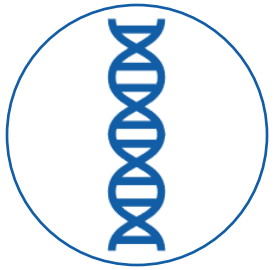
Module 1
What is Duchenne muscular dystrophy (DMD)?

Dyne | Medical Central

Module summary

DMD is a fatal, genetic, muscular disorder[1]

1 in 3,500 to 1 in 5,000 newborn boys are affected[2,3]



DMD is caused by mutations in the *DMD* gene[4]

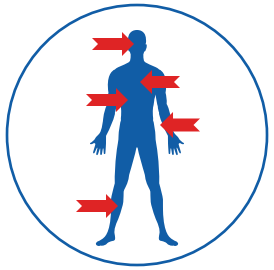
These mutations result in greatly reduced or completely absent production of dystrophin protein[2,5]

Dystrophin is essential for muscle structure, function, and preservation[6–8]

As a key component of the DAPC, dystrophin stabilizes the muscle membrane during contraction[8–11]

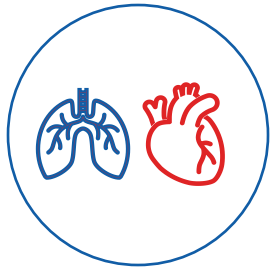
Lack of dystrophin causes progressive loss of muscle strength in individuals with DMD[12–14]

Without dystrophin, muscle fibers degenerate and are replaced with fat and fibrotic tissue[12–14]



Dystrophin deficiency manifests in a multisystemic manner[15]

Skeletal, smooth, and cardiac muscle are affected, as well as the CNS[15]



Progressive muscle weakness results in loss of ambulation and ultimately death due to cardiorespiratory failure[12,16]

Life expectancy is severely reduced in individuals with DMD[17]

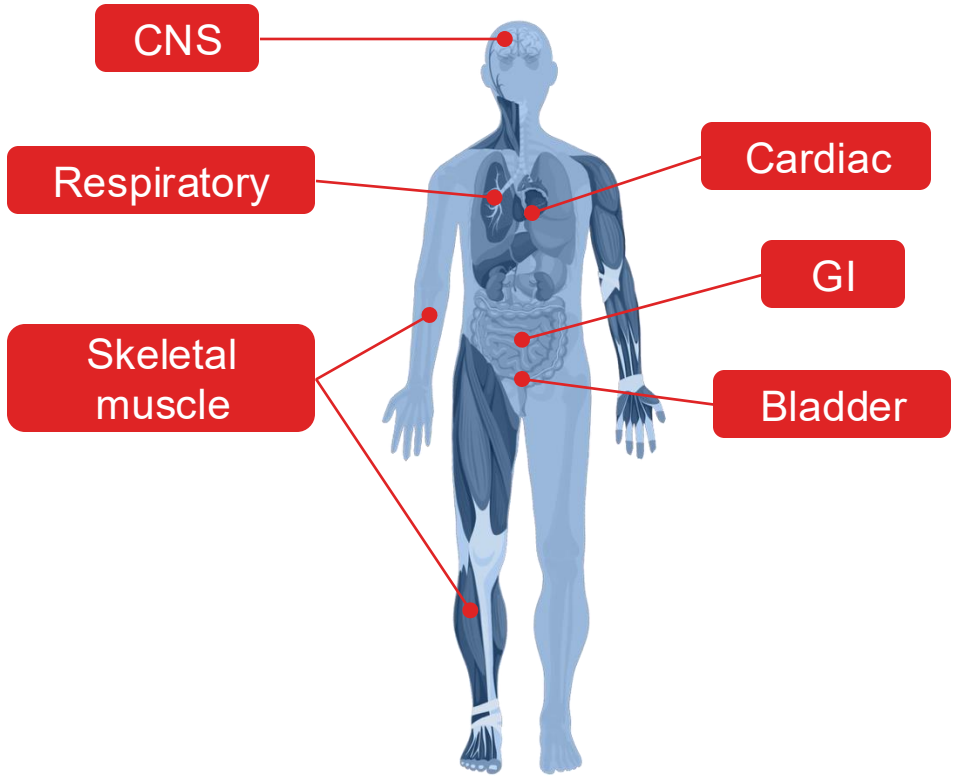
CNS, central nervous system; DAPC, dystrophin-associated protein complex; DMD, Duchenne muscular dystrophy.

1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 2. Crisafulli S, et al. *Orphanet J Rare Dis.* 2020;15:141; 3. Emery AE. *Neuromuscul Disord.* 1991;1:19–29; 4. Aartsma-Rus A, et al. *J Med Genet.* 2016;53:145–151; 5. de Feraudy Y, et al. *Ann Neurol.* 2021;89:280–292; 6. Ervasti JM, Campbell KP. *J Cell Biol.* 1993;122:809–823; 7. Claflin DR, Brooks SV. *Am J Physiol Cell Physiol.* 2008;294:C651–C658; 8. Rybakova IN, Patel JR, Ervasti JM. *J Cell Biol.* 2000;150:1209–1214; 9. Yoshida M, Ozawa E. *J Biochem.* 1990;108:748–752; 10. Zhao J, et al. *Hum Mol Genet.* 2016;25:3647–3653; 11. Petrof BJ, et al. *Proc Natl Acad Sci USA.* 1993;90:3710–3714; 12. Hoffman EP, Brown RH, Jr, Kunkel LM. *Cell.* 1987;51:919–928; 13. Watkins SC, Cullen MJ. *Neuropathol Appl Neurobiol.* 1985;11:447–460; 14. Marden FA, et al. *Skeletal Radiol.* 2005;34:140–148; 15. Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473:1813–1839; 16. Lionarons JM, et al. *Life.* 2021;11:772; 17. Broomfield J, et al. *Neurology.* 2021;97:e2304–e2314.

What is DMD?

- DMD is a rare, X-linked, recessive, progressive neuromuscular disorder affecting males, caused by lack of functional dystrophin protein[1,2]
- Mutations of the *DMD* gene result in greatly reduced or absent production of dystrophin protein, essential for muscle structure, function, and preservation[3–7]
  - Dystrophin deficiency affects skeletal, smooth, and cardiac muscle, as well as the CNS[8]
  - Individuals with DMD typically exhibit:[2,9]
    - Progressive muscle weakness in the initial years of their lives
    - Loss of ambulation in the second decade
    - Life-threatening complications due to respiratory or cardiac failure

Manifestations of DMD are multisystemic[1]



DMD is a rare, progressive and multisystemic neuromuscular disorder, caused by a lack of functional dystrophin protein[1,2,8]

DMD, Duchenne muscular dystrophy.
Image from BioRender.

1. Gao QQ, et al. *Compr Physiol.* 2015;5:1223–1239; 2. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 3. Claflin DR, Brooks SV. *Am J Physiol Cell Physiol.* 2008;294:C651–C658; 4. Ervasti JM, Campbell KP. *J Cell Biol.* 1993;122:809–823; 5. Hoffman EP, Brown RH, Jr, Kunkel LM. *Cell.* 1987;51:919–928; 6. de Feraudy Y, et al. *Ann Neurol.* 2021;89:280–292; 7. Ohlendieck K, et al. *Neurology.* 1993;43:795–800; 8. Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473(12):1813–1839; 9. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:347–361.

How common is DMD and how does it affect lifespan?

Incidence: 1 in 3,500 to 5,000 newborn males[1,2]

Prevalence: 7.1 cases per 100,000 males[1]

Prevalence (US): ~12,000 males[1]

Prevalence (EU): ~16,000 males[1]

Prevalence (Japan): 7.1 per 100,000 males[1*]

Prevalence (Hong Kong): 9.8 per 100,000 males[1*]

Life expectancy

- Overall
  - Median: 22 years[3]
  - Maximum: 44.4 years[3]
- For individuals with DMD born after 1990
  - Median: 28.1 years, which may be influenced by the widespread introduction of steroids and ventilatory support[3,4]

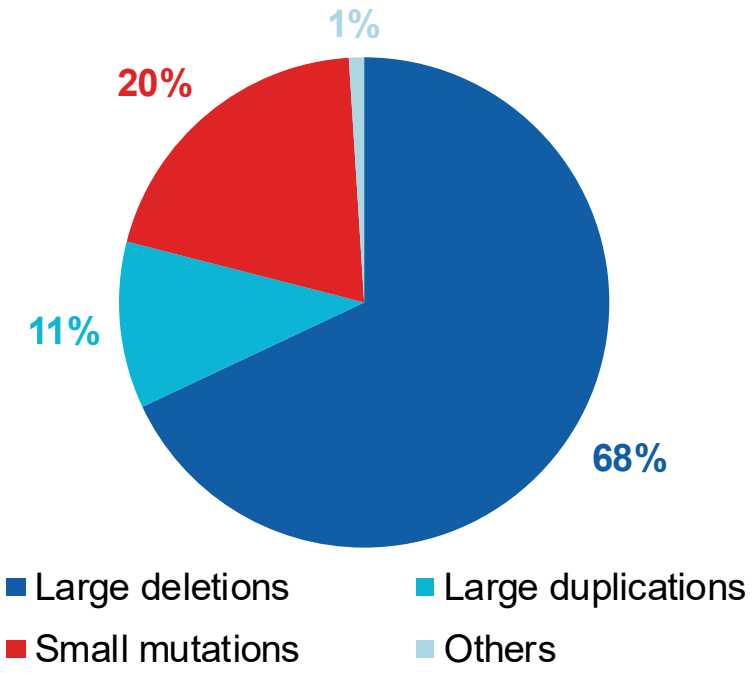
DMD is a fatal, genetic, muscular disorder affecting 1 in 3,500 to 5,000 newborn males[1,2]

*Few studies are available in this region, and all data are from 1985–2001.
DMD, Duchenne muscular dystrophy; EU, European Union; US, United States.
1. Crisafulli S, et al. *Orphanet J Rare Dis*. 2020;15:141; 2. Emery AE. *Neuromuscul Disord*. 1991;1:19–29; 3. Broomfield J, et al. *Neurology*. 2021;97:e2304-e2314; 4. Landfeldt E. et al. *Eur J Epidemiol*. 2020;35:643–653.

What types of mutations in the *DMD* gene cause DMD?

- Mutations in the *DMD* gene result in greatly reduced production or complete lack of dystrophin protein, essential for muscle structure, function, and preservation[1–5]
- Approximately one-third of DMD cases are due to spontaneous mutations[6]
- The most common molecular defects in individuals with DMD are large exon deletions, which occur in approximately 70% of all mutations[6]

Deletions account for more than two-thirds of DMD cases[6]



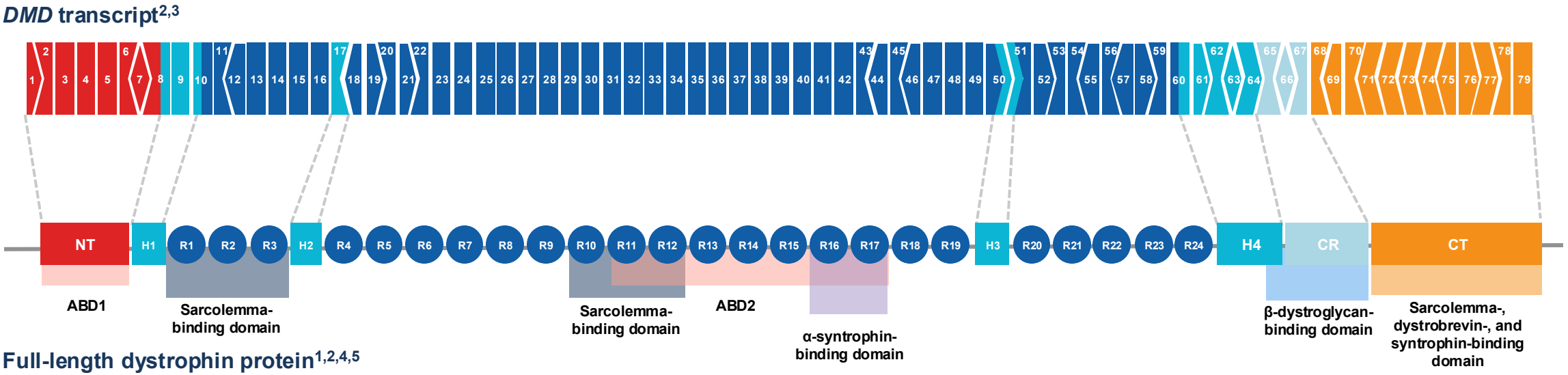
~90% of deletions in the *DMD* gene occur in two hotspot regions: exons 45 to 55 (up to 74%) and exons 2 to 20 (15%)[7]

DMD, Duchenne muscular dystrophy.

1. Claflin DR, Brooks SV. *Am J Physiol Cell Physiol*. 2008;294:C651–C658; 2. Ervasti JM, Campbell KP. *J Cell Biol*. 1993;122:809–823; 3. Hoffman EP, Brown RH, Jr, Kunkel LM. *Cell*. 1987;51:919–928; 4. de Feraudy Y, et al. *Ann Neurol*. 2021;89:280–292; 5. Ohlendieck K, et al. *Neurology*. 1993;43:795–800; 6. Bladen CL, et al. *Hum Mutat*. 2015;36:395–402; 7. Tuffery-Giraud S, et al. *Hum Mutat*. 2009;30:934–945.

How do exons of the *DMD* transcript map to the dystrophin protein domains?

The *DMD* gene, one of the largest known human genes, encodes dystrophin (427 kDa)[1]



Legend:[2,4]

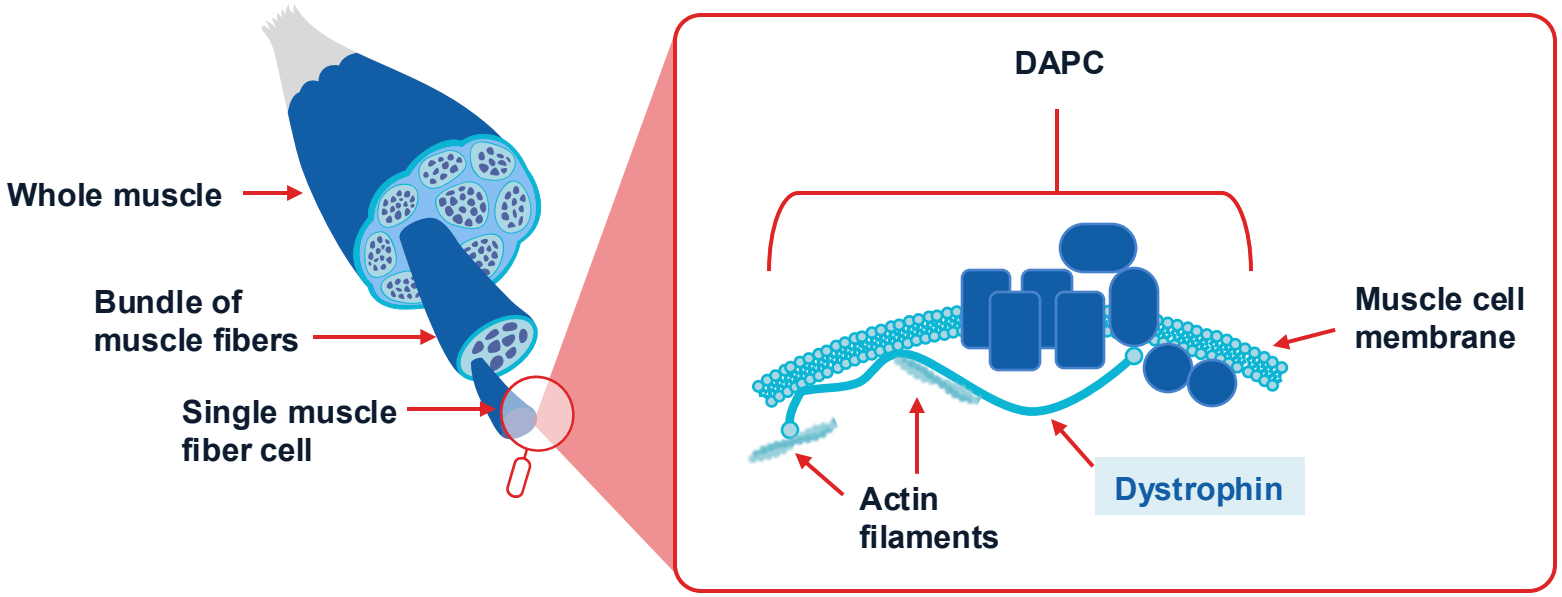
- NT — N-terminus
- H — Hinge domain
- R — Rod domain (spectrin-like repeat)
- CR — Cysteine-rich domain
- CT — C-terminus

ABD, actin binding domain; CR, cysteine rich; CT, C-terminus (carboxy-terminus); DMD, Duchenne muscular dystrophy; H, hinge; NT, N-terminus; R, spectrin-like repeat.

1. Gao QQ, et al. *Compr Physiol*. 2015;5:1223–1239; 2. Roberts RG, et al. *Genomics*. 1993;16:536–538; 3. Zhang Y, et al. *Physiol Rev*. 2018;98:1205–1240; 4. Zhao J, et al. *Hum Mol Genet*. 2016;25:3647–3653; 5. Adams ME, et al. *Hum Mol Genet*. 2018;27:2978–2985.

What role does dystrophin play in maintaining muscle integrity?

Dystrophin, a Key Protein in the Dystrophin-Associated Protein Complex (DAPC), Is Expressed in the Sarcolemma of Skeletal and Cardiac Muscle Fibers[1–3]



As part of the DAPC, dystrophin stabilizes the muscle membrane during contraction[4,5]

Mechanical trauma in the absence of dystrophin leads to Ca^{2+} dysregulation and free radical formation, resulting in muscle damage and degeneration[6]

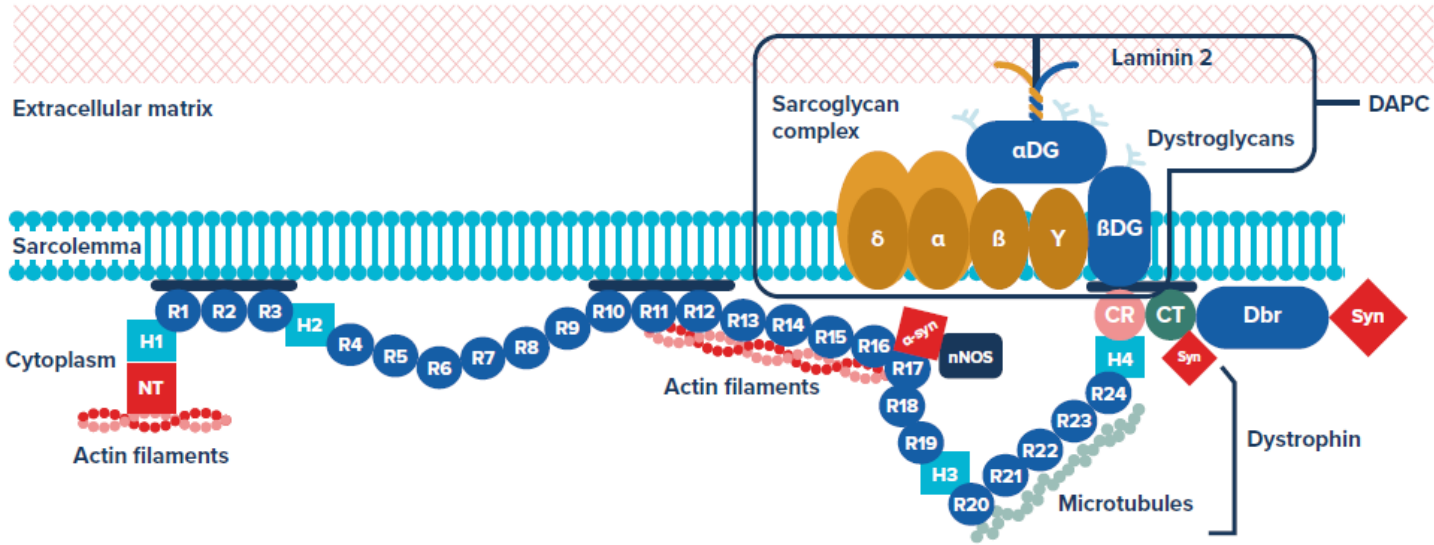
DAPC, dystrophin-associated protein complex.

1. Yoshida M, Ozawa E. *J Biochem*. 1990;108:748–752; 2. Zhao J, et al. *Hum Mol Genet*. 2016;25:3647–3653; 3. Gao QQ, McNally EM. *Compr Physiol*. 2015;5:1223–1239; 4. Petrof BJ, et al. *Proc Natl Acad Sci USA*. 1993;90:3710–3714; 5. Rybakova IN, Patel JR, Ervasti JM. *J Cell Biol*. 2000;150:1209–1214; 6. Mosqueira M, et al. *Med Res Rev*. 2013;33:1174–1213.

What role does dystrophin play in the dystrophin-associated protein complex (DAPC)?

Dystrophin is a core component of the dystrophin-associated protein complex (DAPC)[1–4]

- The DAPC stabilizes the muscle membrane during contraction to prevent contraction-induced damage[1,2]
- As part of the DAPC, dystrophin plays a role in linking the contractile apparatus to the membrane and providing support against mechanical stress[1,2]

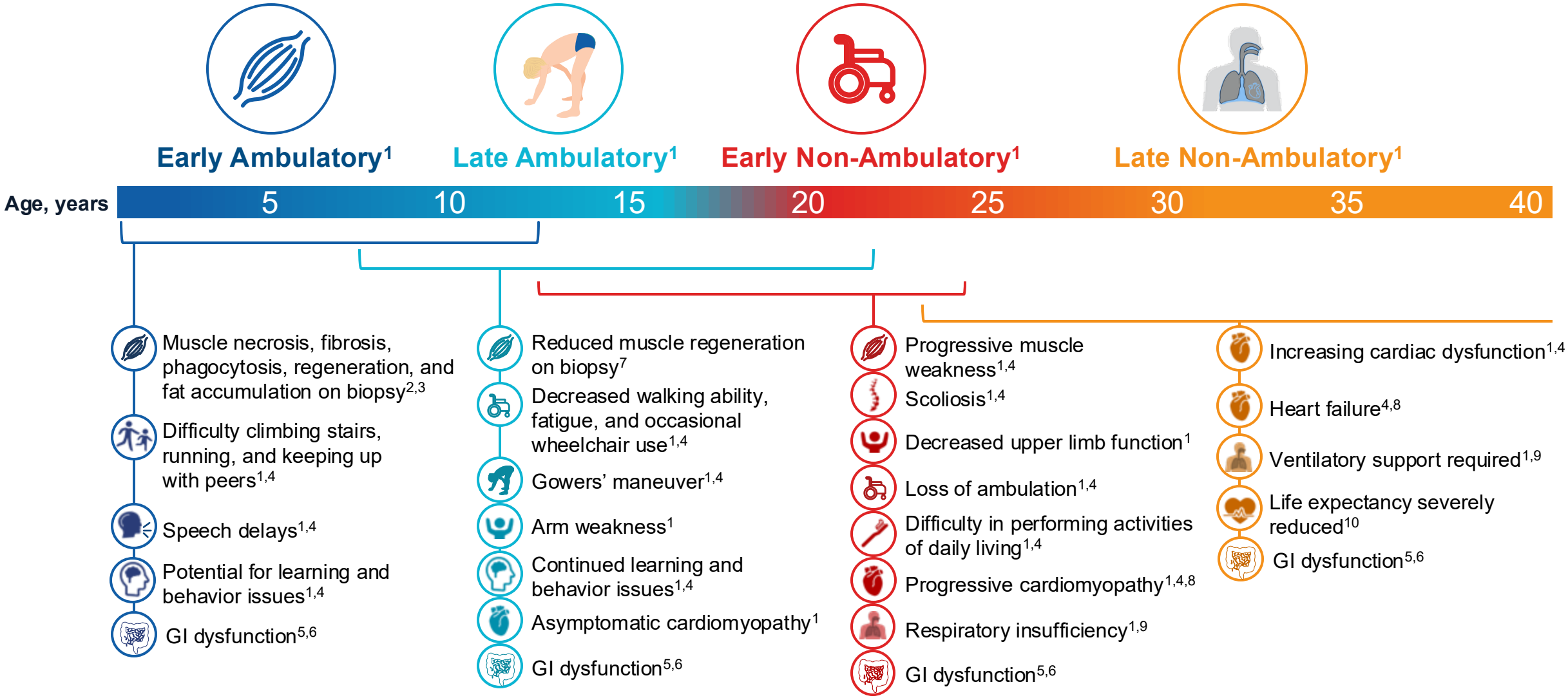


Lack of dystrophin causes muscle fibers to degenerate and be replaced with fat and fibrotic tissue leading to progressive loss of muscle strength in individuals with DMD[5–7]

CR, cysteine rich; CT, carboxy-terminus; DAPC, dystrophin-associated protein complex; Dbr, dystrobrevin; DG, dystroglycan; DMD, Duchenne muscular dystrophy; H, hinge; nNOS, neuronal nitric oxide synthase; NT, N-terminus; R, spectrin-like repeat; Syn, syntrophin.
Image used with permission of The Author, from Zhao J, et al. *Hum Mol Genet*. 2016;25:3647–3653; permission conveyed through Copyright Clearance Center, Inc.

1. Gao QQ, McNally EM. *Compr Physiol*. 2015;5:1223–1239; 2. Constantin B. *Biochim Biophys Acta*. 2014;1838:635–642; 3. Zhao J, et al. *Hum Mol Genet*. 2016;25:3647–3653; 4. Adams ME, et al. *Hum Mol Genet*. 2018;27:2978–2985; 5. Hoffman EP, Brown RH, Jr, Kunkel LM. *Cell*. 1987;51:919–928; 6. Watkins SC, Cullen MJ. *Neuropathol Appl Neurobiol*. 1985;11:447–460; 7. Marden FA, et al. *Skeletal Radiol*. 2005;34:140–148.

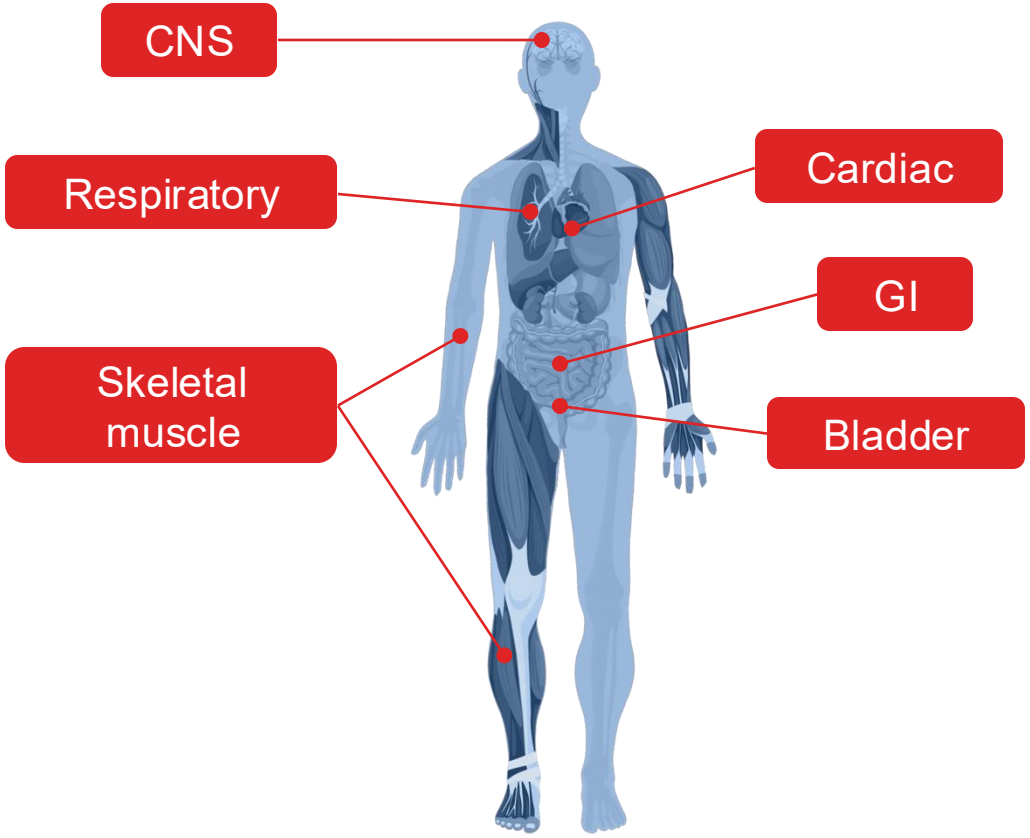
How do clinical manifestations of DMD progress over time?



Age ranges in this graphic are aligned with the Parent Project Muscular Dystrophy Care Guidelines definition of DMD disease stages (childhood', 'late childhood/adolescence/young adulthood', adolescence/young adulthood', 'adulthood').[1]
DMD, Duchenne muscular dystrophy; GI, gastrointestinal.

1. Parent Project Muscular Dystrophy. Care Guidelines By Stage. https://www.parentprojectmd.org/care/care-guidelines/by-stage/. Accessed September 24, 2025; 2. Bradley WG, et al. *J Neurol Neurosurg Psychiatry*. 1972;35:451–455;
3. Li W, et al. *Neuromuscul Disord*. 2015;25:375–380; 4. Bushby K, et al. *Lancet Neurol*. 2010;9:77–93; 5. Jaffe KM, et al. *Arch Phys Med Rehabil*. 1990;71:742–744; 6. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267;
7. Cardone N, et al. *Acta Neuropathol Commun*. 2023;11:167; 8. Duan D, et al. *Nat Rev Dis Primers*. 2021;7:13; 9. Childs AM, et al. *Thorax*. 2024;79:476–485; 10. Broomfield J, et al. *Neurology*. 2021;97:e2304–e2314.

What are the multisystemic manifestations of dystrophin deficiency?



Dystrophin deficiency affects skeletal, smooth, and cardiac muscle, as well as the CNS

CNS, central nervous system; GI, gastrointestinal.
Image from BioRender.
Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473:1813–1839.