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Childhood activity on progression in limb girdle muscular dystrophy 2I

Brianna N Brun, BS[1], **Shelley RH Mockler, DSc**[2], **Katie M Laubscher, DPT**[2], **Carrie M Stephan, MA**[1], **Julia A Collison, BS**[1], **M. Bridget Zimmerman, PhD**[3], and **Katherine D Mathews, MD**[1,4]

[1]Department of Pediatrics, University of Iowa Hospitals and Clinics, USA

[2]Center for Disabilities and Development, University of Iowa Children's Hospital, USA

[3]Department of Biostatistics, College of Public Health, University of Iowa, USA

[4]Department of Neurology, University of Iowa Hospitals and Clinics, USA

Abstract

Limb girdle muscular dystrophy 2I is a slowly progressive muscular dystrophy due to mutations in the Fukutin-related protein (*FKRP*) gene. Clinicians are frequently asked if physical activity is harmful for pediatric patients with limb girdle muscular dystrophy 2I. The primary objective of this study was to determine if there is a relationship between self-reported childhood activity level and motor function and respiratory function in older children and adults with limb girdle muscular dystrophy 2I. We compared retrospective self-reported middle school activity level and sport participation with age at onset of weakness, 10-meter walk test and forced vital capacity later in life in 41 participants with *FKRP* mutations. We found no relationship between activity level in childhood and disease course later in life, suggesting that self-directed physical activity in children with limb girdle muscular dystrophy 2I does not negatively affect disease progression and outcome.

Keywords

Muscular dystrophies; α-dystroglycan; dystroglycanopathy; FKRP; exercise

Corresponding Author: Brianna Brun, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Iowa City, IA 52242, Ph: 319-356-1851, Fax: 319-384-8818, brianna-brun@uiowa.edu.

Author Contributions

BNB helped with study design, performed data analysis, data interpretation, and wrote the initial draft of the manuscript. SRHM, KML, CMS, and JAC assisted with data collection and provided critical review of the manuscript. MBZ performed statistical analysis, data interpretation, and provided critical review of the manuscript. KDM conceptualized and designed the study, performed data analysis, and provided critical review of the manuscript. All authors approved the final version of the manuscript.

Declaration of Conflicting Interests

The authors disclose no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statistical analysis was conducted by M. Bridget Zimmerman, PhD, Department of Biostatistics, College of Public Heath, University of Iowa, Iowa City, IA

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Introduction

The dystroglycanopathies are a group of autosomal recessive muscular dystrophies characterized by reduced or absent glycosylation of alpha dystroglycan, an extracellular component of the dystrophin glycoprotein complex.[1] Of the 18 currently known genes involved in alpha dystroglycan glycosylation, mutations in fukutin-related protein (*FKRP*) are the most common in Northern European populations. *FKRP* mutations typically result in limb girdle muscular dystrophy type 2I, manifested by proximal muscle weakness with varying age at onset, elevated CK, normal intelligence, late stage cardiomyopathy and respiratory insufficiency. Less commonly mutations in *FKRP* cause congenital muscular dystrophy.[2] There is an *FKRP* founder mutation (c.826C>A; p L276I) that is identified in heterozygous or homozygous state in virtually all patients.[3] Those homozygous for c. 826C>A tend to have a milder phenotype.[2,3]

Clinicians are regularly asked about appropriate physical activity for children with muscular dystrophy. Animal studies show accelerated muscle injury following eccentric exercise in models of dystrophin glycoprotein complex-related muscular dystrophies.[4–7] As a result, care guidelines for Duchenne muscular dystrophy (a dystrophin glycoprotein complex related muscular dystrophy) recommend gentle, submaximal exercise and stretching.[8] These recommendations are often applied to other related forms of muscular dystrophies. In contrast, research in humans[9–11] has shown that exercise can result in increased strength, even in those with dystrophin glycoprotein complex related muscular dystrophies, and can be encouraged. Thus, we were interested in exploring if self-reported high activity in childhood was associated with either better or worse motor function or pulmonary function later in life in a cohort of participants with limb girdle muscular dystrophy 2I.

Methods

Participants

All individuals with mutations in *FKRP* who are enrolled in a dystroglycanopathy natural history study (clinicaltrials.gov NCT00313677) were included in this study. Entry criteria for the natural history study included evidence of dystroglycanopathy based on elevated creatine kinase, muscle pathology, documented mutations in one of the known genes, or abnormal glycosylation of alpha dystroglycan in cultured fibroblasts. There are no predefined exclusion criteria for the natural history study. Clinical data was collected at entry into the study and updated annually. Inclusion in the current study was limited to those for whom we have self-reported middle school activity data.

Ethical Approval

The University of Iowa institutional review board (IRB) approved this study. Informed consent was obtained from all participants at enrollment in the natural history study. Additional written consent to release medical information was obtained for collection and review of medical records.

Self-reported data

A physical activity questionnaire was completed by all subjects during their first research assessment as part of the natural history study (supplemental file). Participants were asked to estimate their overall level of physical activity at different age ranges (grade school, middle school, high school, age 20–30, and >30 years old) using a Likert scale from 0 to 10, where 0 was little physical activity, 5 was moderate physical activity, and 10 was athletic or very active. They were also asked whether or not they participated in sports and lessons (e.g., swimming, dance, martial arts) for each age group (yes/no). We chose the reported activity during middle school (typically ages 11–14 years) for this analysis because it maximized the number of participants with analyzable data, and self-perceptions of ability during this age range are more accurate than early ages.[12]

Age at onset of disease was defined as the first symptom of motor weakness as reported by subjects, confirmed by medical record review where possible.

Motor function

As part of the natural history study, a number of motor outcome measures were collected. We chose to use the 10-meter walk test as a measure of motor function for this analysis because this measure has the most complete dataset in our cohort. The 10-meter walk test was administered by a trained physical therapist for all ambulatory individuals who were over 2 years of age and able to cooperate. If orthotics were used by the participant during normal activity, they were permitted during the timed test. Other aids (e.g., cane, walker) were not permitted. Participants were encouraged to walk or run as fast as they could do safely. Timing was started when the physical therapist said “go” and stopped after the second foot cleared the finish line. Participants were encouraged to continue past the 10-meter mark to prevent slowing down prior to completing the task.

10-meter walk test times from the most recent research assessment were converted to speed (cm/s), thus speed was zero cm/s for non-ambulatory individuals. For individuals who lost ambulation prior to their first research assessment, clinical data was reviewed to determine age at loss of ambulation. Walking speeds were compared to age and sex matched normative “maximum gait speed” values reported by Bohannon et al 1997 though pediatric normative values were not available. Thus, all individuals under age 20 were excluded from analysis of walking speeds. Individual z-scores were calculated based on these normative values and were used for statistical analysis.

Pulmonary function

Individuals had forced vital capacity measured at each research visit using a Renaissance portable pulmonary function machine by a physical therapist or a nurse experienced in the testing. In the current study, forced vital capacity percent predicted while sitting was used to evaluate respiratory function as it standardizes results against age, sex, and height based controls.

Statistical analysis

One-way analyses of variance (ANOVA) with test of mean contrast for a linear trend were performed to evaluate the association of self-reported middle school activity level or participation in sports/lessons with the two outcome measures, forced vital capacity and 10-meter walk test z-scores. In addition, since duration of disease may be associated with the outcome measures, a second analysis with duration of disease as covariate was also performed. Spearman correlation was used to evaluate the relationship between self-reported middle school activity level and participation in sports and lessons using three categorical variables (not involved, involved in sports or lessons, and involved in both sports and lessons), and between onset of disease and self-reported middle school activity level. To compare 10-meter walk test z-score between those with and without activity induced myoglobinuria, a two-tailed t-test was performed. Two-tailed t-tests were performed to compare age of onset, 10-meter walk test z-score, and middle school activity level between those with and without cardiomyopathy. A significance level of $p \leq 0.05$ was chosen for all statistical analyses.

Results

Out of the 59 individuals with FKRP mutations enrolled in the natural history study, we identified 41 individuals (69.5%)for whom middle school activity level questionnaire data was available. The 18 excluded subjects had not yet reached middle school at the time of enrollment. This group had earlier onset of weakness (mean = 5 years) and was skewed toward individuals with heterozygous mutations compared to the analyzed group. All 41 subjects had spirometry and age at onset data analyzed. The 10-meter walk cohort was limited to those ≥20 years old (n = 28) based on the published normative data. Two individuals had missing data for the 10-meter walk test, leaving 26 individuals available for the motor function analysis. Demographics are summarized in Table 1. The sub-group (>20 years old) analyzed for motor function is heavily skewed toward individuals with homozygous c.826C>A mutations. This reflects the age distribution by genotype of the cohort in general; individuals with compound heterozygous mutations are younger than individuals with homozygous c.826C>A mutations.

We found no significant relationship between retrospective self-reported level of middle school activity and 10-meter walk test in adulthood ($p = 0.81$; figure 1A). Similarly, we found no significant relationship between forced vital capacity and middle school activity levels ($p = 0.56$; figure 1B). Nineteen individuals (46%) had forced vital capacity greater than 80% of predicted. For both measures we found a wide range in our measures of function later in life at each of the reported levels of activity in middle school. For analyses using duration of disease as a covariate, no significant relationship was found between middle school activity level and either outcome measure:10-meter walk test ($p = 0.83$) or FVC ($p = 0.74$).

To determine the relationship between age of onset and middle school activity level, we compared these variables in two populations: the entire cohort and a subset with onset after age 12. For the entire cohort, there was a positive correlation ($r = 0.46$) between age of onset and self-rated middle school physical activity level ($p < 0.001$). In the subset of individuals

with onset after age 12 (n = 19), no significant relationship was found between age of onset and middle school activity level (figure 1C). Of the 4 individuals with self-reported middle school activity of 6, 75% had onset prior to age 20 compared to only 1 individual (activity level 8) in the remainder of those with onset after age 12.

To determine if a relationship between subjective activity level and sports/lesson participation existed, we compared self-reported middle school activity level to involvement in sports and lessons (figure 2) and found a positive correlation ($r = 0.61$, $p < 0.0001$). No individual self-rating activity at 5 or lower participated in sports, and only 4 (44%) took lessons. All individuals (n = 18) self-rating activity at 8 or higher participated in sports and/or lessons, and 8 (44%) of these individuals participated in both sports and lessons. There was no statistically significant relationship between involvement in sports and/or lessons and 10-meter walk test ($p = 0.41$) or forced vital capacity ($p = 27$).

We also looked at presence/absence of at least one episode of myoglobinuria to see if those who were more active were more likely to report myoglobinuria and to see if such episodes had any effect on later walk speed. Nine individuals (22%) of this cohort reported myoglobinuria, and of those individuals, 89% (n = 8) had middle school activity levels above 6. Two tailed t-test showed no significant difference between mean 10-meter walk test z-score comparing those with and without activity-induced myoglobinuria ($p = 0.42$).

Cardiomyopathy can occur in LGMD2I and can also affect motor function. Ten (24%) of the total cohort and six (23%) of the motor function cohort have had at least one abnormal echocardiogram, indicating cardiomyopathy. Age of onset of cardiomyopathy ranged from 13 to 48 years (middle school is generally 12–14 years). Age at onset was indeterminate in four individuals (ages 15, 30, 34 and 36 years) for whom the first echocardiogram was abnormal. All of these echocardiograms were done as part of routine health care, not because of symptoms. Middle school activity level ranged from 2 to 10 for individuals with cardiomyopathy and was not significantly different from those without cardiomyopathy ($p = 0.18$). Two tailed t-test showed no significant difference between mean 10-meter walk test z-score between those with and without cardiomyopathy ($p = 0.23$).

Discussion

We found that self-reported level of physical activity, from little activity to very active, and participation in sports did not correlate with performance on 10-meter walk test or spirometry later in life in a population of individuals with limb girdle muscular dystrophy 2I. Similarly, no relationship was found between middle school activity level and age of onset of weakness in individuals with onset after middle school. There was large variation in function within groups suggesting that other factors are more influential on progression of disease than earlier activity level.

Previous research investigating the effects of exercise programs in individuals with muscular dystrophy have included primarily adults and heterogenous groups of neuromuscular disorders with small numbers of individuals with limb girdle muscular dystrophy. Strength training regimens have shown modest improvements in muscle strength.[10,13,14] Aerobic

training, alone or in combination with strength training, appears to be beneficial in heterogeneous populations of adults with neuromuscular disorders[15,16] and cohorts of individuals with limb girdle muscular dystrophy 2I.[9] A systematic review of previous research showed negligible adverse effects of exercise therapy.[17]

Physical activity in pediatric populations is primarily studied in healthy individuals and rarely in those with rapidly progressing muscular dystrophies such as Duchenne muscular dystrophy. In boys with Duchenne muscular dystrophy, exercise regimes have shown little to no benefit,[18,19] while animal models show muscle damage following eccentric exercise.[4–7] In the current study, individuals who participated in a high level of physical activity in childhood did not have a slower walking speed on the 10-meter walk test later in life than those who were less active, as would be expected if this activity level had a net detrimental effect on muscle, nor did they have an earlier onset of symptomatic muscle weakness. As one would predict, individuals with earlier onset of weakness reported lower middle school activities when evaluating the entire cohort. Even among those who reported onset of disease-related weakness after age 12, we observed that a lower activity (rated 6, figure 1C) subgroup had earlier onset than those with higher activity levels. We suspect this reflects self-selection of lower activity by individuals who may have been experiencing subtle weakness or fatigue

Cardiopulmonary function in individuals with neuromuscular disease has been shown to improve following aerobic exercise, equivalent to improvements in deconditioned healthy controls. [9,15,20] Improvements are presumably related to countering the deconditioning that accompanies weakness.[21] Our study did not identify significant positive correlations between middle school activity level and pulmonary or motor function later in life based on limited outcome measures. Comparing those with and without cardiomyopathy, we were unable to identify a statistically significant difference between motor function or middle school activity level, suggesting that our motor function results were not affected by co-morbid cardiomyopathy. Further, in most cases, cardiomyopathy in our analyzed cohort had onset after middle school so is unlikely to have affected self-reported activity level.

We previously reported a high incidence (27%, similar to 22% in the present cohort) of exercise-induced myoglobinuria in individuals with limb girdle muscular dystrophy 2I.[22] The activities we reported associated with myoglobinuria support the impression here that individuals with limb girdle muscular dystrophy 2I are often quite active (e.g., weightlifting, swimming, wrestling) and are consistent with our current observation that this group described themselves as active in middle school (rated ≥6). It is interesting that individuals with activity-induced myoglobinuria did not have worse function in adulthood.

Limitations of this study include the small sample size and reliance on retrospective self-reported data. Previous research has shown that many variables including lower education level, maleness, and increased age may lead to overestimation of self-reported physical activity levels.[23] Estimation errors may be more prevalent in this population as they were reporting middle school activity level. The normative data used in this study was gathered from subjects on a 7.62-meter course rather than a 10-meter course. Since speed values were used rather than time for completion, the overall effect of this difference should be minimal.

Finally, age at onset and the two measures of function later in life (10-meter walk test and forced vital capacity) used in this analysis do not capture all aspects of the disease. There could be effects of exercise that we did not measure.

The question of whether a child with a genetic diagnosis of muscular dystrophy should be allowed to participate in self-selected activities, including organized sports, often arises in clinic, and there is little data available to support our clinical answers. The results of this study, together with previous studies, suggest that for individuals with limb girdle muscular dystrophy 2I (particularly those with milder phenotypes who are homozygous for the c.826C>A variant) being active in later childhood does not correlate with slower walking speed or decreased pulmonary function later in life. For those who were pre-symptomatic in middle school, activity was not correlated with age at onset of weakness. This preliminary study provides additional reassurance about the effect of self-selected activity in individuals with limb girdle muscular dystrophy 2I and suggests that participation in sports and physical activity during childhood does not negatively affect later function. It remains important for physicians to consider all aspects of an individual's health, such as cardiac function, prior to offering advice about activity level. Future studies using prospective data collection and long-term follow-up could further our understanding of the impact of childhood activity on all aspects of function later in life for individuals with muscular dystrophy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Muntoni F, Torelli S, Wells DJ, Brown SC. Muscular dystrophies due to glycosylation defects: diagnosis and therapeutic strategies. Curr Opin Neurol. 2011; 24(5):437–442. [PubMed: 21825985]
2. Mercuri E, Brockington M, Straub V, et al. Phenotypic spectrum associated with mutations in the fukutin-related protein gene. Ann Neurol. 2003; 53(4):537–542. [PubMed: 12666124]
3. Brockington M, Yuva Y, Prandini P, et al. Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C. Hum Mol Genet. 2001; 10(25):2851–2859. [PubMed: 11741828]
4. Weller B, Karpati G, Carpenter S. Dystrophin-deficient mdx muscle fibers are preferentially vulnerable to necrosis induced by experimental lengthening contractions. J Neurol Sci. 1990; 100(1–2):9–13. [PubMed: 2089145]

5. Dick J, Vrbova G. Progressive deterioration of muscles in mdx mice induced by overload. Clin Sci (Lond). 1993; 84(2):145–150. [PubMed: 8382579]
6. Moens P, Baatsen PH, Marechal G. Increased susceptibility of EDL muscles from mdx mice to damage induced by contractions with stretch. J Muscle Res Cell Motil. 1993; 14(4):446–451. [PubMed: 7693747]
7. Petrof BJ. The molecular basis of activity-induced muscle injury in Duchenne muscular dystrophy. Mol Cell Biochem. 1998; 179(1–2):111–123. [PubMed: 9543354]
8. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 2010; 9(2):177–189. [PubMed: 19945914]
9. Sveen ML, Jeppesen TD, Hauerslev S, Krag TO, Vissing J. Endurance training: an effective and safe treatment for patients with LGMD2I. Neurology. 2007; 68(1):59–61. [PubMed: 17200494]
10. Sveen ML, Andersen SP, Ingelsrud LH, et al. Resistance training in patients with limb-girdle and becker muscular dystrophies. Muscle Nerve. 2013; 47(2):163–169. [PubMed: 23169433]
11. Berthelsen MP, Husu E, Christensen SB, Prahm KP, Vissing J, Jensen BR. Anti-gravity training improves walking capacity and postural balance in patients with muscular dystrophy. Neuromuscul Disord. 2014; 24(6):492–498. [PubMed: 24684860]
12. Nicholls JG. Development of perception of own attainment and causal attributions for success and failure in reading. J Educ Psychol. 1979; 71(1):94–99. [PubMed: 438417]
13. McCartney N, Moroz D, Garner SH, McComas AJ. The effects of strength training in patients with selected neuromuscular disorders. Med Sci Sports Exerc. 1988; 20(4):362–368. [PubMed: 3173043]
14. Aitkens SG, McCrory MA, Kilmer DD, Bernauer EM. Moderate resistance exercise program: its effect in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1993; 74(7):711–715. [PubMed: 8328892]
15. Florence JM, Hagberg JM. Effect of training on the exercise responses of neuromuscular disease patients. Med Sci Sports Exerc. 1984; 16(5):460–465. [PubMed: 6513764]
16. Ansved T. Muscular dystrophies: influence of physical conditioning on the disease evolution. Curr Opin Clin Nutr Metab Care. 2003; 6(4):435–439. [PubMed: 12806218]
17. Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil. 2007; 88(11):1452–1464. [PubMed: 17964887]
18. Vignos PJ Jr, Watkins MP. The effect of exercise in muscular dystrophy. JAMA. 1966; 197(11): 843–848. [PubMed: 5952771]
19. de Lateur BJ, Giaconi RM. Effect on maximal strength of submaximal exercise in Duchenne muscular dystrophy. Am J Phys Med. 1979; 58(1):26–36. [PubMed: 434131]
20. Wright NC, Kilmer DD, McCrory MA, Aitkens SG, Holcomb BJ, Bernauer EM. Aerobic walking in slowly progressive neuromuscular disease: effect of a 12-week program. Arch Phys Med Rehabil. 1996; 77(1):64–69. [PubMed: 8554477]
21. Kilmer DD. Response to aerobic exercise training in humans with neuromuscular disease. Am J Phys Med Rehabil. 2002; 81(11 Suppl):S148–150. [PubMed: 12409819]
22. Mathews KD, Stephan CM, Laubenthal K, et al. Myoglobinuria and muscle pain are common in patients with limb-girdle muscular dystrophy 2I. Neurology. 2011; 76(2):194–195. [PubMed: 21220724]
23. Dyrstad SM, Hansen BH, Holme IM, Anderssen SA. Comparison of self-reported versus accelerometer-measured physical activity. Med Sci Sports Exerc. 2014; 46(1):99–106. [PubMed: 23793232]

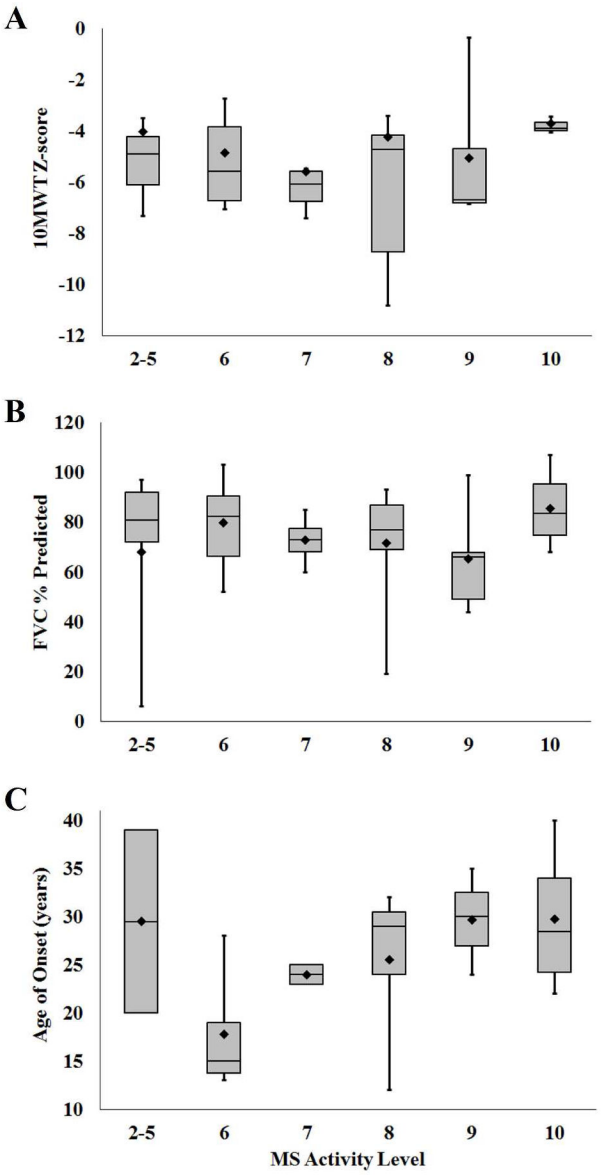

Figure 1.

Box plot of **(A)** 10-meter walk test time (10MWT) z-scores, **(B)** forced vital capacity (FVC) percent predicted, and **(C)** age of onset by middle school (MS) activity levels. Box plots show median values (middle line), 50th percentile (box outline), minimum/maximum (whiskers), and mean (diamond).

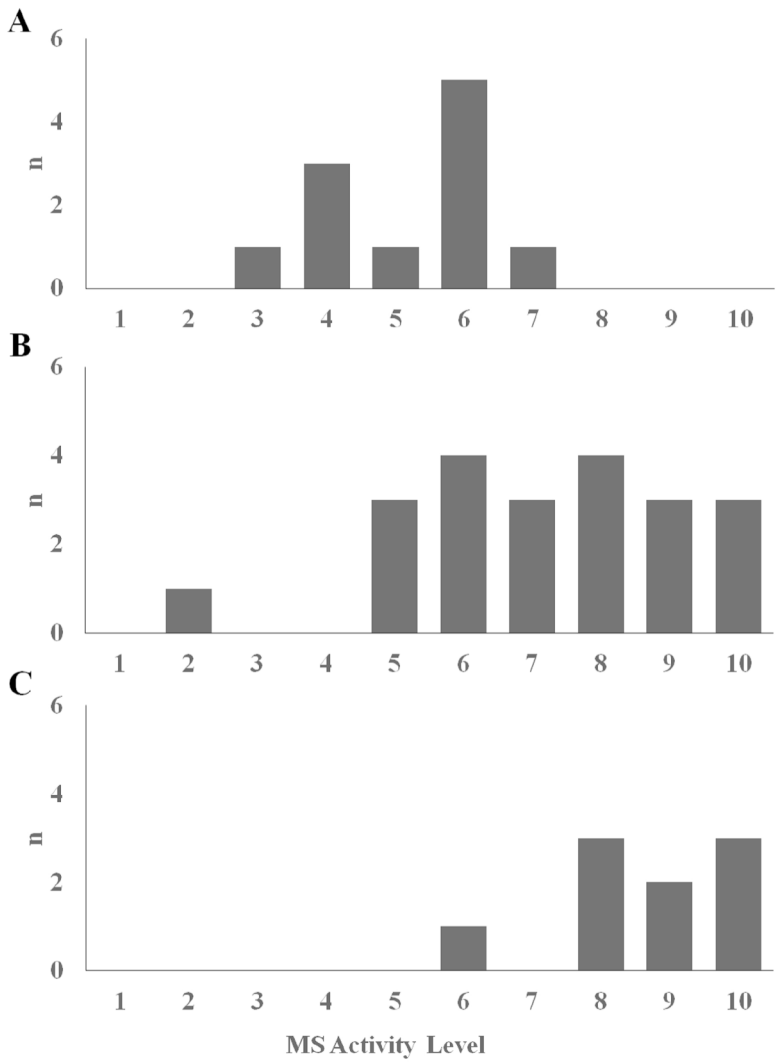

Figure 2.

Bar graphs depicting number of individuals **(A)** not involved in sports/lessons, **(B)** involved in sports or lessons, and **(C)** involved in both sports and lessons across middle school activity levels.

Table 1

Participant Demographics

	Whole cohort (n=41)	Motor function cohort (n=26)
Female	21 (51%)	15 (58%)
Age at last exam (range, mean, SD)	12–72 (33, 13.5)	25–72 (40, 10.7)
Homozygous for c. 826C>A	27 (66%)[1]	22 (85%)
Age at completion of survey (years)		
10–25	15 (37%)	4 (15%)
26–35	10 (24%)	9 (35%)
>35	16 (39%)	13 (50%)
Mean, SD; median	30, 13.6; 32	36, 11.6; 36
Middle school activity level (mean, SD; median)	7.0, 2.1; 7.0	7.4, 1.8; 7.5
10MWT z-score (mean, SD; median)	---	−4.66, 2.09; −4.86
FVC % predicted; sitting (mean, SD; median)	74.1, 23.0; 77	74.6, 19.3; 74
Cardiomyopathy[2]	10 (24.3%)	6 (23.1%)
Age at onset (years)		
<10	17 (41%)	5 (19%)
10–19	9 (22%)	8 (31%)
20–29	8 (20%)	8 (31%)
≥30	7 (17%)	5 (19%)
Mean, SD; median	14.5, 11.9; 11.0	18.1, 10.6; 16.0
Myoglobinuria	9 (22%)	7 (27%)

SD: standard deviation; 10MWT: 10-meter walk test; FVC: forced vital capacity; 1: 12 (29%) had compound heterozygous mutations, and 2 (5%) were homozygous for c.1100T>C. 2: cardiomyopathy was defined as ejection fraction < 55% or shortening fraction < 28%.