blood samples were obtained for DNA banking and creatine kinase (CK) analysis. Where possible, electrophysiological studies and open muscle biopsies were performed on the patients and cardiac assessments were undertaken.

DNA Studies

DNA was extracted from whole blood, as described elsewhere (Greenberg et al. 1987). Oligonucleotide primers designed to amplify 43 microsatellite loci shown to be linked to eight candidate genes including *CMD* (chromosome 6) (Hillaire et al. 1994), *FCMD* (chromosome 9) (Toda et al. 1994), *LGMD1A* (chromosome 5) (Weber et al. 1991; Speer et al. 1992), *LGMD2A* (chromosome 15) (Allamand et al. 1995), *LGMD2B* (chromosome 2) (Bashir et al. 1994; Passos-Bueno et al. 1995), *LGMD2C* (chromosome 13) (Ben-Othmane et al. 1992), *LGMD2E* (chromosome 4) (Lim et al. 1995), and *MPD1* (chromosome 14) (Laing et al. 1995) were obtained from Research Genetics. Forty-one DNA samples were genotyped according to protocols reported elsewhere (Sirugo et al. 1992; Rodius et al. 1994), with minor modifications. Alleles for each microsatellite locus were sized with respect to CEPH individual 134702. Allele designations can be found in the Genome Database (GDB 5.6 and 6.0).

Linkage Analysis

Linkage analysis was performed by using the LINKAGE programs (versions 5.1 and 5.2) (Lathrop and Lalouel 1984; Lathrop et al. 1984, 1986) and the FASTLINK version (3.0P) of the LINKAGE programs (Cottingham et al. 1993; Schäffer et al. 1994; Schäffer 1996). MLINK was used for two-point analysis of an autosomal recessive trait with complete penetrance under the assumption that all ancestors were unaffected. Disease-allele frequency was assumed to be .05 for the founders of the kindred, and marker allele frequencies initially were assumed to be equal but subsequently were estimated by using ILINK for chromosome 2p loci. To screen for linkage, two-point linkage analysis initially was performed on the subset of the kindred, comprising the patients, their typed relatives, and close ancestors but without any consanguinity or marriage loops (fig. 2). After suggestive linkage to chromosome 2p loci was found, the additional genealogical information was used to analyze the complex pedigree (fig. 1). The subset of the kindred was also used for the construction of haplotypes, by using seven microsatellite loci most closely linked to *LGMD2B: D2S327-D2S292-D2S291-D2S145-D2S286-D2S169-D2S329* (fig. 2) (GDB 5.6 map symbol C2M59) (Passos-Bueno et al. 1995). The most parsimonious haplotypes were selected, under the assumption that a minimal number of recombination events and no marker mutations occurred. Haplotypes were inferred where individuals were not typed.

Results

Pedigree and Clinical Description

The extended kindred showing nine affected individuals and four consanguinity loops is presented in figure 1. Segregation of the disease in the pedigree is consistent with autosomal recessive inheritance. Several consanguineous matings were identified, and at least one parent of every affected individual was confirmed to be a descendant of one founder couple, seven generations back (fig. 1). For two carrier mothers, however, it was not possible to establish a link to this founder couple. Clinical data from the nine affected individuals are presented in table 1. In summary, all patients noted their onset of weakness in adolescence and, at presentation, demonstrated features of either predominantly proximal or distal wasting and weakness. Extraocular and facial muscles were spared in all patients. Two of the patients (patients 1 and 2) manifested predominantly the MM

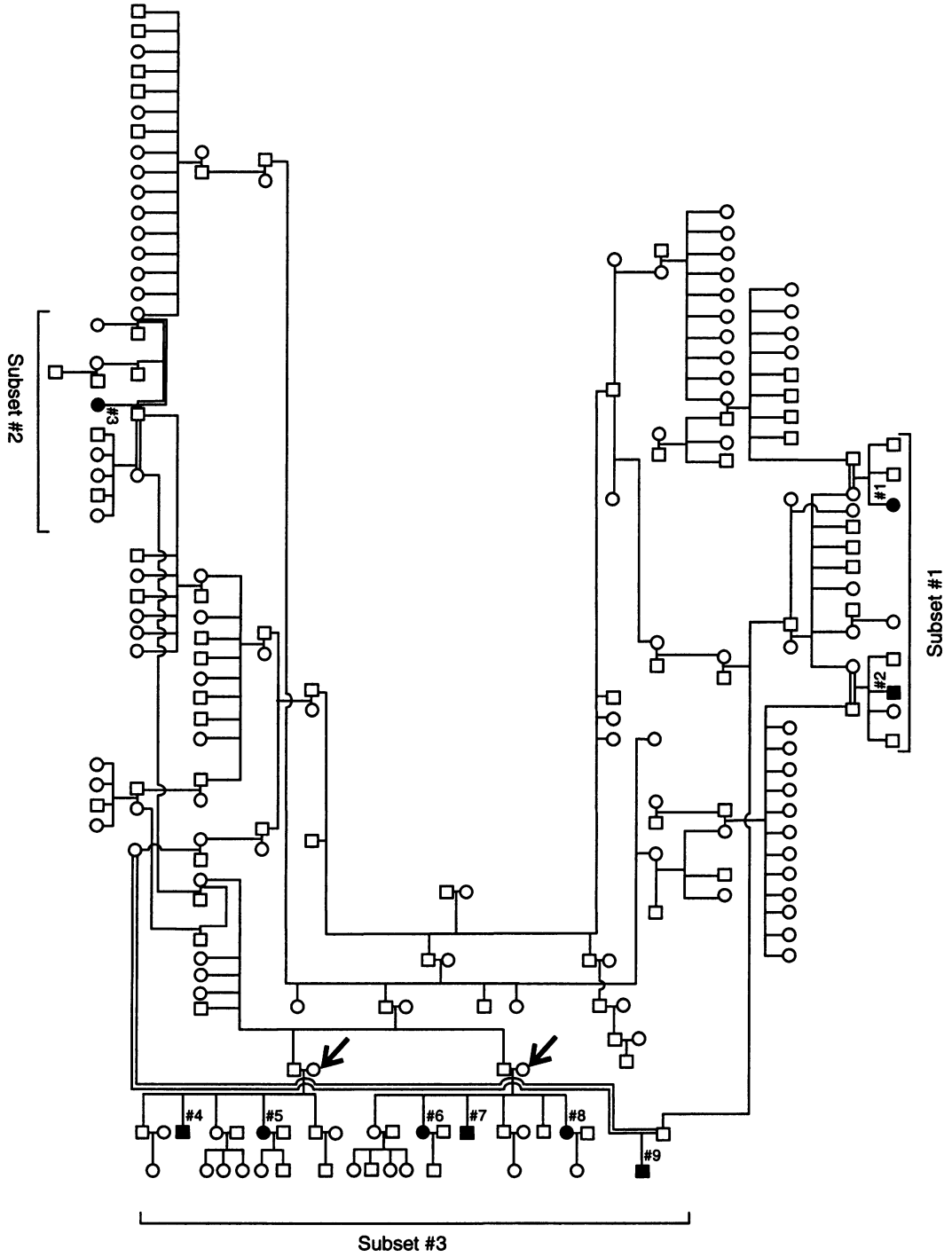

Figure 1 Pedigree of a large aboriginal kindred in which LGMD and MM are segregating. Patients 1 and 2 are affected with MM, and patients 3–9 are affected with LGMD (table 1). Arrows indicate the two parents who cannot be linked to the founder couple. The subset of this pedigree that was used in linkage and haplotype analyses is indicated with brackets. The pedigree has seven consanguinity and marriage loops. Consanguinity is indicated by double lines.

phenotype, with distal wasting, distal weakness, grossly elevated CK, and slow progression of disease to involve proximal muscles. Seven patients (patients 3–9) presented with predominantly proximal wasting and weakness (LGMD); all have shown distal involvement, and all but patient 9 are currently nonambulatory. Muscle biopsies all demonstrated dystrophic changes of varying degrees, and findings were similar in LGMD and MM

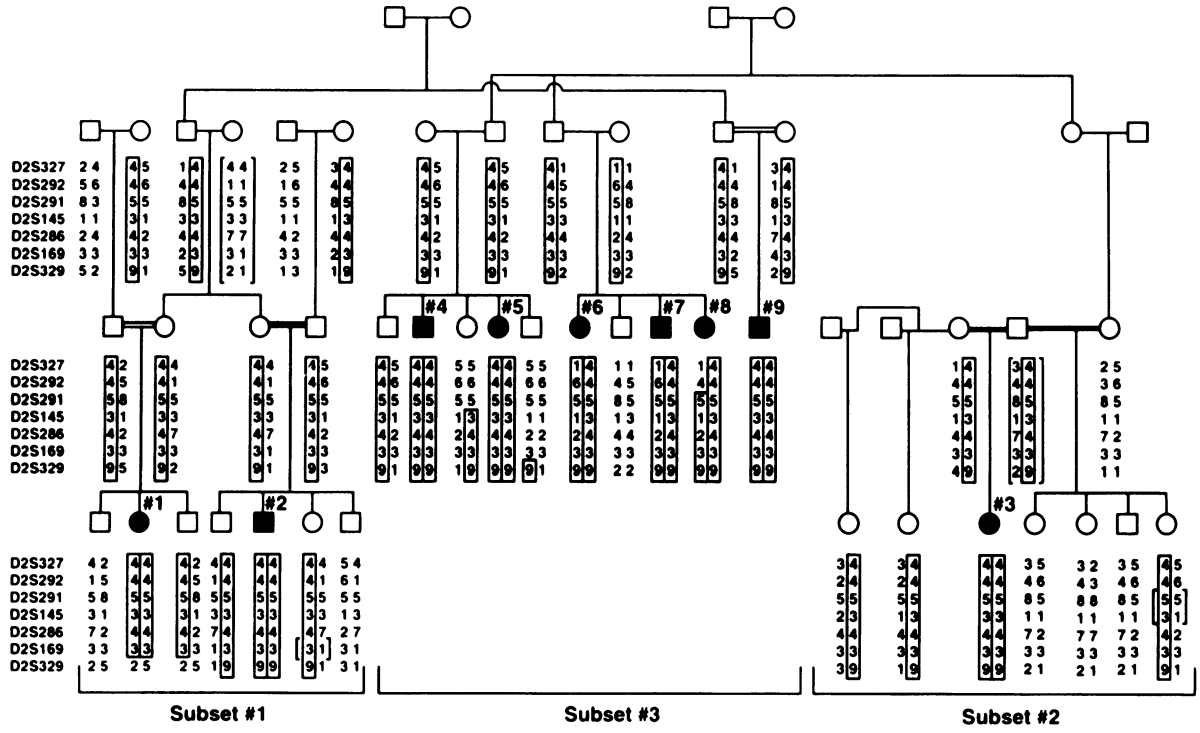

Figure 2 Haplotype analysis of the subset of the kindred (pedigree without loops). Genotypes are indicated for seven microsatellite loci linked to *LGMD2B*. The two haplotypes associated with LGMD are boxed; brackets indicate inferred haplotypes; consanguinity is indicated by double lines; and patient designation is as in figure 1. Unaffected individuals are designated by unblackened symbols.

patients. No cardiac disease was evident clinically in affected individuals, but only two have had formal assessments with electrocardiography and echocardiography. All but two obligate carrier parents were available for study, and all had normal muscle strength. The obligate-carrier mothers had CK levels of 45–131 U/liter (normal = 25–110 U/liter), with a median of 90 U/liter and a mean of 73 U/liter. The obligate-carrier fathers had CK levels of 105–350 U/liter (normal = 52–175 U/liter), with a median of 195 U/liter and a mean of 218 U/liter. CK levels of siblings of patients studied were 75–372 U/liter, and all were asymptomatic.

Linkage Analysis

In the subset of the pedigree (fig. 2), linkage was excluded for seven candidate regions, with two-point LOD scores <-2.0 for at least one of the markers in each region (data not shown). Two-point analysis of the disease versus 19 microsatellite markers linked to *LGMD2B* (Bashir et al. 1994; Gyapay et al. 1994; Passos-Bueno et al. 1995) on the subset of the pedigree, under the assumption of equally frequent marker alleles, gave LOD scores suggestive of linkage for several markers but >3.0 only for *D2S286* (data not shown). The marker-allele frequencies were then estimated, considering the marker locus to be unlinked to the disease, for the subset of the pedigree and for the complex pedigree with seven consanguinity and marriage loops (fig. 1), to minimize false-positive results for linkage (Terwilliger and Ott 1994) of LGMD/MM to *LGMD2B* in this kindred (table 2). The incorporation of additional information on linkage phase and identity by descent in the complex pedigree resulted in six markers, in an interval of 20 cM, with maximum LOD scores $Z(\hat{\theta}) > 3.0$ (table 2). These $Z(\hat{\theta})$'s for marker-allele frequencies that were estimated at a recombination fraction (θ) of .5 will be underestimates when there is linkage (Terwilliger and Ott 1994). To assess how conservative this approach was (table 2), the $Z(\hat{\theta})$'s were computed by estimating allele frequencies as nuisance parameters (Terwilliger and Ott 1994) for the six markers that had LOD scores >3.0 for linkage to LGMD/MM: *D2S136*—$Z(\hat{\theta}) = 4.60$, $\hat{\theta} = .025$; *D2S327*—$Z(\hat{\theta}) = 5.43$, $\hat{\theta} = .0$; *D2S292*—$Z(\hat{\theta}) = 3.41$, $\hat{\theta} = .033$; *D2S145*—$Z(\hat{\theta}) = 3.65$, $\hat{\theta} = .00$; *D2S286*—$Z(\hat{\theta}) = 4.11$, $\hat{\theta} = .00$; and *D2S329*—$Z(\hat{\theta}) = 4.59$, $\hat{\theta} = .030$.

Extended haplotypes constructed by using the seven loci most closely linked to *LGMD2B*—*D2S327-D2S292-D2S291-D2S145-D2S286-D2S169-D2S329* (fig. 2)—indicate that six of the nine patients (patients 1–5 and 9) including both LGMD and MM phenotypes were homozygous for a three-locus core haplotype, *D2S291-D2S145-D2S286,* that spans 4 cM. The three other patients (patients 6–8), all with the LGMD pheno-

Table 1

Clinical Data on Patients

Patient	Age at Onset	Age at Presentation (years)	Presenting Symptoms	CK[a] (U/liter)	Muscle Biopsy	Electromyography	Diagnosis	Present Status (Age [in years])
1	Mid teens	20	Unusual gait	9,251	Mild dystrophic changes with muscle-cell necrosis	...	MM	Ambulatory (25)
2	Mid teens	20	Weakness in legs, difficulty climbing stairs	13,470	End-stage dystrophy	Myopathic/neuropathic	MM	Ambulatory (24)
3	Early teens	14	Falling, difficulty getting up	12,120	...	Active myopathy	LGMD	Wheelchair (28)
4	Mid teens	19	Difficulty running	6,100	...	...	LGMD	Wheelchair (31)
5	Late teens	20	Difficulty running	8,810	Dystrophic	...	LGMD	Wheelchair (25)
6	Early teens	16	Inability to run or climb stairs	>4,000	Dystrophic	...	LGMD	Wheelchair (42)
7	Mid teens	19	Could not play sports, waddling gait	13,510	...	...	LGMD	Wheelchair (36)
8	Mid teens	23	Inability to run	6,040	...	...	LGMD	Wheelchair (40)
9	Late teens	25	Sore legs, loss of muscle bulk	10,320	Dystrophic	...	LGMD	Ambulatory (25)

[a] Normal values for females are 25–110 U/liter, and those for males are 52–175 U/liter.

type, carried this haplotype on their paternal chromosome and inherited a different haplotype from their aboriginal mother, whose ancestry did not trace back to the founder couple. No unaffected individual in this kindred studied to date is homozygous for or carries both core haplotypes shown to be linked to *LGMD2B*.

Discussion

The two different phenotypes observed in these patients, one with a predominantly distal muscle involvement and the other with a more proximal muscle involvement, are consistent with diagnoses of MM and LGMD, respectively. Both LGMD and MM recently have been mapped to the same chromosomal region on chromosome 2p1 (Bashir et al. 1994; Bejaoui et al. 1995; Passos-Bueno et al. 1995). Our findings of significant evidence for linkage of LGMD/MM to six chromosome 2p loci provides strong evidence that the myopathy in this kindred also maps to this region of chromosome 2p and thus is compatible with these diagnoses.

This is the first reported kindred that exhibits both of these phenotypes. Occurrence of distal and proximal myopathy in a single consanguineous kindred is reminiscent of a Finnish family described by Udd (1992). As in the family that we studied, the distal and proximal myopathy cannot be distinguished by CK elevation or muscle-pathology findings, although in the families studied by Udd the age at onset differs whereas in the aboriginal family that we studied it does not.

Haplotype analysis has established that the disease gene segregates with two different core haplotypes of the candidate region. This suggests that there are two mutant alleles of independent origin. In retrospect, this is compatible with the observation that genealogical reconstruction using multiple sources of information could not link two carrier mothers to the founder couple (fig. 1). With our evidence for linkage to *LGMD2B* in this kindred, haplotype analysis can now be used in predicting the carrier status of the unaffected siblings of the patients. Carrier status cannot be predicted on the basis of CK levels, sinces they are elevated only in some obligate-carrier parents.

Mapping of both LGMD and MM in different families to the same chromosomal region has led to the suggestion that these are the result of allelic variants of the same gene (Bejaoui et al. 1995). At first glance, the observation of two different haplotypes harboring the disease-causing mutations in the family that we studied seems to be compatible with this idea. However, the different haplotypes do not distinguish between the two phenotypes. Rather, four patients with LGMD and both MM patients are homozygous for the common haplotype. This observation makes it unlikely, at least in the

Table 2

LOD Scores for Linkage of LGMD/MM to Chromosome 2p Markers, for the Subset without Loops (SP) and the Pedigree with Seven Loops (P)

Locus (Genetic Distance[a] [in cM]) and Pedigree[b]	LOD Score at θ =					
	.00	.01	.05	.10	.20	.30
D2S136 (6):						
SP	2.13	2.14	2.08	1.88	1.34	.76
P	3.06	3.40	3.42	3.02	2.03	1.11
D2S327 (0):						
SP	2.55	2.50	2.27	1.97	1.35	.72
P	4.89	4.76	4.21	3.55	2.33	1.27
D2S292 (2):						
SP	−∞	1.37	1.78	1.73	1.32	.80
P	−∞	2.98	3.20	2.92	2.12	1.29
D2S145 (4):						
SP	1.37	1.34	1.20	1.02	.65	.31
P	3.28	3.17	2.75	2.26	1.37	.68
D2S286 (8):						
SP	3.05	2.98	2.67	2.29	1.54	.86
P	4.03	3.91	3.45	2.90	1.89	1.04
D2S329:						
SP	−∞	2.28	2.58	2.39	1.70	.95
P	−∞	3.96	4.10	3.67	2.52	1.39

NOTE.—Thirteen other microsatellite markers were also examined on chromosome 2p (*D2S337, D2S386, D2S147, D2S166, D2S380, D2S134, D2S290, D2S379, D2S282, D2S285, D2S358, D2S291,* and *D2S169*) but are not included in this table because they had maximum LOD scores <3.0 for linkage to LGMD/MM, for the pedigree with seven loops.

[a] From the next marker in this table; map order and genetic distances were taken from GDB 5.6 (map symbol C2M59).

[b] Marker-allele frequencies were estimated for the SP and P pedigree data, with the marker locus considered to be unlinked to LGMD/MM.

family that we studied, that the different phenotypes are explained by allelic heterogeneity. Instead, the most likely explanation is that the same disease-causing mutation underlies both clinical phenotypes, which differ as a result of additional genetic and/or environmental factors. If this explanation is supported once the gene and the disease-causing mutation(s) have been identified, then this pedigree may lend itself to the search for these additional factors.

Acknowledgments

We are indebted to the patients and their families, the elders and chiefs of the Sagkeeng First Nation in Manitoba, and Phil Fontaine, Chief of Manitoba First Nations, for their participation in this study. We also thank Dr. Alejandro Schäffer for providing the FASTLINK programs (version 3.0P), and we thank Mary Fujiwara for helpful discussion. This work was supported by the Medical Research Council of Canada, the Muscular Dystrophy Association of Canada, the Canadian Genetic Diseases Network, the Childrens' Hospital of Winnipeg Research Foundation, the Manitoba Medical Services Foundation, and the Paul H. T. Thorlakson Foundation Fund.

References

Allamand V, Broux O, Richard I, Fougerousse F, Chiannilkulchai N, Bourg N, Brenguier L, et al (1995) Preferential localization of the limb-girdle muscular dystrophy type 2A gene in the proximal part of a 1-cM 15q15.1-q15.3 interval. Am J Hum Genet 56:1417–1430

Bashir R, Strachan T, Keers S, Stephenson A, Mahjneh I, Marconi G, Nashef L, et al (1994) A gene for autosomal recessive limb-girdle muscular dystrophy maps to chromosome 2p. Hum Mol Genet 3:455–457

Bejaoui K, Hirabayashi K, Hentati F, Haines JL, Ben-Hamida C, Belal S, Miller RG, et al (1995) Linkage of Miyoshi myopathy (distal autosomal recessive muscular dystrophy) locus to chromosome 2p12-14. Neurology 45:768–772

Ben-Othmane K, Ben-Hamida M, Pericak-Vance MA, Ben-Hamida C, Blel S, Carter SC, Bowcock AM, et al (1992) Linkage of Tunisian autosomal recessive Duchenne-like muscular dystrophy to the pericentromeric region of chromosome 13q. Nat Genet 2:315–317

Ben Othmane K, Speer MC, Stauffer J, Blel S, Middleton L, Ben Hamida C, Etribi A, et al (1995) Evidence for linkage disequilibrium in chromosome 13–linked Duchenne-like muscular dystrophy (LGMD2C). Am J Hum Genet 57:732–734

Bönnemann CG, Modi R, Noguchi S, Mizuno Y, Yoshida M, Gussoni E, McNally EM, et al (1995) β-Sarcoglycan (A3b) mutations cause autosomal recessive muscular dystrophy with loss of the sarcoglycan complex. Nat Genet 11:266–272

Brooke MH (ed) (1986) A clinician's view of neuromuscular diseases. Williams & Wilkins, Baltimore

Bushby KMD (1995) Diagnostic criteria for the limb-girdle muscular dystrophies: report of the ENMC consortium on limb-girdle dystrophies. Neuromusc Disord 5:71–74

Bushby KMD, Beckmann JS (1995) Report of the 30th and 31st ENMC International Workshop on the limb-girdle muscular dystrophies—proposal for a new nomenclature. Neuromusc Disord 5:337–344

Cottingham RW Jr, Idury RM, Schäffer AA (1993) Faster sequential genetic linkage computations. Am J Hum Genet 53:252–263

Greenberg CR, Hamerton JL, Nigli M, Wrogemann K (1987) DNA studies in a family with Duchenne muscular dystrophy and a deletion at Xp21. Am J Hum Genet 41:128–137

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) The 1993–94 Généthon human genetic linkage map. Nat Genet 7:246–249

Hästbacka J, de la Chapelle A, Kaitila I, Sistonen P, Weaver A, Lander E (1992) Linkage disequilibrium mapping in isolated founder populations: diastrophic dysplasia in Finland. Nat Genet 2:204–211

Hillaire D, Leclerc A, Fauré S, Topaloglu H, Chiannilkulchaï N, Guicheney P, Grinas L, et al (1994) Localization of merosin-negative congenital muscular dystrophy to chromo-

some 6q2 by homozygosity mapping. Hum Mol Genet 3: 1657–1661

Laing NG, Laing BA, Meredith C, Wilton SD, Robbins P, Honeyman K, Dorosz S, et al (1995) Autosomal dominant distal myopathy: linkage to chromosome 14. Am J Hum Genet 56:422–427

Lander ES, Botstein D (1986) Mapping complex genetic traits in humans: new methods using a complete rflp linkage map. Cold Spring Harbor Symp Quant Biol 51:49–62

Lathrop GM, Lalouel JM (1984) Easy calculations of lod scores and genetic risks on small computers. Am J Hum Genet 36:460–465

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Lathrop GM, Lalouel JM, White RL (1986) Construction of human linkage maps: likelihood calculations for multilocus linkage analysis. Genet Epidemiol 3:39–52

Lim LE, Duclos F, Broux O, Bourg N, Sunada Y, Allamand V, Meyer J, et al (1995) β-Sarcoglycan: characterization and role in limb-girdle muscular dystrophy linked to 4q12. Nat Genet 11:257–265

Noguchi S, McNally EM, Ben Othmane K, Hagiwara Y, Mizuno Y, Yoshida M, Yamamoto H, et al (1995) Mutations in the dystrophin-associated protein γ-sarcoglycan in chromosome 13 muscular dystrophy. Science 270:819–822

Passos-Bueno MR, Bashir R, Moreira ES, Vainzof M, Marie SK, Vasquez L, Iughetti P, et al (1995) Confirmation of the 2p locus for the mild autosomal recessive limb-girdle muscular dystrophy gene (LGMD2B) in three families allows refinement of the candidate region. Genomics 27: 192–195

Richard I, Broux O, Allamand V, Fougerousse F, Chiannilkulchai N, Bourg N, Brenguier L, et al (1995) Mutations in the proteolytic enzyme calpain 3 cause limb-girdle muscular dystrophy type 2A. Cell 81:27–40

Roberds SL, Leturcq F, Allamand V, Piccolo F, Jeanpierre M, Anderson RD, Lim LE, et al (1994) Missense mutations in the adhalin gene linked to autosomal recessive muscular dystrophy. Cell 78:625–633

Rodius F, Duclos F, Wrogemann K, Le Paslier D, Ougen P, Billault A, Belal S, et al (1994) Recombinations in individuals homozygous by descent localize the Friedreich ataxia locus in a cloned 450-kb interval. Am J Hum Genet 54: 1050–1059

Schäffer AA (1996) Faster linkage analysis computations for pedigrees with loops or unused alleles. Hum Hered 46:226–235

Schäffer AA, Gupta SK, Shriram K, Cottingham RW Jr (1994) Avoiding recomputation in linkage analysis. Hum Hered 44:225–237

Sirugo G, Keats B, Fujita R, Duclos F, Purohit K, Koenig M, Mandel JL (1992) Friedreich ataxia locus in Louisiana Acadians: demonstration of a founder effect by analysis of microsatellite-generated extended haplotypes. Hum Genet 50:559–566

Speer MC, Gilchrist JM, Chutkow JG, McMichael R, Westbrook CA, Stajich JM, Jorgenson EM, et al (1995) Evidence for locus heterogeneity in autosomal dominant limb-girdle muscular dystrophy. Am J Hum Genet 57:1371–1376

Speer MC, Yamaoka LH, Gilchrist JH, Gaskell CP, Stajich JM, Vance JM, Kazantsev A, et al (1992) Confirmation of genetic heterogeneity in limb-girdle muscular dystrophy: linkage of an autosomal dominant form to chromosome 5q. Am J Hum Genet 50:1211–1217

Speer MC, Yamaoka LH, Gilchrist JM, Westbrook C, Stajich JM, Gaskell CP, Roses AD, et al (1993) Evidence for genetic heterogeneity in the dominant form of limb-girdle muscular dystrophy. Am J Hum Genet Suppl 53:1082

Terwilliger JD, Ott J (1994) Handbook of human genetic linkage. Johns Hopkins University Press, Baltimore

Toda T, Ikegawa S, Okui K, Kondo E, Saito K, Fukuyama Y, Yoshioka M, et al (1994) Refined mapping of a gene responsible for Fukuyama-type congenital muscular dystrophy: evidence for strong linkage disequilibrium. Am J Hum Genet 55:946–950

Udd B (1992) Limb-girdle type muscular dystrophy in a large family with distal myopathy: homozygous manifestation of a dominant gene? J Med Genet 29:383–389

Weber JL, Polymeropoulos MH, May PE, Kwitek AE, Xiao H, McPherson JD, Wasmuth JJ (1991) Mapping of human chromosome 5 microsatellite DNA polymorphisms. Genomics 11:695–700

Yamanouchi Y, Arikawa E, Arahata K, Ozawa E, Nonaka I (1995) Limb-girdle muscular dystrophy: clinical and pathologic reevaluation. J Neurol Sci 129:15–20

Yamaoka LH, Westbrook CA, Speer MC, Gilchrist JM, Jabs EW, Schweins EG, Stajich JM, et al (1994) Development of a microsatellite genetic map spanning 5q31-q33 and subsequent placement of the LGMD1A locus between D5S178 and IL9. Neuromuscul Disord 4:471–475