Dystrophin and Sarcoglycans Are Key Proteins Necessary for Maintaining Muscle Function[1,2]

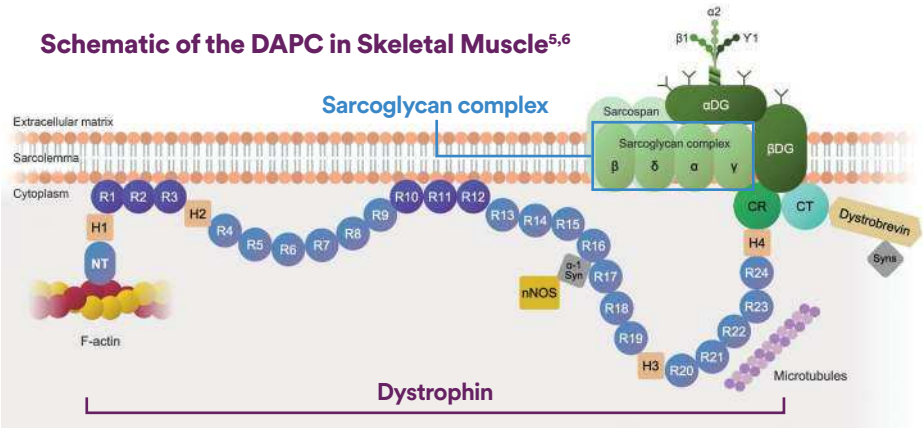
SCAN TO VIEW DUCHENNE MECHANISM OF DISEASE VIDEO

The dystrophin-associated protein complex (DAPC) is essential for muscle integrity and preventing damage during normal muscle contraction[3-5]

Dystrophin, within the DAPC, acts as a shock absorber, linking the intracellular cytoskeleton to the extracellular matrix to protect the sarcolemma from contraction-induced damage[7]

Pathogenic variants in *DMD*, the gene that encodes for dystrophin can lead to the absence of dystrophin or expression of shortened forms at reduced levels.[1,4,8,9] **Duchenne muscular dystrophy (DMD)** is caused by a lack of functional dystrophin[10]

Schematic of the DAPC in Skeletal Muscle[5,6]



The natural history of dystrophinopathies has shown that **shortened dystrophin containing key domains may retain a high degree of functionality**, leading to an atypically milder disease course[11,12]

The sarcoglycan complex is composed of 4 subunits (α-, β-, γ-, and δ-sarcolycan) and is critical for the assembly and stability of the DAPC[13]

The association between the 4 sarcoglycan proteins occurs in the endoplasmic reticulum prior to membrane localization, where the absence of one sarcoglycan can disrupt the proper localization of the others[13-16]

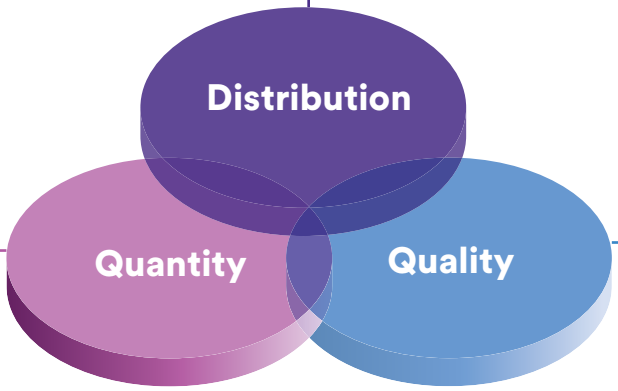
Sarcoglycanophathies are a type of limb-girdle muscular dystrophy (LGMD) caused by pathogenic variants in the genes encoding α-, β-, γ-, and δ-sarcolycan[13]

Without membrane-associated proteins like dystrophin (absent in DMD) or β-sarcoglycan (absent in LGMD2E/R4), the other proteins of the DAPC cannot assemble at the sarcolemma to protect it from damage[6,13]

What Matters Most for the Dystrophin Protein?

Dystrophin is primarily expressed in skeletal and cardiac muscles and in the brain. In preclinical models, low levels of dystrophin expressed in a **majority of myofibers results in improved pathology** compared with high levels of dystrophin in a smaller number of fibers[17,18]

Individuals with low quantity of dystrophin expression **had delays in markers of disease progression** and produced milder phenotypes of the disease compared with individuals who had no dystrophin[19,20]



Not all variations of dystrophin produce the same phenotype. Expression of shortened dystrophin containing specific functional domains **resulted in less severe** forms of muscular disease[21-24]

See reverse side for more information

Disruption of the Dystrophin-Associated Protein Complex Leads to Progressive Muscular Dystrophy[2,13]

In DMD and LGMDs, there is little potential for recovery of muscle tissue after damage[25-27]

Reversible process[25,26]

Muscle necrosis/Inflammation
Muscle fiber necrosis results in phagocytosis and inflammation

Immune cells

Injury
Skeletal muscle contraction causes damage

Muscle damage

Regeneration
Active regeneration of muscle to replace or repair damaged fibers

Irreversible process[25,26]

Fibrosis → **Muscle loss**

Myofiber necrosis and inflammation cause replacement of muscle tissue with fat and fibrotic tissue

Severe loss of muscle tissue

Fibrotic tissue

Loss of satellite cell niche[25,28]
Myofiber breakdown is not compensated for by satellite cell proliferation

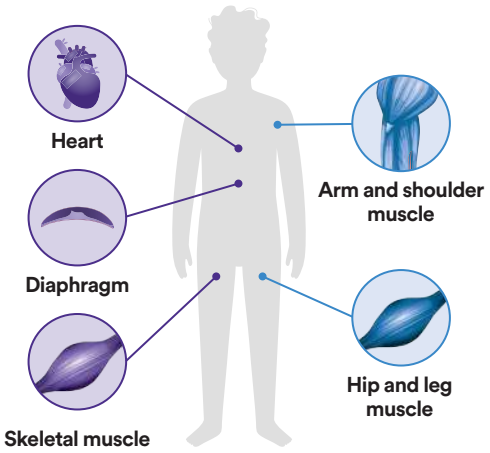
Loss of muscle tissue leads to progressive deterioration of functional abilities and cardiopulmonary complications in people with DMD or β-sarcoglycanopathy[1,10,13]

DMD is a severe form of muscular dystrophy characterized by progressive muscle weakness, and most patients will lose ambulation within half of their second decade of life[10,29]

Muscle damage in DMD can occur at birth and developmental delays are typically apparent in the first decade of life[30-32]

During adolescence, cardiac and respiratory muscle deterioration can lead to life-threatening complications[6,10]

Various pathogenic variants in the *DMD* gene can lead to differences in dystrophin expression, resulting in **diverse phenotypes and disease trajectories**[35-38]



LGMDs are characterized by progressive weakness and wasting in proximal girdle muscles, eventually advancing to the arms and legs[13]

LGMDs typically present in childhood with proximal lower limb weakness; however, the age of onset for sarcoglycanopathies in particular can range from 3 to 20 years[33,34]

Distinct LGMD subtypes differ in age of onset, disease severity, progression rate, and timing of complications. In β-sarcoglycanopathy (LGMD2E/R4), progressive muscle degeneration leads to loss of ambulation, respiratory impairment, cardiac involvement, and often premature death[13,33,34,39]

Disease heterogeneity can confound the diagnostic and treatment journey. Genetic testing is critical for a timely and accurate diagnosis, and determining patient eligibility for therapy and clinical trials[13,32,40,41]

Abbreviations: CR, cysteine-rich; CT, carboxy terminus; DAPC, dystrophin-associated protein complex; DG, dystroglycan; DMD, Duchenne muscular dystrophy; *DMD*, the gene that encodes dystrophin; F-actin, actin filament; H, hinge; LGMD, limb-girdle muscular dystrophy; LOA, loss of ambulation; nNOS, neuronal nitric oxide synthase; NT, amino terminus; R, spectrin-like repeat; SGCA, α-sarcoglycan; SGCB, β-sarcoglycan; SGCG, δ-sarcoglycan; Syn, syntrophin.

References: 1. Aartsma-Rus A, et al. *Muscle Nerve*. 2006;34(2):135-144. 2. Liewluck T and Malone M, et al. *Muscle Nerve*. 2018;58(2):167-177. 3. Kole R, et al. *Nat Rev Drug Discov*. 2012;11(2):125-140. 4. Verhaart IEC and Aartsma-Rus A. In: Zaher A., ed. *Neuromuscular Disorders*. Intech 2012 (Chapter 3):55-81. 5. Wan L, et al. *Nature*. 2025;637(8048):1252-1260. 6. Elangkovan J, et al. *Neuromusucl Dis*. 2021;8 S303-S316. 7. Le S, et al. *ACS Nano*. 2018;12(12):12140-12148. 8. Bushby K, et al. *Lancet Neurol*. 2010;9(1):77-93. 9. Nicolas A, et al. *Hum Mol Genet*. 2015;24(5):1267-1279. 10. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17(3):251-267. 11. Wells DJ, et al. *Hum Mol Genet*. 1995;4(8):1245-1250. 12. England SB, et al. *Nature*. 1990;343(6254):180-182. 13. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 14. Sandonà D, Betto R. *Expert Rev Mol Med*. 2009;11e28. 15. Soheili T, et al. *Hum Mutat*. 2012;33(2):429-439. 16. Xie Z, et al. *Orphanet J Rare Dis*. 2019;14(1)43. 17. The Human Protein Atlas. DMD. Accessed January 15, 2026. https://www.proteinatlas.org/ENSG00000198947-DMD/tissue#expression_summary 18. van Westering TLE, et al. *J Cachexia Sarcopenia Muscle*. 2020;11(2):578-593. 19. de Feraudy Y, et al. *Ann Neurol*. 2021;89(2):280-292. 20. Waldrop MA, et al. *Neuromuscul Disord*. 2018; 28(2):116-121. 21. Davies KE, Vogt J. *Neuromuscul Disord*. 2024:39:5-9. 22. Passos-Bueno MR, et al. *Hum Mol Genet*. 1994;3(6):919-922. 23. Morandi L, et al. *Neuromuscul Disord*. 1993;3(1):65-70. 24. Koenig M, et al. *Am J Hum Genet*. 1989;45(4):498-506. 25. Klingler W, et al. *Acta Myol*. 2012;31(3):184-195. 26. Rosenberg AS, et al. *Sci Transl Med*. 2015;7(299):299rv4. 27. Muscular Dystrophy Association (2023). Duchenne Muscular Dystrophy (DMD): Causes/Inheritance. Accessed January 15, 2026.https://www.mda.org/disease/duchenne-muscular-dystrophy/causes-inheritance 28. Cappellari O, et al. *Cells*. 2020;9(7):1659. 29. Muntoni F, et al. *PLoS One*. 2019;14(9):e0221097. 30. Hathout Y, et al. *Proc Natl Acad Sci U S A*. 2015;112(23):7153-7158. 31. Moat SJ, et al. *Clin Chem*. 2017;63(4):908-914. 32. Ciafaloni E, et al. *J Pediatr*. 2009;155(3):380-385. 33. Semplicini C, et al. *Neurology*. 2015;84(17):1772-1781. 34. Wicklund MP, Kissel JT. *Neurol Clin*. 2014;32(3):729-749. 35. Aartsma-Rus A, et al. *J Med Genet*. 2016;53(3):145-151. 36. Gao R, et al. *J Hum Genet*. 2015; 60(8):435-442. 37. Chesshyre M, et al. *J Cachexia Sarcopenia Muscle*. 2022;13(2):1360-1372. 38. Pickart AM, et al. *J Genet Couns*. 2025;34(1):e1892. 39. Murphy AP, Straub V. *J Neuromuscul Dis*. 2015;2(s2):S7-S19. 40. Narayanaswami P, et al. *Neurology*. 2014;83(16):1453-1463. 41. Mercuri E, et al. *Front Pediatr*. 2023;11:1276144.

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