

# Rhabdomyosarcoma in a Patient With Duchenne Muscular Dystrophy: A Possible Association

Erika Chandler, MD<sup>1</sup> , Lauren Rawson<sup>2</sup>, Robert Debski, MD<sup>3</sup>,  
Kerry McGowan, MD<sup>1,4</sup> , and Arpita Lakhota, MD<sup>1,4</sup>

## Abstract

Duchenne muscular dystrophy (DMD), caused by a mutation in the DMD gene, is known to be associated with co-morbidities including cardiomyopathy, respiratory failure, neuromuscular scoliosis and intellectual disability. Animal studies have explored the susceptibility of dystrophin-deficient mice with the development of myogenic tumors. While there is adequate literature describing both DMD and rhabdomyosarcoma (RMS) separately, there has yet to be a comprehensive literature review investigating the possibility that patients with DMD may be at a higher risk of developing RMS and other myogenic tumors. We present the case of a pediatric patient with DMD who developed alveolar RMS and review the literature for susceptibility to development of myogenic tumors in cases of DMD gene mutation.

## Keywords

Duchenne muscular dystrophy, genetics, mutation, neurooncology, pediatric, risk factors

Received June 22, 2021. Received revised July 22, 2021. Accepted for publication August 5, 2021.

## Introduction

The most common type of *muscular dystrophy* is Duchenne muscular dystrophy (DMD), an X-linked recessive disorder which primarily affects males. DMD originates from alterations to the DMD gene which encodes the dystrophin protein, located on the short arm of the X chromosome.<sup>1</sup> The DMD gene is the largest known human gene, which in turn creates a higher mutation rate compared to other human genes. As a result, there are over 4000 types of deletions, duplications, and point changes that have been identified in the DMD gene.<sup>2</sup> The dystrophin protein is essential for the structure of skeletal and cardiac muscle. Without a functional dystrophin, the muscle is fragile and easily damaged.

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, consisting of malignant rhabdomyoblasts, a precursor to skeletal muscle cells, with an incidence of 4.5 cases per million children per year.<sup>3,4</sup> Subtypes of RMS include embryonal RMS (ERMS), alveolar RMS (ARMS), and pleomorphic RMS.<sup>5</sup> ERMS is considered to be more common, but ARMS has a poorer prognosis,<sup>6</sup> and is more commonly seen in adolescents and young adults. ARMS has been associated with specific chromosomal translocations that also

affect prognosis. These translocations are between PAX3, PAX7, and FOXO1<sup>7</sup> resulting in fusion proteins, PAX3/FKHR (*t*(2:13) and PAX7/FKHR *t*(1:13), respectively.<sup>5,8</sup> ARMS is the only subtype of RMS that has these characteristic chromosomal translocations.<sup>9</sup> Interestingly, our patient had FOXO1 rearrangement, which has been associated with poorer outcomes in RMS.<sup>7</sup>

## Case Report

A 5-year-old male with a history of DMD (deletion exon 45-62), diagnosed at 2.5 years of age and being managed on chronic corticosteroids, presented for evaluation of a mass on his right forearm, which was initially noticed after a fall

<sup>1</sup>University of Louisville, Louisville, USA

<sup>2</sup>Princeton University, Princeton, USA

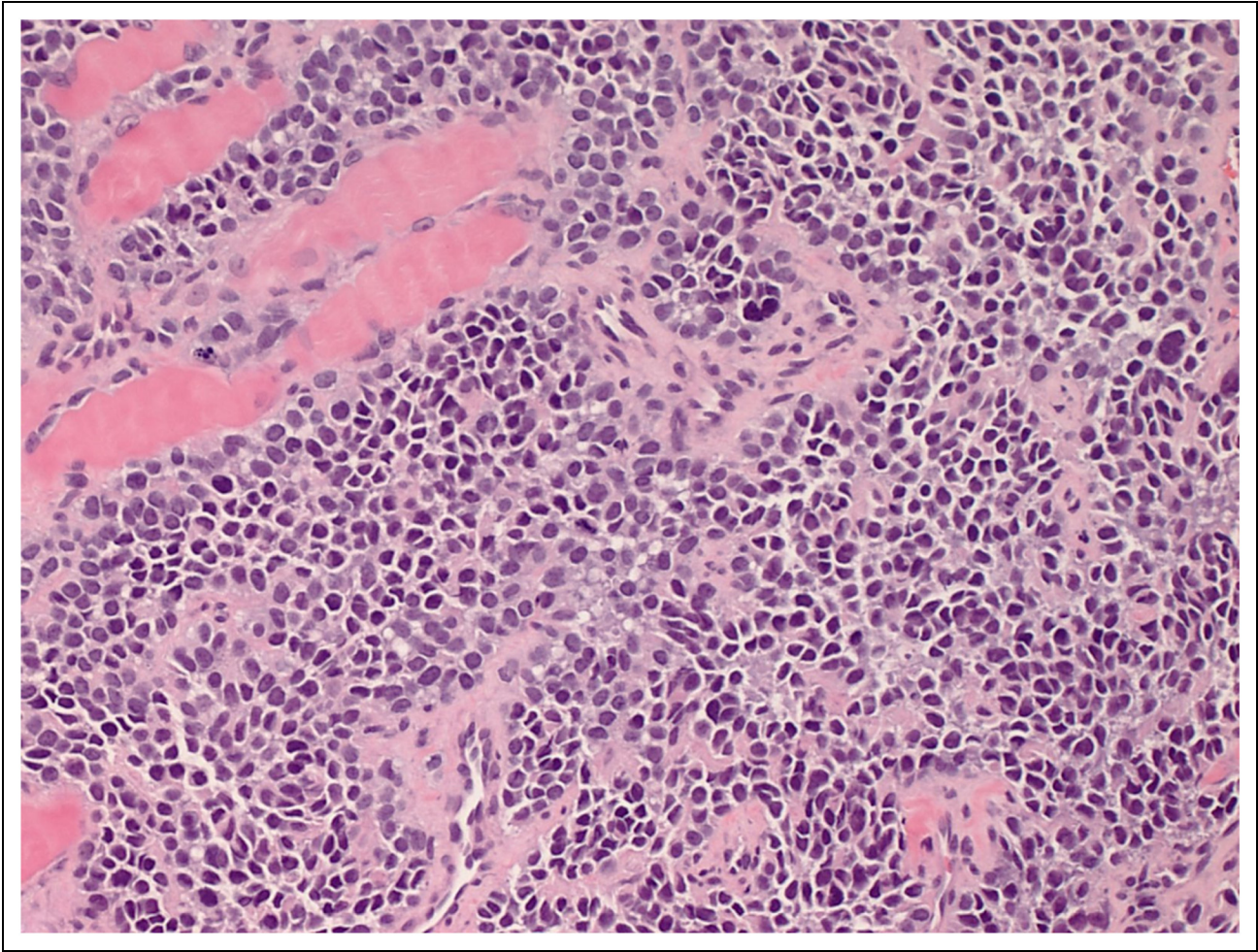
<sup>3</sup>Norton Healthcare, Louisville, USA

<sup>4</sup>Norton Children's Medical Group, Louisville, USA

## Corresponding Author:

Erika Chandler, Child Neurology, University of Louisville, Louisville, USA.  
Email: eboliv01@louisville.edu





**Figure 1.** Malignant tumor infiltrating the skeletal muscle. Hematoxylin and eosin (H&E), 200 $\times$ .

on an outstretched hand a few days prior. Ultrasound showed a “focal solid mass measuring 4.1  $\times$  1.6  $\times$  3 cm” with heterogeneity and vascular appearance. He underwent an incisional biopsy of the lesion, and pathology showed an ARMS (Figures 1 to 3) FISH positive for FOXO1 rearrangement. Gross total resection was completed with sentinel node biopsy confirming lymph node involvement. Staging workup was negative with no evidence of bone or bone marrow involvement. Based on pathologic findings, he was diagnosed with intermediate-risk RMS requiring treatment with both chemotherapy and radiation. At present (~18 months after diagnosis), he has completed radiation and is receiving maintenance chemotherapy. Most recent imaging has shown stable disease with no further evidence of metastasis.

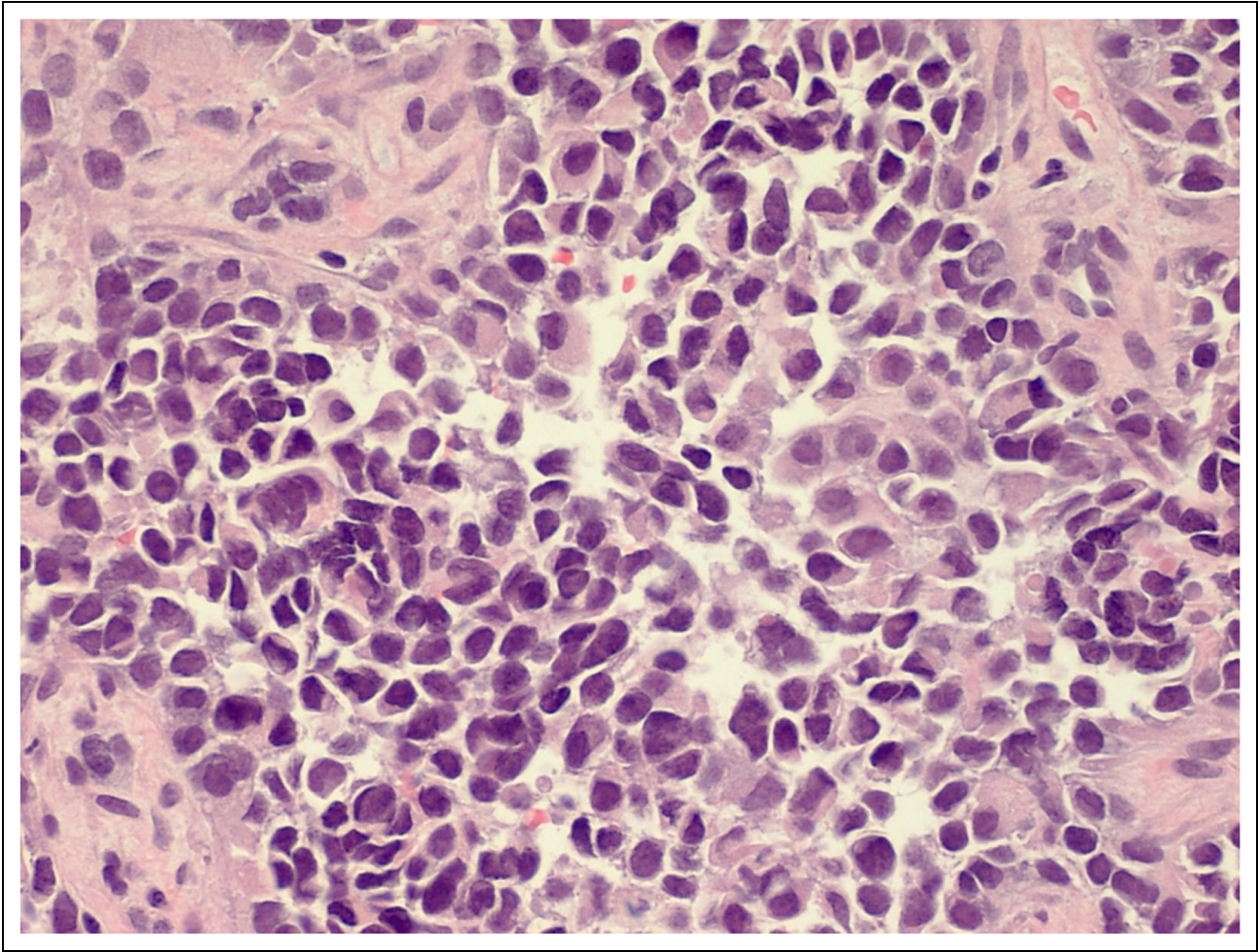
## Discussion

There are limited reports of the role of DMD gene in tumorigenesis highlighted in animal models. In fact, there are only 2 case reports of patients with DMD developing RMS. The first described a 4-year-old boy who was diagnosed with DMD, and approximately 7 months later developed abdominal, pelvic, and

left leg pain. Incisional biopsy of inguinal lymph nodes was performed, and pathology was consistent with metastatic ARMS.<sup>1</sup> The second case was a 7-year-old male with DMD who developed parotid swelling after local trauma. Pathologic examination of the parotid mass confirmed ERMS.<sup>10</sup> Neither of the specific dystrophin mutations in these patients are available in their publications. Our patient is the second reported case of a patient with DMD and the alveolar subtype of RMS.

The most relevant *in vivo* model that supports the hypothesis that patients with DMD may be at risk for developing RMS is the mdx mouse model, which lacks dystrophin. In longevity studies, these mice were histologically found to have a similar generation-regeneration cycle that results in pseudohypertrophy of muscle fibers that is seen in human patients. In one study, it was found that older mdx mice were at risk of developing muscle tumors similar to the human form of ARMS. The 6 of 94 mdx mice developed RMS and 3 of 6 developed ARMS. Only 3 of 83 wild-type (WT) mice developed tumors, none of which were RMS.<sup>11</sup> This unique development has been further supported by the fact that RMS has not been found to develop spontaneously in WT mice or mice that express a functional dystrophin.<sup>12</sup>





**Figure 2.** Malignant tumor with discohesive “alveolar” growth pattern. Hematoxylin and eosin (H&E), 400 $\times$ .

In addition to ARMS, there may be a risk for developing RMS in patients with muscular dystrophy due to mutations in the dystrophin-associated glycoprotein (DAG) complex. Dystrophin stabilizes the muscle fiber sarcolemma by interacting with DAG, resulting in the linking of the muscular cytoskeleton to the extracellular matrix.<sup>13</sup> This complex is composed of alpha and beta subunits<sup>14</sup> Secondary dystroglycanopathies are caused by mutations in the glycosyltransferase encoding genes: fukutin related protein or LARGE. This leads to impaired glycosylation of the alpha subunit of the DAG.<sup>13</sup> One study showed that mdx mice or mice with a mutated alpha sarcoglycan spontaneously develop ERMS.<sup>7</sup> In this study, 9% of dystrophin-deficient mdx mice, and 5% of alpha sarcoglycan knockout mice, developed ERMS of skeletal muscles. While the WT mice developed tumors, none were myogenic tumors.<sup>7</sup> This study reinforces that a dysfunctional dystrophin, whether that be due to a knockout mutation (the mdx mouse), or a dystroglycanopathy (alpha sarcoglycan knockout mice), has been associated with the development of RMS.

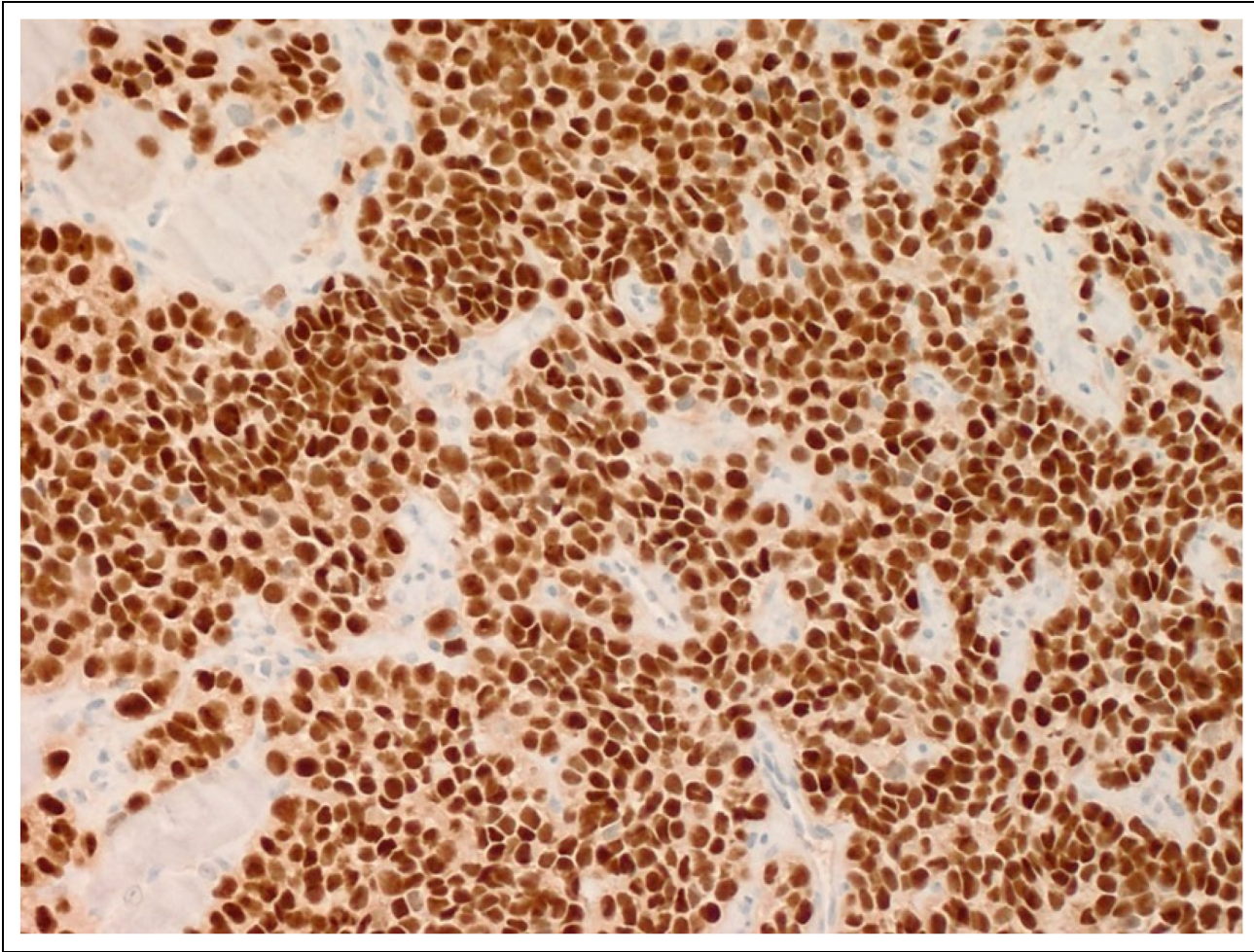
Finally, other studies have suggested that dystrophin may play a role as an antimetastatic factor.<sup>15</sup> In a study of high-grade

myogenic cancers including RMS, leiomyosarcomas (LMS), and gastrointestinal stromal tumors (GISTs), researchers found that dystrophin expression was absent or weak in 100% of metastatic ERMS, 62% of metastatic LMS, and 75% of high-risk GISTs.<sup>15</sup> When the specific dystrophin isoform studied was re-expressed, it inhibited the invasiveness and migration in GIST, ERMS, and LMS. Therefore, it has been proposed that dystrophin acts as a tumor suppressor by inhibiting myogenic sarcoma cell migration, invasion, anchoring, and invadopodia formation.<sup>15</sup>

## Conclusions

While there are very few case reports associating RMS and DMD, we feel it is important to explore this connection further. There is an abundance of literature in animal models that shows dystrophin-deficient mice have susceptibility to developing spontaneous RMS. The development of RMS in the three reported cases (including ours) was likely not coincidental. If these two rare conditions are associated, a high index of suspicion would be required from providers for timely diagnosis of RMS in patients with DMD.





**Figure 3.** Myogenin immunohistochemical stain, 200 ×.

Future directions for scientific research would be exploring specific dystrophin mutations and their relationship to developing RMS and other tumors of myogenic origin. Thus far, there has been no literature examining the prevalence of specific mutations in DMD and the subtype of RMS. Patients with DMD are now living longer with current therapies and supportive care. It is important to recognize that with therapeutic advances the cancer risk may not be mitigated. With both DMD and RMS being rare diseases, *multidisciplinary* disease-specific multicenter registries will play a large role in collecting this data over time, and review of this data would provide valuable insights into this association in humans.


#### Declaration of Conflicting Interests


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

#### Funding

The authors received no financial support for the research, authorship and/or publication of this article.

#### ORCID iDs

Erika Chandler  <https://orcid.org/0000-0002-7705-6833>

Kerry McGowan  <https://orcid.org/0000-0002-6519-0381>

#### References

1. Roszbach HC, Lacson A, Grana NH, Barbosa JL. Duchenne muscular dystrophy and concomitant metastatic alveolar rhabdomyosarcoma. *J Pediatr Hematol Oncol.* 1999;21(6):528-530.
2. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve.* 2006;34(2):135-144. doi:10.1002/mus.20586
3. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975–2005. *Cancer.* 2009;115(18):4218-4226. doi:10.1002/cncr.24465
4. Ries LAG, Smith MA, Gurney LG, et al. Cancer incidence and survival among children and adolescents: United States SEER program 1975–1999. National Cancer Institute, SEER Program. 1999; NIH Pub. No. 99-4649.

5. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. *Nat Rev Dis Primers*. 2019;5(1):1. Published 2019 Jan 7. doi:10.1038/s41572-018-0051-2
6. Newton WAJr, Soule EH, Hamoudi AB, et al. Histopathology of childhood sarcomas, intergroup rhabdomyosarcoma studies I and II: clinicopathologic correlation. *J Clin Oncol*. 1988;6(1):67-75. doi:10.1200/JCO.1988.6.1.67
7. Fernandez K, Serinagaoglu Y, Hammond S, Martin LT, Martin PT. Mice lacking dystrophin or alpha sarcoglycan spontaneously develop embryonal rhabdomyosarcoma with cancer-associated p53 mutations and alternatively spliced or mutant Mdm2 transcripts. *Am J Pathol*. 2010;176(1):416-434. doi:10.2353/ajpath.2010.090405
8. Gang EJ, Darabi R, Bosnakovski D, et al. Engraftment of mesenchymal stem cells into dystrophin-deficient mice is not accompanied by functional recovery. *Exp Cell Res*. 2009;315(15):2624-2636. doi:10.1016/j.yexcr.2009.05.009
9. Hosur V, Kavirayani A, Riefler J, et al. Dystrophin and dysferlin double mutant mice: a novel model for rhabdomyosarcoma. *Cancer Genet*. 2012;205(5):232-241. doi:10.1016/j.cancergen.2012.03.005
10. Jakab Z, Szegedi I, Balogh E, Kiss C, Oláh E. Duchenne muscular dystrophy-rhabdomyosarcoma, ichthyosis vulgaris/acute monoblastic leukemia: association of rare genetic disorders and childhood malignant diseases. *Med Pediatr Oncol*. 2002;39(1):66-68. doi:10.1002/mpo.10043
11. Chamberlain JS, Metzger J, Reyes M, Townsend D, Faulkner JA. Dystrophin-deficient mdx mice display a reduced life span and are susceptible to spontaneous rhabdomyosarcoma. *FASEB J*. 2007;21(9):2195-2204. doi:10.1096/fj.06-7353com
12. Harper SQ, Hauser MA, DelloRusso C, et al. Modular flexibility of dystrophin: implications for gene therapy of Duchenne muscular dystrophy. *Nat Med*. 2002;8(3):253-261. doi:10.1038/nm0302-253
13. Schmidt WM, Uddin MH, Dysek S, et al. DNA damage, somatic aneuploidy, and malignant sarcoma susceptibility in muscular dystrophies. *PLoS Genet*. 2011;7(4):e1002042. doi:10.1371/journal.pgen.1002042
14. Martin LT, Glass M, Dosunmu E, Martin PT. Altered expression of natively glycosylated alpha dystroglycan in pediatric solid tumors. *Hum Pathol*. 2007;38(11):1657-1668. doi:10.1016/j.humpath.2007.03.025
15. Wang Y, Marino-Enriquez A, Bennett RR, et al. Dystrophin is a tumor suppressor in human cancers with myogenic programs. *Nat Genet*. 2014;46(6):601-606. doi:10.1038/ng.2974