Title

The CINRG Becker Natural History Study: Baseline characteristics.

Journal

Muscle and Nerve, 62(3)

Authors

Clemens, Paula
Niizawa, Gabriela
Feng, Jia
et al.

Publication Date

2020-09-01

DOI

10.1002/mus.27011

Peer reviewed

Published in final edited form as:

Muscle Nerve. 2020 September ; 62(3): 369–376. doi:10.1002/mus.27011.

The CINRG Becker Natural History Study: Baseline Characteristics

Paula R. Clemens, MD[1], **Gabriela Niizawa**[2], **Jia Feng**[3], **Julaine Florence**[4], **Andrea Smith D'Alessandro, MS**[2], **Lauren P. Morgenroth, MS**[5], **Ksenija Gorni, MD**[6], **Michela Guglieri, MD**[7], **Anne Connolly, MD**[4], **Matthew Wicklund, MD**[8], **Tulio Bertorini, MD**[9], **Jean K. Mah, MD**[10], **Mathula Thangarajh, MD, PhD**[3], **Edward Smith, MD**[11], **Nancy Kuntz, MD**[12], **Craig M. McDonald, MD**[13], **Erik K. Henricson**[13], **Saila Upadhyayula, MD**[14], **Barry Byrne, MD, PhD**[15], **Georgios Manousakis, MD**[16], **Amy Harper, MD**[17], **Elena Bravver, MD**[17], **Susan Iannaccone, MD**[18], **Christopher Spurney, MD**[3], **Avital Cnaan, PhD**[3], **Heather Gordish-Dressman, PhD**[3], **CINRG BNHS Investigators**

[1]University of Pittsburgh School of Medicine and Department of Veterans Affairs Medical Center, Pittsburgh, PA

[2]University of Pittsburgh School of Medicine, Pittsburgh, PA

[3]Children's National Medical Center, Washington DC

[4]Washington University, St. Louis, MO

[5]TRiNDS, Pittsburgh, PA

[6]Centro Clinico Nemo Hospital, Milan, Italy

[7]Newcastle University, Newcastle Upon Tyne, UK

[8]Hershey Medical Center, Hershey, PA

[9]University of Tennessee, Memphis, TN

[10]Alberta Children's Hospital, Calgary, Alberta, Canada

[11]Duke University Medical Center, Durham, NC

[12]Lurie Children's Hospital, Chicago, IL

[13]University of California, Davis, Sacramento, CA

[14]Children's Healthcare of Atlanta, Atlanta, GA

[15]University of Florida, Gainesville, FL

[16]University of Minnesota, Minneapolis, MN

[17]Carolinas Medical Center, Charlotte, NC

Corresponding Author: Paula R. Clemens, MD, Room A506 Scaife Hall, University of Pittsburgh School of Medicine, 3550 Terrace Street, Pittsburgh, PA 15261, clempr@upmc.edu.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest: None of the authors has any conflict of interest to disclose.

[18]University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Introduction—We performed an observational, natural history study of males with in-frame dystrophin gene deletions causing Becker muscular dystrophy (BMD).

Methods—A prospective natural history study collected longitudinal medical, strength and timed function assessments.

Results—Eighty-three participants with genetically confirmed BMD were enrolled (age range 5.6 to 75.4 years). Lower extremity function and the percentage of participants who retained ambulation declined across the age span. The largest single group of participants had in-frame deletions that corresponded to an out-of-frame deletion treated with an exon 45 skip to restore the reading frame. This group of 54 participants showed similarities in baseline motor functional assessments when compared to the group of all others in the study.

Discussion—A prospective natural history cohort with in-frame dystrophin gene deletions offers the potential to contribute to clinical trial readiness for BMD and to analyze therapeutic benefit of exon skipping for Duchenne muscular dystrophy.

Keywords

Becker muscular dystrophy; musculoskeletal; dystrophinopathy; clinical features

Introduction

Becker muscular dystrophy (BMD) presents clinically between childhood and adult years demonstrating high variability of symptoms, signs and rate of disease progression. Like Duchenne muscular dystrophy (DMD), BMD is a genetic muscle disorder due to mutations in the dystrophin gene.[1] The majority of dystrophin gene mutations that cause BMD are in-frame deletions that preserve the open reading frame of dystrophin translation, predicted to result in an internally-deleted, truncated dystrophin protein that retains its amino and carboxy termini.[2] Patients with BMD caused by in-frame deletions in dystrophin often have a slower rate of clinical decline than patients with DMD.[3] Emerging therapies for patients with DMD use antisense oligonucleotides to induce alternative splicing, so called ‘exon skipping’, to expand a deletion mutation in the dystrophin mRNA in such a way that the open reading frame is restored.[4–6] Through restoration of a partially functional dystrophin protein in muscle, exon skipping could ameliorate the DMD phenotype.

A prior study correlating clinical phenotype with muscle dystrophin expression for 17 patients with BMD reported that those patients with the highest levels of muscle dystrophin expression were most likely to be asymptomatic.[7] Kesari et al. also found that the variability of clinical phenotype associated with a specific in-frame dystrophin deletion is reflected in variable dystrophin expression levels.[8] Interestingly, among 10 patients in this study who each had the same apparent mutation, an in-frame exon 45–47 deletion, the quantity of 400kDa-dystrophin protein varied from 5–80% of normal levels as assessed by Western blot. The muscle histopathology was also quite variable between patients. Studies of genotype –

phenotype correlation in BMD performed over the last 30 years have found it difficult to correlate specific clinical presentations of disease with genotype.[1, 7–10]

Despite the clinical variability of the BMD phenotype,[3, 9, 11, 12] clinical and patient experience with BMD could help to inform the potential therapeutic benefit of exon skipping therapy applied as a treatment for patients with DMD. Those DMD-causing deletions that are amenable to an exon 51 skip are most frequent, followed by a group of mutations that include those amenable to either an exon 45 or exon 53 skip.[13]

The Cooperative International Neuromuscular Research Group (CINRG) Becker Natural History Study was initially designed to enroll those patients with BMD whose in-frame dystrophin deletions, which corresponded to an exon skip by exon 45, 51 or 53, would restore the reading frame of an out-of-frame, DMD-causing mutation to inform the potential of exon skipping to be therapeutic for patients with DMD. Later in recruitment, we extended eligibility to participants with any deletion mutation in the dystrophin gene that was predicted to be in-frame. We present here the baseline characteristics of all participants in the CINRG Becker Natural History Study.

Methods

Study design and participants

The CINRG Becker Natural History Study enrolled patients age 4 years or older with BMD. Genetic confirmation of a dystrophin gene deletion that was predicted to retain the reading frame was performed by the central CINRG genetic counselor. During the recruitment period when the first 13 participants were enrolled, the protocol eligibility criteria specified an in-frame deletion that corresponded to the result of an exon 45, 51 or 53 skip that would restore an out-of-frame deletion to in-frame (Protocol version 1.1 dated December 4, 2013). However, this restriction was lifted by a protocol amendment (Protocol version 2.0 dated July 25, 2014) allowing participants to have any deletion in the dystrophin gene provided that it was predicted to retain the reading frame. The only exclusion criteria was investigator-assessed inability to comply with the protocol. Participants were enrolled at 16 study sites in 4 countries. Utilizing the CINRG research group, a global network of neuromuscular clinical study sites trained to measure outcomes reliably,[14, 15] this study included participants from the United States, Canada, the United Kingdom and Italy. The protocol was approved by institutional review boards at each participating center. Participants or caregivers gave written informed consent before enrolling, with children providing assent as appropriate.

Procedures

Demographic information and the protocol specified assessments were collected at the baseline visit (Supplemental Table 1). The assessments performed in this study followed the CINRG procedures that have been previously described in detail.[16] All functional assessments were collected by a trained clinical evaluator. Loss of ambulation was defined as the inability to complete the time to run/walk 10 meters test (TTRW). When possible, echocardiographic values were measured by the central study cardiologist from locally collected echocardiogram images; otherwise, they are taken from the clinical

echocardiogram report. Percent predicted pulmonary function test assessments were calculated using the Hankinson equations. For the purpose of percent predicted calculations, equations for Caucasians were applied to those participants indicating Asian or Mixed race.

Statistical analysis

All analyses consisted of summary statistics calculated overall and by decade of age (<20 years, 20 to <40 years, and 40 years or older). Summary statistics included numbers and percentages for outcomes that are categorical; numbers, mean, standard deviation, median, and minimums and maximums for outcomes that are continuous.

Results

Population Characteristics

Between March 2012 and March 2016, 83 participants enrolled in the CINRG Becker Natural History Study. The age range at enrollment was 5.6 to 75.4 years. Descriptive statistics are shown with median age for each of 3 cohorts of participants grouped by age of <20 years, 20 to <40 years and ≥40 years (Table 1). Median site enrollment was 5 with a range of 1–11 participants. Eight out of 83 (9.6%) were treated with glucocorticoids. Vital signs and concomitant medications were collected and were unremarkable.

Dystrophin Gene Mutations

The enrollment by deletion is shown (Table 2). The majority of participants had a deletion corresponding to an exon 45 skip. A few participants had a deletion corresponding to both an exon 45 and 51 skip or an exon 45 and 53 skip. Although the original study design intended to analyze data according to exon skip group, only the group with a deletion corresponding to an exon 45 skip had sufficient numbers to permit a sub-group analysis. The broad age and functional range within the mutation groups, along with the minority of participants not having an exon 45 skip mutation, does not allow a representative comparison between mutation groups.

Ambulatory Status

No patient less than age 20 years in the study had lost ambulation at baseline. Although one participant did not complete the TTRW at baseline, he is included in those who are ambulatory because he was able to complete the TTRW at subsequent visits. The percentage of participants who lost ambulation increased with age, especially in those older than 50 years (Supplemental Figure 1A).

Ambulation status was evaluated as a function of deletion corresponding to a frame-restoring skip of exon 45, 51 or 53 (Supplemental Figure 1B). Five participants are represented twice because their deletion corresponds to 2 of the frame-restoring exon skipping groups. Although the number of participants in the group with a frame-restoring skip of exon 53 was small, no participant over 20 years of age retained ambulation.

Functional Status

The baseline functional characteristics are presented as a function of age in 20-year intervals (Table 3). Only those who completed the TTRW then attempted the six minute walk test (6MWT), and this test was performed by all but 2 eligible participants. The percentage of participants who could do the 6MWT decreased from 94% in the <20 years old cohort to 78% in the 20 to 40 years old cohort to 50% in the older than 40 years old cohort. In addition, within those that could perform the test, the average 6MWT distance decreased with age, with the caveat that the range of distance walked was wide at all ages. The mean and median velocity for TTRW and the time to climb four steps test (TTCLIMB), performed by ambulatory participants, also decreased with age. The median velocity of the time to stand (TTSTAND) from supine decreased with age. The study design directed performance of TTSTAND from a chair for those participants who were unable to stand from the floor but could stand from a chair. Note that several participants who were able to complete the TTSTAND from supine also completed the TTSTAND from a chair. One participant in the 20–40 age group and 11 participants in the 40+ group could not stand from supine. Performance of upper extremity measures of 9-hole peg test and PUL did not vary significantly across the age range.

Brooke and Vignos scales of upper and lower extremity functional status, respectively, characterized global function. There was significant variability, and overall a lower level of function (increase in score) correlated with higher age, particularly across the 3 lowest grades on each scale (Table 4).

Quantitative muscle strength

Baseline values for quantitative muscle strength are presented by age group (Table 5). For most measures, the mean value decreased across the age span. There is significant variability between participants for each measure in each age group. Note that there is missing data in cases where an assessment was not done due to patient preference or technical difficulties with equipment.

Pulmonary function

Baseline values for spirometry are presented by age group (Supplemental Table 2). Assessments across the age span did not suggest significant decline with increasing age. Of note, the study enrolled 14 participants aged 5 to <11 years and spirometry may be unreliable under age 7 years.

Cardiac function

Cardiac function was assessed in participants by clinically collected ECG (data not shown) and echocardiogram (Supplemental Table 3). Since data collection was limited to clinically-obtained studies, the availability of this data was variable. There were no clinically significant abnormalities recorded by ECG. The median ejection fraction showed a mild decrease with older age.

Subgroup analysis based on exon skip group

The only subgroup of participants in this study with sufficient number of individuals for a separate sub-analysis was the group that corresponds to an exon 45 skip. The other sub-groups that correspond to either an exon 51 or exon 53 skip had insufficient numbers to analyze separately. The out-of-frame dystrophin gene deletions that are known to cause DMD and would be restored to the open reading frame with an additional exon 45 deletion includes deletions 12–44, 18–44, 44, 46, 46–47, 46–48, 46–49, 46–51, 46–53, 46–57, 46–59, and 46–60. We examined baseline characteristics in this exon 45 skip subset of participants that had a total number of participants of 54 (17 with age <20 years, 16 with age 20-<40 years and 21 with age 40+ years). The patterns of outcome assessments were not different for this subset when compared to the remaining participants that did not fall in the exon 45 skip subset (data not shown). Among the exon 45 skip subgroup the earliest age of transitioning to full-time wheelchair use was 30 years.

Discussion

The CINRG Becker Natural History Study is one of very few prospective natural history studies of patients with BMD.[3, 9, 11, 12, 17] There have also been a number of retrospective analyses of patients with BMD collected in single or multiple site studies with a focus on correlations of phenotype with genetic mutation and dystrophin protein expression in muscle.[1, 7–10] A significant challenge presented by the clinical presentation of BMD is the variations in age of symptom onset, pattern of clinical involvement of skeletal and cardiac muscle and the rate of progression of limb weakness and cardiomyopathy.[12, 17] In the cross-sectional analysis presented here of patients at enrollment in the longitudinal, observational CINRG Becker Natural History Study, the breadth of the clinical phenotype of BMD is evident.

Therapeutic development for DMD has involved both mutation-specific and mutation-independent strategies. Of the mutation-specific strategies, the approach of exon skipping to restore the reading frame of frame-shifting deletions has the potential to have a therapeutic effect on the largest number of patients with DMD. Approximately 70–75% of patients with DMD have a frame-shifting deletion in the dystrophin gene. With full implementation of exon skipping, nearly all dystrophin deletions that cause DMD could be restored to an open reading frame that would permit translation of an internally deleted, truncated dystrophin protein. The first exon skipping interventions for DMD that were approved by the Food and Drug Administration are morpholinos that result in exon 51[5, 18] and exon 53 skipping.[19, 20] Furthermore, there has been 1 Japan PMDA regulatory approval for an exon 53 morpholino for DMD.[20] Additional chemistries and exon targets for dystrophin exon skipping are under study by multiple research groups.

Because of the therapeutic promise of exon skipping therapy for patients with DMD, there has been increased interest in the phenotypes associated with BMD genotypes that correspond to the exon-skipped DMD genotypes. The previous study by Bello et al.[17] enrolled 28 participants with BMD whose dystrophin deletion mutations corresponded to an exon 45 skip and 10 participants whose mutations corresponded to an exon 51 skip. Overall, the exon 51 skip group had a milder phenotype as assessed by performance on timed

function tests than the exon 45 skip group, and the difference was independent of an age effect. Moreover, another previous study correlating muscle dystrophin expression and phenotype with BMD genotype found a higher mean level of muscle dystrophin expression by Western blot for an exon 51 skip group as compared to an exon 53 skip group.[7] Because of small numbers of participants in any exon skip group except for the exon 45 skip group in the present study, similar comparisons between exon skip groups could not be made. Similar to our results, however, Bello et al.[17] observed a negative correlation between all functional measures and age.

Loss of ambulation has a notable effect on quality of life in both DMD and BMD. In DMD, this loss of function occurs over a relatively narrow window of 8–16 years and is delayed by 2.1 – 4.4 years by treatment with glucocorticoid medication.[21] Furthermore, natural history studies of DMD have identified an association between loss of ambulation and patients with DMD corresponding to certain exon skip groups[22] The loss of ambulation milestone for DMD has been shown to be a meaningful clinical indicator of progression of disease and is highly correlated with muscle functional measures used commonly in clinical trials. In DMD, age of loss of ambulation is predictive of the inevitable markers of clinical progression of need for ventilatory support and survival.[21] Age of loss of ambulation in BMD, while known to be highly variable, has not been clearly correlated with genotype or subsequent milestones of clinical progression. Bello et al. generated Kaplan-Meier plots of loss of ambulation across the age span according to mutation group and muscle dystrophin quantity.[17] In the current study, the frequency of loss of ambulation at baseline increased with increasing age, especially after the age of 50 years. In the total cohort, 15 participants were non-ambulatory at baseline based on the criterion that they were unable to perform the TTRW assessment. Of these 15, 9 reported full-time wheelchair use. Of these 9 participants, the youngest age of transitioning to full-time wheelchair use was 20 years.

Timed function measures have demonstrated utility for the projection of clinical progression and in the assessment of a glucocorticoid treatment response in patients with DMD.[21, 23] These relationships are only beginning to be established for patients with BMD.[17] For timed function measures that reflect lower extremity function, we observed a decline in function with increasing age similar to Bello et al.[17] Overall these results suggest that lower extremity timed function tests and North Star Ambulatory Assessment (NSAA) could serve as outcome measures for clinical treatment trials in BMD that lead to functional improvements or delay of progression, especially if studies are of relatively long duration. In the current study, quantitative measures of muscle strength demonstrate a lower level of strength of proximal upper extremity and proximal lower extremity muscles in the oldest age group (>40 years) overall.

In contrast to lower extremity function, upper extremity function as assessed by 9-Hole Peg Test, did not appear to decline across the age span in the current study. This finding diverges from the pattern observed in DMD where upper extremity function measured by this test is progressively lost across the age span.[21] In the current study, there is insufficient data on the Performance of the Upper Limb (PUL) assessment to make a confident conclusion based on that test. The 9-Hole Peg Test and PUL are not likely to be sensitive to change in patients

with BMD unless an intervention resulted in a definitive improvement in function, rather than a delay in decline.

The Brooke[24] and Vignos[25] scales are functional measures that reflect progression of arm and leg weakness, respectively, and have previously been used in the functional evaluation of patients with DMD.[16] This assessment of disability across the age span in the current study was observed by both scales across the first 3 grades, which largely reflect proximal extremity function. These observations in participants with BMD for the Brooke and Vignos functional scales may suggest utility of these assessments in future clinical trials.

Pulmonary function did not vary significantly across the broad age span of this baseline assessment for the entire cohort. Therefore, these measures may be important as safety measures in clinical trials and are not likely to be useful efficacy measures. For this report's study, cardiac measures were limited to clinically-performed studies. In future studies of the utility of cardiac outcome measures, study-based [i]collection would be recommended. Previous studies of patients with BMD have suggested that a severe cardiac phenotype is observed in a minority of patients, does progress over time and does not clearly correlate with mutation or between family members with the same mutation.[12, 26, 27]

A limitation of the current study was the inability to correlate patient phenotype with muscle dystrophin quantity due to not having muscle dystrophin data, as could be done by a subset of prior studies.[9, 11, 17] Despite the inherent limitations of variable sample quality and the potential of sampling bias, the general observation in these prior studies is that greater amounts of muscle dystrophin protein content assessed by muscle biopsy taken from patients with BMD is positively correlated with all functional measures used to evaluate phenotype. A further limitation is that the cohort does not represent a racially diverse group despite enrolling participants from multiple locations across the world.

In summary, the baseline measures in a prospective, longitudinal, observational study of patients with BMD provide an initial snapshot of the variability of clinical presentation across the age span and are in general agreement with other cross-sectional studies.[3, 9, 11, 12, 17] Limitations of the study are inherent in the variability of the disease manifestations and their course of progression. Subsequent analysis of longitudinal data and patient reported outcome data from this cohort will expand our understanding of disease progression and will contribute to clinical trial readiness for BMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We dedicated researchers at the CINRG network sites that contributed to this project: University of Pittsburgh: Hoda Abdel-Hamid, Kathryn Brown, Karen Karnevas; Children's National Medical Center: Sally Evans, Rachel Walega, Lauren Carruthers, Katherine Kundrat, Bemnete Tadesse, Alynn Toles; Washington University: Alyssa Sonsoucie, Betsy Malkus, Catherine Siener, Rebecca Oschwald; Centro Clinico Nemo Hospital: Marco Gualandris, Cristina Grandi, Luca Mauro, Alessandra Di Bari, Elisa Pavesi; Newcastle University: Meredith James, Anna Mayhew, Robert Muni, Dionne Reynolds; Hershey Medical Center: Aiesha Ahmed, Anne Haulman, Victoria Kern, Heidi Runk, Matthew Bankert; University of Tennessee: Ana Phillips, Robert Henegar; Alberta Children's Hospital:

Angela Chiu, Karla Sanchez; Duke University Medical Center: Laura Case, Julie Coats, Karen Cornett, Andrea Hartzell; Lurie Children's Hospital: Colleen Blomgren, Carolyn Hyson, Theresa Oswald, Duncan Schulte, Lauren Webb; University of California, Davis: Candace Aguilar, Erica Goude, Alina Nicorici; Children's Healthcare of Atlanta: Han Phan, Kimberly Carvell, Saadia Khizer; University of Florida: Manuela Corti, Samantha Norman; University of Minnesota: Molly Stark, Natalya Alassy,; Carolinas Medical Center: Mohammed Sanjak, Anja Little, Brittany J. Neelands; University of Texas Southwestern Medical Center: Holly Lawrence, Lisa LaMotte, Leslie Nelson.

Funding for this study was provided by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (P50 AR060836-01). Travel funding for participants in this study was provided by the Muscular Dystrophy Association.

The authors take full responsibility for the contents of this manuscript, which do not represent the views of the Department of Veterans Affairs or the U.S. Government.

Abbreviations

BMD	Becker muscular dystrophy
CINRG	Cooperative International Neuromuscular Research Group
DMD	Duchenne muscular dystrophy
EK	Egen Klassifikation
PUL	Performance of the Upper Limb
NSAA	North Star Ambulatory Assessment
TTCLIMB	Time to climb 4 steps
TTRW	Time to run/walk 10 meters
TTSTAND	Time to rise to a standing position
6MWT	Six minute walk test

References

1. Beggs AH, Hoffman EP, Snyder JR, Arahata K, Specht L, Shapiro F, et al. Exploring the molecular basis for variability among patients with Becker muscular dystrophy: Dystrophin gene and protein studies. Am J Hum Genet 1991; 49:54–67. [PubMed: 2063877]
2. Hoffman EP, Fischbeck KH, Brown RH, Johnson M, Medori R, Loike JD, et al. Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. N Engl J Med 1988; 318:1363–1368. [PubMed: 3285207]
3. Bushby KM and Gardner-Medwin D. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. I. Natural history. J Neurol 1993; 240:98–104. [PubMed: 8437027]
4. Yokota T, Lu QL, Partridge T, Kobayashi M, Nakamura A, Takeda S, et al. Efficacy of systemic morpholino exon-skipping in Duchenne dystrophy dogs. Ann Neurol 2009; 65:667–76. [PubMed: 19288467]
5. Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol 2013; 74:637–47. [PubMed: 23907995]
6. Cirak S, Arechavala-Gomeza V, Guglieri M, Feng L, Torelli S, Anthony K, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet 2011; 378:595–605. [PubMed: 21784508]

7. Anthony K, Cirak S, Torelli S, Tasca G, Feng L, Arechavala-Gomeza V, et al. Dystrophin quantification and clinical correlations in Becker muscular dystrophy: implications for clinical trials. Brain 2011; 134:3547–59. [PubMed: 22102647]

8. Kesari A, Pirra LN, Bremadesam L, McIntyre O, Gordon E, Dubrovsky AL, et al. Integrated DNA, cDNA, and protein studies in Becker muscular dystrophy show high exception to the reading frame rule. Hum Mutat 2008; 29:728–737. [PubMed: 18348289]

9. Bushby KM, Gardner-Medwin D, Nicholson LV, Johnson MA, Haggerty ID, Cleghorn NJ, et al. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. II. Correlation of phenotype with genetic and protein abnormalities. J Neurol 1993; 240:105–112. [PubMed: 8437017]

10. Yuan R, Yi J, Xie Z, Zheng Y, Han M, Hou Y, et al. Genotype-phenotype correlation in Becker muscular dystrophy in Chinese patients. J Hum Genet 2018; 63:1041–1048. [PubMed: 29976999]

11. van den Bergen JC, Wokke BH, Janson AA, van Duinen SG, Hulsker MA, Ginjaar HB, et al. Dystrophin levels and clinical severity in Becker muscular dystrophy patients. J Neurol Neurosurg Psychiatry 2014; 85:747–53. [PubMed: 24292997]

12. McDonald CM, Abresch RT, Carter GT, Fowler WM Jr., Johnson ER and Kilmer DD. Profiles of neuromuscular diseases. Becker's muscular dystrophy. Am J Phys Med Rehabil 1995; 74:S93–103. [PubMed: 7576425]

13. Tuffery-Giraud S, Beroud C, Leturcq F, Yaou RB, Hamroun D, Michel-Calemard L, et al. Genotype-phenotype analysis in 2,405 patients with a dystrophinopathy using the UMD-DMD database: a model of nationwide knowledgebase. Hum Mutat 2009; 30:934–45. [PubMed: 19367636]

14. Mayhew JE, Florence JM, Mayhew TP, Henricson EK, Leshner RT, McCarter RJ, et al. Reliable surrogate outcome measures in multicenter clinical trials of Duchenne muscular dystrophy. Muscle Nerve 2007; 35:36–42. [PubMed: 16969838]

15. Escolar DM, Henricson EK, Mayhew J, Florence J, Leshner R, Patel KM, et al. Clinical evaluator reliability for quantitative and manual muscle testing measures of strength in children. Muscle Nerve 2001; 24:787–793. [PubMed: 11360262]

16. McDonald CM, Henricson EK, Abresch RT, Han JJ, Escolar DM, Florence JM, et al. The cooperative international neuromuscular research group Duchenne natural history study--a longitudinal investigation in the era of glucocorticoid therapy: design of protocol and the methods used. Muscle Nerve 2013; 48:32–54. [PubMed: 23677550]

17. Bello L, Campadello P, Barp A, Fanin M, Semplicini C, Soraru G, et al. Functional changes in Becker muscular dystrophy: implications for clinical trials in dystrophinopathies. Sci Rep 2016; 6:32439.

18. Charleston JS, Schnell FJ, Dworzak J, Donoghue C, Lewis S, Chen L, et al. Eteplirsen treatment for Duchenne muscular dystrophy: Exon skipping and dystrophin production. Neurology 2018; 90:e2146-e2154.

19. Frank DE, Schnell FJ, Akana C, El-Husayni SH, Desjardins CA, Morgan J, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. Neurology 2020.

20. Clemens PR, Rao VK, Connolly AM, Harper AD, Mah JK, Smith EC, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. JAMA Neurol 2020; published online doi: 10.1001/jamaneurol.2020.1264.

21. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet 2018; 391:451–461. [PubMed: 29174484]

22. Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S, et al. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. Neurology 2016; 87:401–9. [PubMed: 27343068]

23. Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, Arrieta A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease

progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle Nerve 2013; 48:55–67. [PubMed: 23649481]

24. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB and Pellegrino RJ. Clinical trial in Duchenne dystrophy. I. The design of the protocol. Muscle Nerve 1981; 4:186–97. [PubMed: 7017401]
25. Vignos PJ Jr., , Spencer GE Jr., and Archibald KC. Management of progressive muscular dystrophy in childhood. JAMA 1963; 184:89–96. [PubMed: 13997180]
26. Hoogerwaard EM, de Voogt WG, Wilde AA, van der Wouw PA, Bakker E, van Ommen GJ, et al. Evolution of cardiac abnormalities in Becker muscular dystrophy over a 13-year period. J Neurol 1997; 244:657–63. [PubMed: 9402544]
27. Mavrogeni S, Papavasiliou A, Skouteli E, Magoutas A and Dangas G. Cardiovascular magnetic resonance imaging evaluation of two families with Becker muscular dystrophy. Neuromuscul Disord 2010; 20:717–9. [PubMed: 20630758]

Table 1.

Demographic characteristics

	< 20 years		20 to <40 years		40+ years	
	N=36		N=23		N=24	
Characteristic	**N (%)**	**Mean ± SD Median (min, max)**	**N (%)**	**Mean ± SD Median (min, max)**	**N (%)**	**Mean ± SD Median (min, max)**
Ethnicity						
Non-Hispanic	35 (97%)		23 (100%)		23 (96%)	
Hispanic	1 (3%)		0 (0%)		1 (4%)	
Race						
Caucasian	31 (86%)		21 (91%)		24 (100%)	
Asian	2 (6%)		1 (4%)		0 (0%)	
Multi-race	3 (8%)		1 (4%)		0 (0%)	
Ambulatory						
Yes	36 (100%)		19 (83%)		13 (54%)	
No	0 (0%)		4 (17%)		11 (46%)	
Age (years)	36	12.7 ± 4.0 12.3 (5.6, 19.3)	23	30.3 ± 6.1 31.2 (20.2, 38.1)	24	52.6 ± 8.6 50.4 (43.3, 75.4)
Height (cm)	36	153.0 ± 22.4 156.6 (110.9, 183.7)	23	179.2 ± 7.0 180.9 (165.7, 196.5)	24	182.8 ± 8.1 183.4 (164.0, 195.1)
Weight (kg)	36	48.0 ± 20.9 47.5 (16.2, 104.0)	23	77.1 ± 22.0 75.0 (45.0, 159.0)	23	87.5 ± 16.8 88.2 (56.5, 122.5)

Table 2.

Dystrophin gene deletions

Deletion category	Mutations	Number of participants with deletion N (%)
Deletion corresponding to an exon 45 skip (n=55)	Del 45–46	1 (1.2%)
	Del 45–47	25 (30.1)
	Del 45–48	17 (20.5)
	Del 45–49	7 (8.4)
	Del 45–55	5 (6.0)
Deletion corresponding to either an exon 45 or 51 skip	Del 45–51	1 (1.2)
Deletion corresponding to an exon 51 skip (n=4)	Del 47–51	1 (1.2)
	Del 49–51	3 (3.6)
Deletion corresponding to an exon 53 skip	Del 52–53	1 (1.2)
Deletion corresponding to either an exon 45 or 53 skip (n=4)	Del 45–53	4 (4.8)
Other deletions (n=18)	Del 10–12	4 (4.8)
	Del 48–49	4 (4.8)
	Del 2–7	1 (1.2)
	Del 3–41	1 (1.2)
	Del 5–9	1 (1.2)
	Del 9–16	1 (1.2)
	Del 10–16	1 (1.2)
	Del 10–29	1 (1.2)
	Del 10–39	1 (1.2)
	Del 10–44	1 (1.2)
	Del 19–51	1 (1.2)
	Del 26–34	1 (1.2)

Table 3.

Functional test outcomes

	< 20 years		20 to <40 years		40+ years	
	N=36		N=23		N=24	
Outcome	**N**	**Mean ± SD Median (min, max)**	**N**	**Mean ± SD Median (min, max)**	**N**	**Mean ± SD Median (min, max)**
6 minute walk test (distance traveled - m)	34	418 ± 90 473 (300, 674)	18	385 ± 150 387 (50, 784)	12	327 ± 83 304 (215, 496)
Time to run/walk 10 meters velocity (m/s)	35	2.82 ± 0.77 3.05 (1.09, 4.27)	18	1.60 ± 0.90 1.39 (0.67, 4.20)	13	1.07 ± 0.38 0.98 (0.47, 1.89)
Time to climb 4 stairs velocity (tasks/s)	35	2.13 ± 0.75 2.11 (0.51, 4.00)	17	1.16 ± 0.85 0.87 (0.31, 3.45)	12	0.58 ± 0.34 0.59 (0.14, 1.27)
Time to stand from supine velocity (rises/s)	35	0.40 ± 0.18 0.38 (0.03, 1.00)	18	0.22 ± 0.17 0.17 (0.01, 0.80)	10	0.12 ± 0.08 0.12 (0.02, 0.31)
Time to stand from chair velocity (rises/s)	9	1.33 ± 0.64 1.25 (0.25, 2.50)	3	0.58 ± 0.39 0.50 (0.24, 1.00)	4	0.28 ± 0.29 0.20 (0.04, 0.69)
North Star Ambulatory Assessment (NSAA) score	35	31 ± 5 33 (15, 34)	19	22 ± 9 24 (8, 34)	13	18 ± 7 17 (8, 32)
Egen Klassifikation (EK) score	0		4	8 ± 7 7 (0, 17)	10	5 ± 3 5 (0, 9)
9-hole peg test (pegs/sec)	35	0.91 ± 0.15 0.90 (0.62, 1.20)	23	0.89 ± 0.17 0.90 (0.40, 1.29)	24	0.82 ± 0.22 0.86 (0.32, 1.20)
Performance of the Upper Limb (PUL) score	31	79 ± 2 80 (71, 80)	18	79 ± 3 80 (69, 80)	14	79 ± 2 80 (74, 80)

Table 4.

Brooke and Vignos functional test scales

	< 20 years	**20 to <40 years**	**40+ years**
	N=36	**N=23**	**N=24**
Outcome	**N (%)**	**N (%)**	**N (%)**
Brooke upper limb functional score			
1	32 (91%)	18 (78%)	17 (71%)
2	2 (9%)	2 (9%)	4 (17%)
3	0 (0%)	2 (9%)	3 (13%)
5	0 (0%)	1 (4%)	0 (0%)
Vignos lower extremity function score			
1	32 (91%)	7 (30%)	2 (8%)
2	3 (9%)	10 (44%)	7 (29%)
3	0 (0%)	1 (4%)	3 (13%)
4	0 (0%)	0 (0%)	1 (4%)
5	0 (0%)	0 (0%)	1 (4%)
6	0 (0%)	1 (4%)	2 (8%)
7	0 (0%)	4 (17%)	8 (33%)

Table 5.

Quantitative muscle testing outcomes of force in pounds

	< 20 years		20 to <40 years		40+ years	
	N=36		N=23		N=24	
Outcome	**N**	**Mean ± SD Median (min, max)**	**N**	**Mean ± SD Median (min, max)**	**N**	**Mean ± SD Median (min, max)**
Pinch	32	8 ± 3 8 (1, 8)	21	9 ± 5 10 (1, 19)	22	7 ± 4 8 (1, 15)
Key pinch	32	11 ± 6 10 (1, 25)	21	14 ± 7 15 (1, 25)	24	9 ± 5 9 (2, 18)
Grip	32	41.1 ± 21.5 34.3 (10.6, 89.2)	18	53.0 ± 26.6 47.6 (4.2, 104.3)	23	30.1 ± 21.0 22.8 (5.1, 72.1)
Elbow flexor	29	26.7 ± 14.2 26.7 (5.2, 64.7)	14	33.1 ± 17.9 29.7 (3.8, 64.1)	18	19.6 ± 13.6 17.1 (1.4, 50.6)
Elbow extensor	29	20.8 ± 10.1 19.5 (3.2, 45.0)	14	23.9 ± 13.1 20.7 (7.6, 54.8)	18	16.7 ± 9.7 13.0 (2.1, 39.1)
Shoulder horizontal adduction	29	21.4 ± 11.1 19.0 (8.0, 57.9)	13	23.7 ± 9.7 22.6 (9.8, 49.6)	18	15.8 ± 8.2 15.3 (2.4, 35.7)
Shoulder flexor	28	25.5 ± 12.6 23.8 (8.1, 57.6)	13	40.1 ± 15.4 41.4 (15.5, 70.1)	17	31.1 ± 10.4 31.8 (10.8, 48.7)
Knee extensor	29	44.3 ± 24.6 36.5 (4.5, 102.9)	15	39.3 ± 33.3 28.3 (7.3, 120.9)	18	16.9 ± 14.7 13.4 (4.4, 68.8)
Knee flexor	30	29.5 ± 17.9 23.7 (9.2, 90.8)	15	29.0 ± 20.6 26.0 (4.4, 60.1)	18	10.7 ± 7.8 9.1 (2.1, 30.4)
Hip adduction	28	22.3 ± 10.4 20.2 (4.4, 51.9)	14	24.4 ± 11.8 22.7 (3.6, 44.5)	18	12.7 ± 9.4 11.0 (1.4, 42.0)
Hip abduction	28	26.3 ± 13.8 23.6 (6.2, 60.7)	14	27.9 ± 12.2 26.1 (10.3, 45.9)	18	24.6 ± 13.2 23.1 (2.9, 62.4)