

Understanding dystrophin in DMD

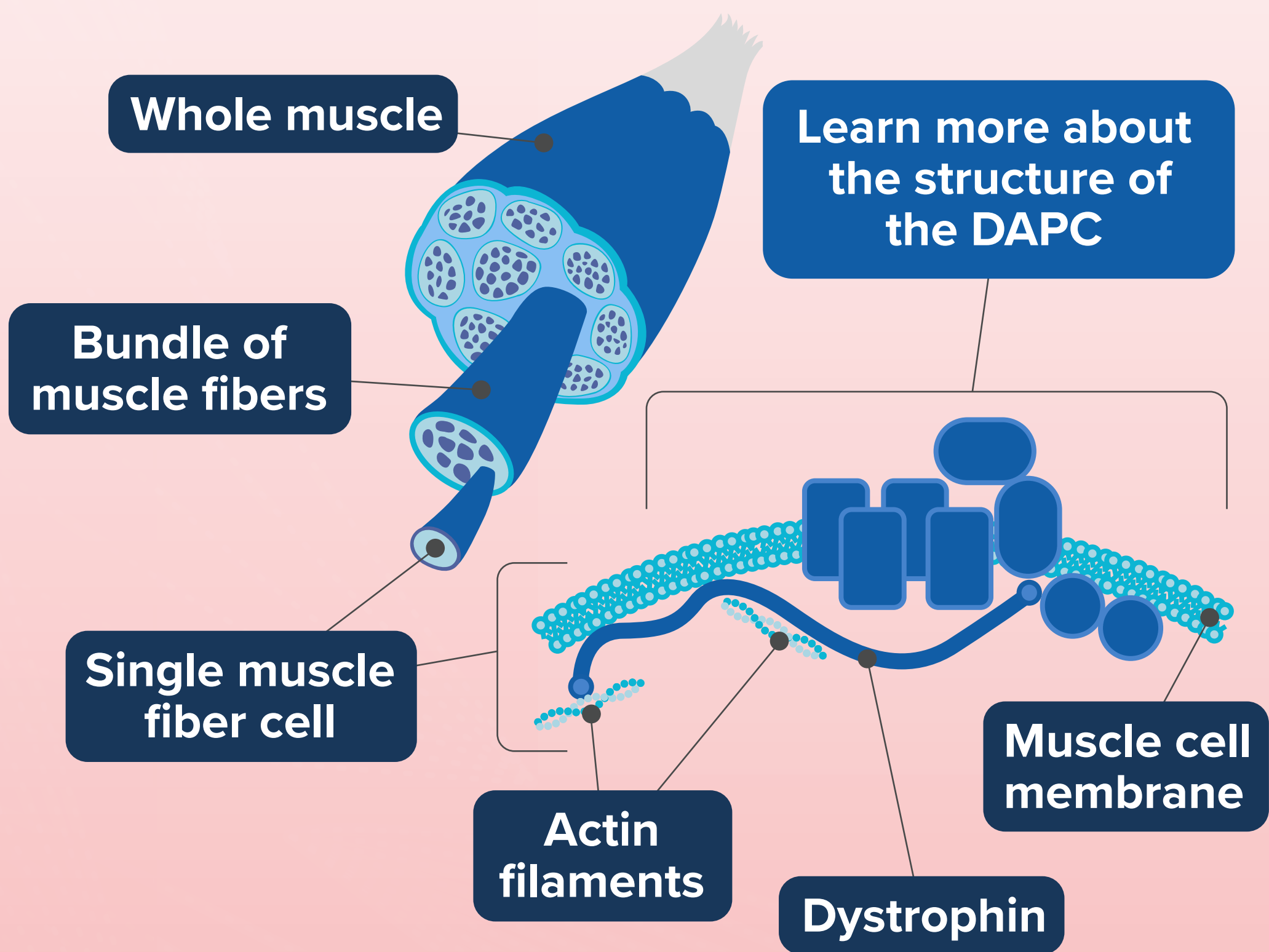
Click on the button below to explore
how mutations in the *DMD* gene impact the
structure and function of dystrophin protein,
and ultimately disease phenotype.

START NOW >

Understanding dystrophin in DMD

The dystrophin protein

The *DMD* gene is one of the largest known human genes and encodes dystrophin, a key protein within the dystrophin-associated protein complex (DAPC).^{1–3} The DAPC comprises several protein groups that stabilize the cell membrane during muscle contraction to prevent contraction-induced damage.^{1,2} In conjunction with the DAPC, dystrophin plays a role in linking the contractile apparatus to the membrane and providing support against mechanical stress.^{1,2}



Which topic would you like to learn more about?

The functional domains of the dystrophin protein

Mutations in the *DMD* gene

Features of exon skipping-produced dystrophin and micro-dystrophin

DAPC, dystrophin-associated protein complex; **DMD**, Duchenne muscular dystrophy.

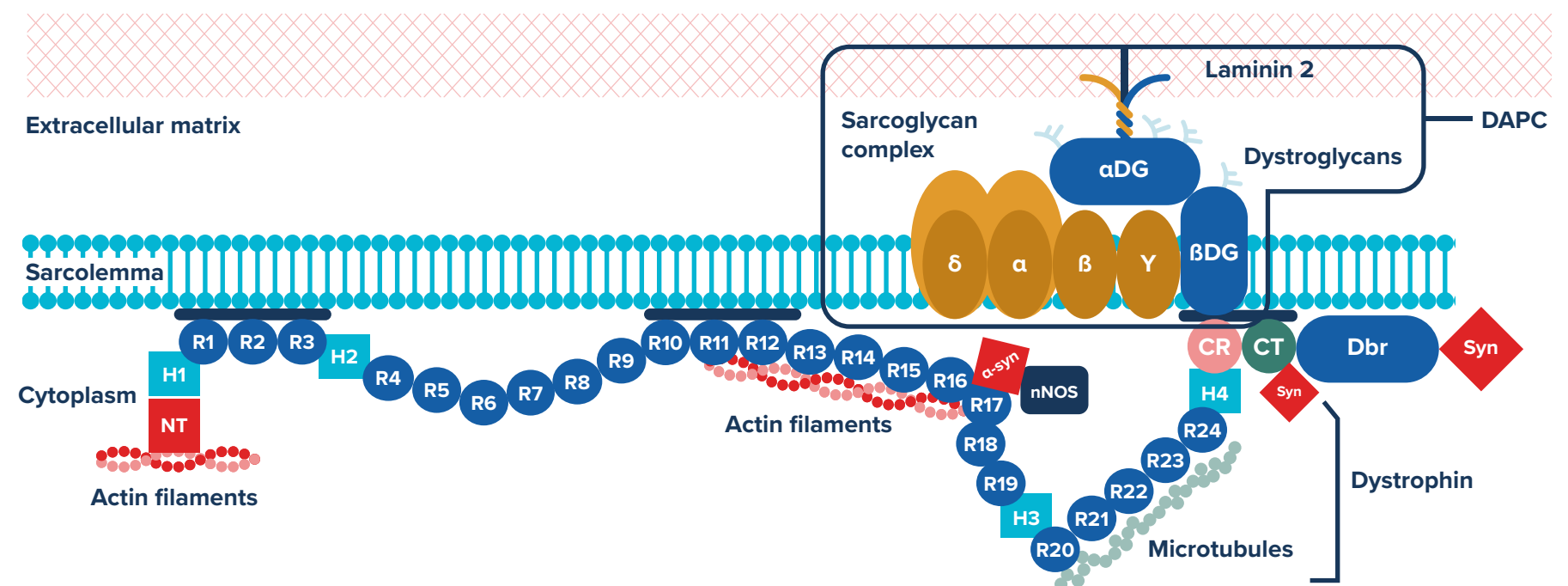
Image references: Gao QQ, McNally EM. *Compr Physiol*. 2015;5(3):1223–39 and Zhao J, et al. *Hum Mol Genet*. 2016;25(17):3647–53.

References: 1. Gao QQ, et al. *Compr Physiol*. 2015;5(3):1223–39; 2. Constantin B. *Biochim Biophys Acta*. 2014;1838(2):635–42; 3. Petrof BJ, et al. *Proc Natl Acad Sci USA*. 1993;90(8):3710–4.



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The structure of the DAPC

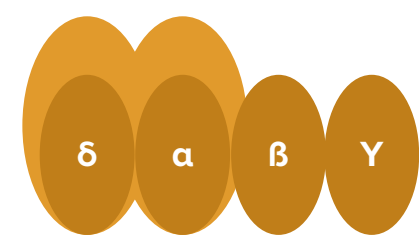


Overview of structures within the DAPC^{1,2}



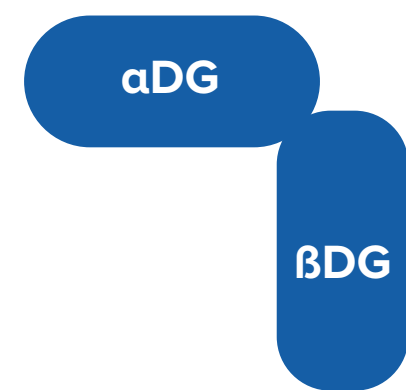
Dystrophin

A protein that links the intracellular cytoskeleton network to transmembrane components of the DAPC.



Sarcoglycan complex

Stabilizes the DAPC by enforcing the link between α- and β-dystroglycan and interacts directly with dystrobrevin, a protein that also binds to dystrophin at the C-terminus. Dystrobrevin plays a role in maintaining the structural integrity of the cell and associates with syntrophin, which is involved in numerous cell signaling pathways.



Dystroglycans

Encoded by one gene (*Dag1*) and cleaved into two subunits post-translation:

- α-dystroglycan – an extracellular protein that acts as a receptor for various extracellular matrix ligands (e.g., laminin, perlecan and agrin).
- β-dystroglycan – a transmembrane protein that anchors α-dystroglycan and dystrophin to the sarcolemma.



Laminin

An extracellular matrix protein that binds to α-dystroglycan, linking the DAPC to the extracellular matrix.

CR, cysteine rich; **CT**, C-terminus (carboxy-terminus); **DAG1**, dystroglycan 1; **DAPC**, dystrophin-associated protein complex; **Dbr**, dystrobrevin; **DG**, dystroglycan; **H**, hinge; **nNOS**, neuronal nitric oxide synthase; **NT**, N-terminus; **R**, spectrin-like repeat; **Syn**, syntrophin.

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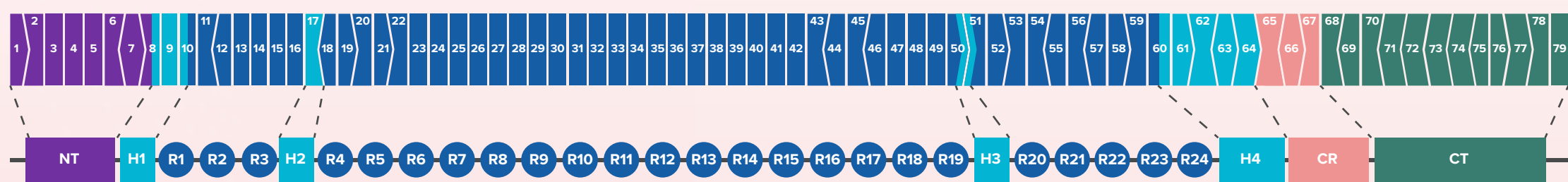
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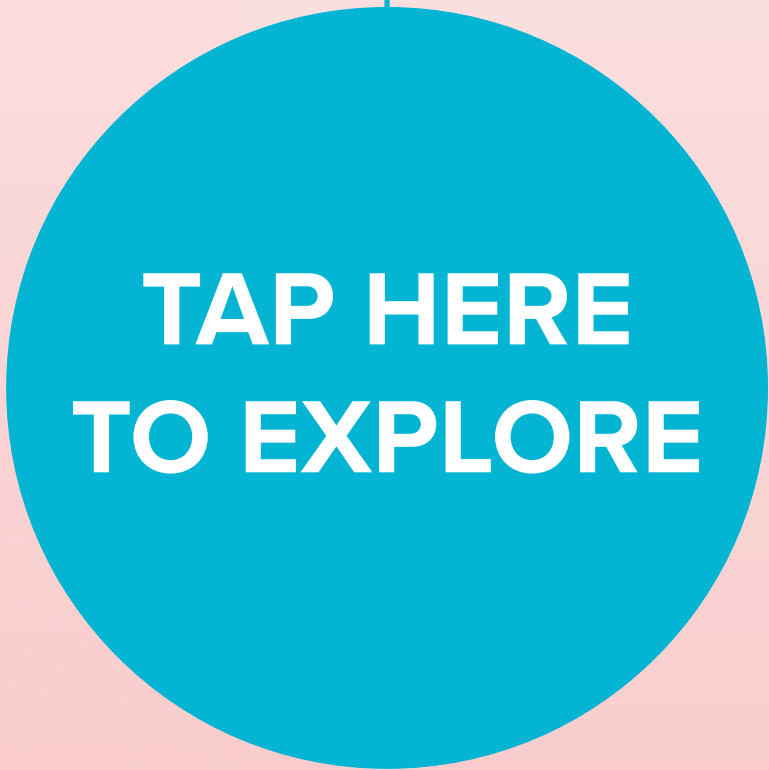
The functional domains of the dystrophin protein

Domains of the dystrophin protein perform a variety of structural and signaling functions in the cell.¹

DMD transcript^{2,3}



Full-length dystrophin protein^{1,2}



Legend^{1,2}

- NT** N-terminus
- H** Hinge domain

- R** Rod domain (spectrin-like repeat)
- CR** Cysteine-rich domain
- CT** C-terminus

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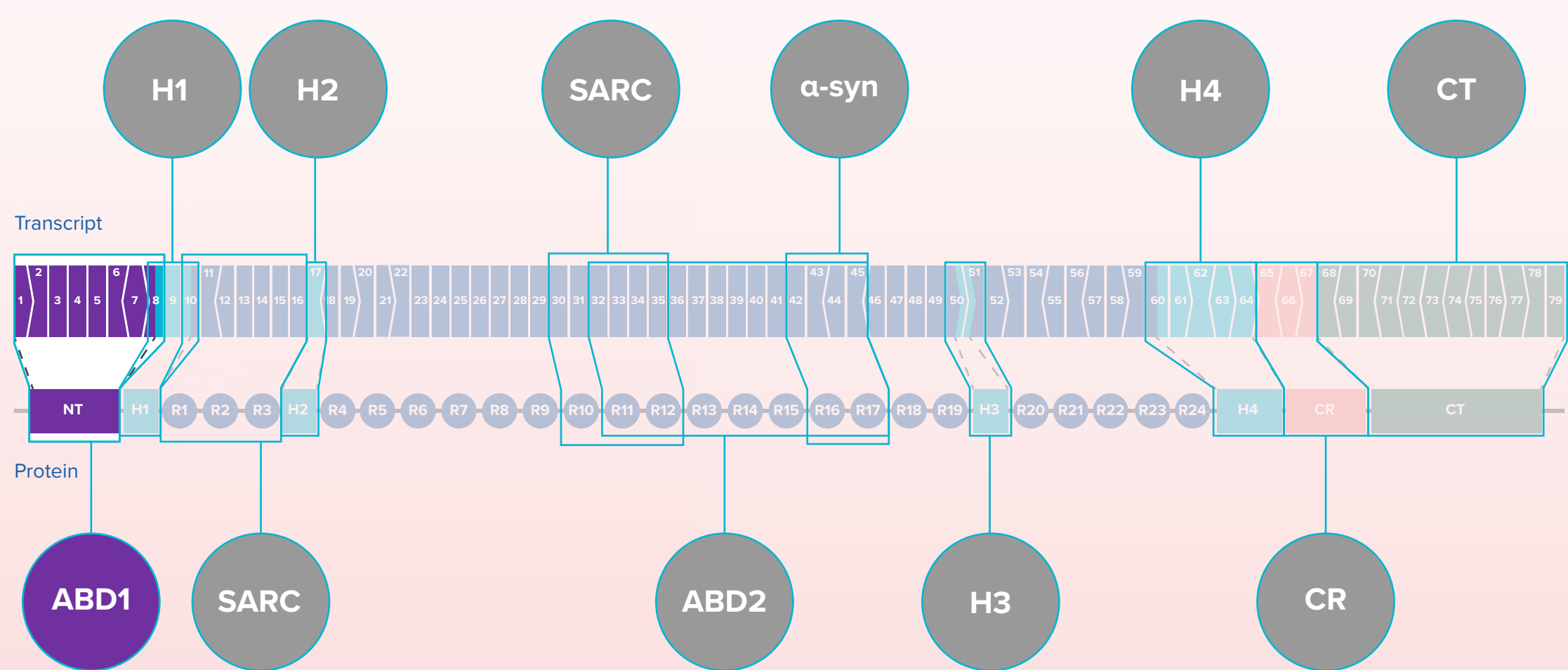
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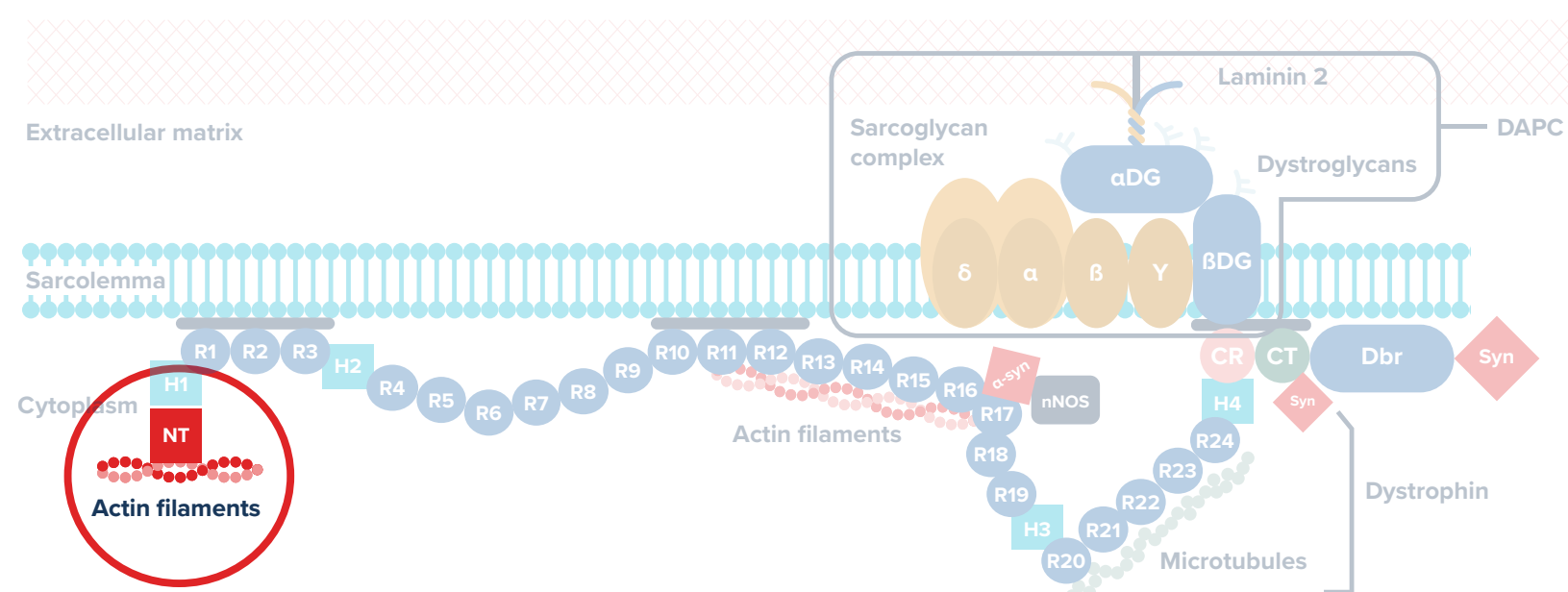
Understanding dystrophin in DMD

Domains of the **dystrophin** protein perform a variety of structural and signaling functions in the cell.¹ **Tap the circles to explore.**



Actin binding domain 1

Exons 1–8 encode the actin binding domain (ABD1) at the N-terminus of the dystrophin protein.^{1,2} It binds to actin filaments, linking dystrophin to the subsarcolemmal actin network. ABD1 is required to support skeletal muscle fiber contraction and protect against myofiber necrosis.³ ABD1 is one of two ABDs on the dystrophin protein.¹



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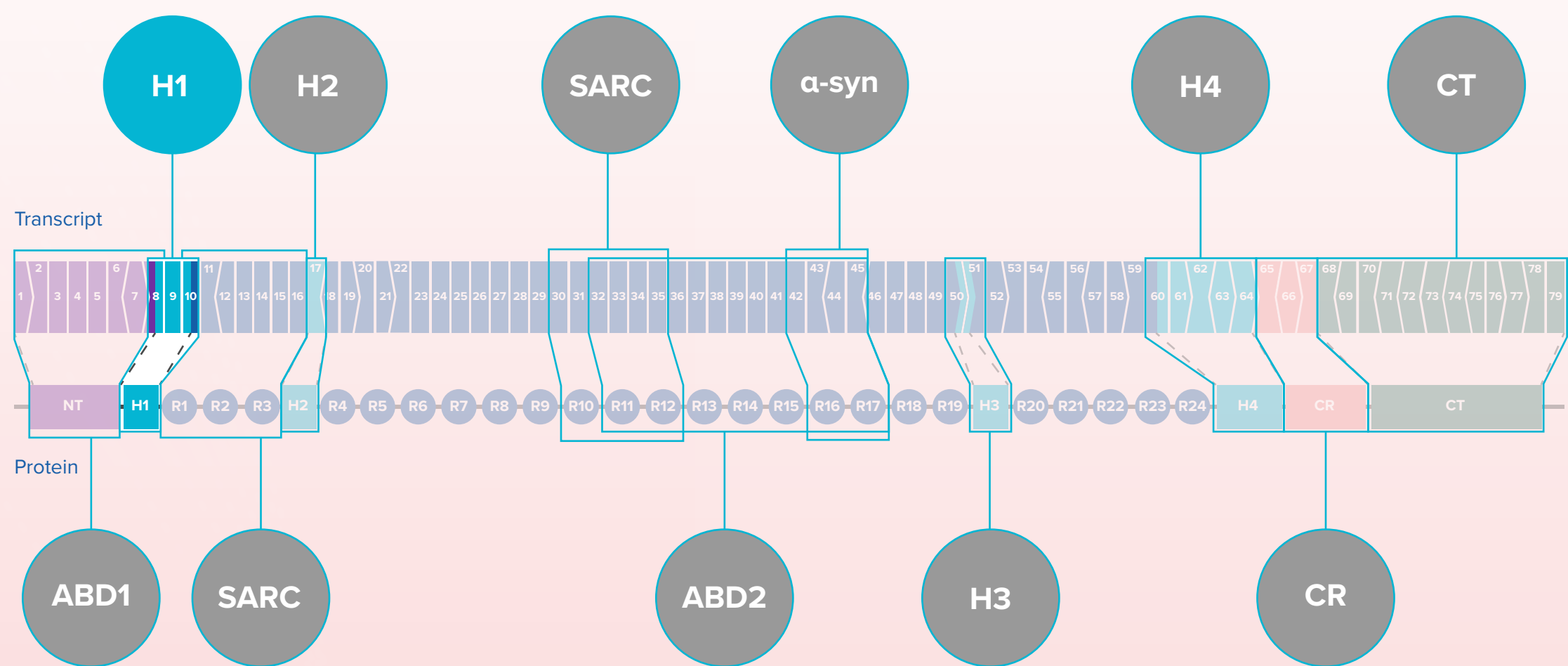
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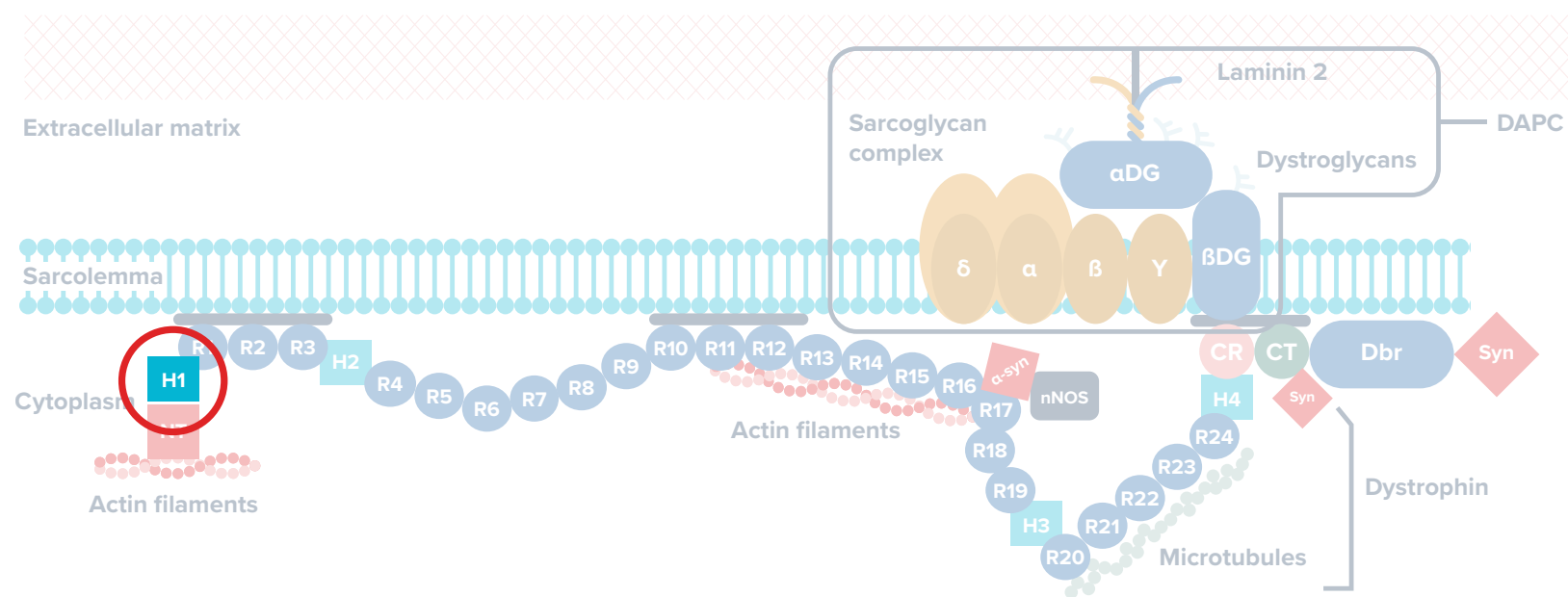
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Domains of the **dystrophin** protein perform a variety of structural and signaling functions in the cell.¹ **Tap the circles to explore.**



Hinge region 1

Exons 8–10 encode hinge region 1 (H1), one of the four short proline-rich hinge regions that give dystrophin flexibility.^{1,2} Removal of H1 does not affect the localization of dystrophin at the sarcolemma but has been shown to lead to functional deficiency in muscle force (i.e., strength or tension exerted by muscles during contraction) in *mdx* (i.e., dystrophin-deficient) mice.³



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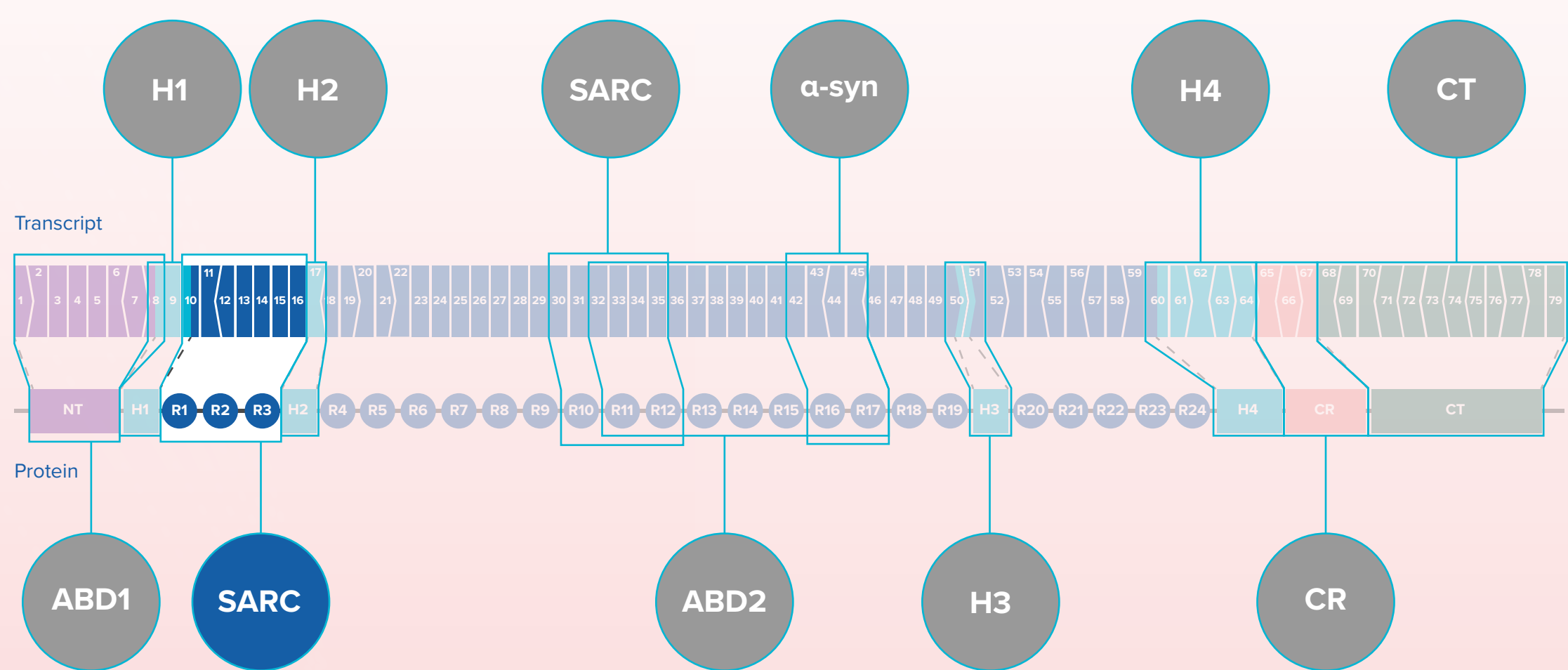
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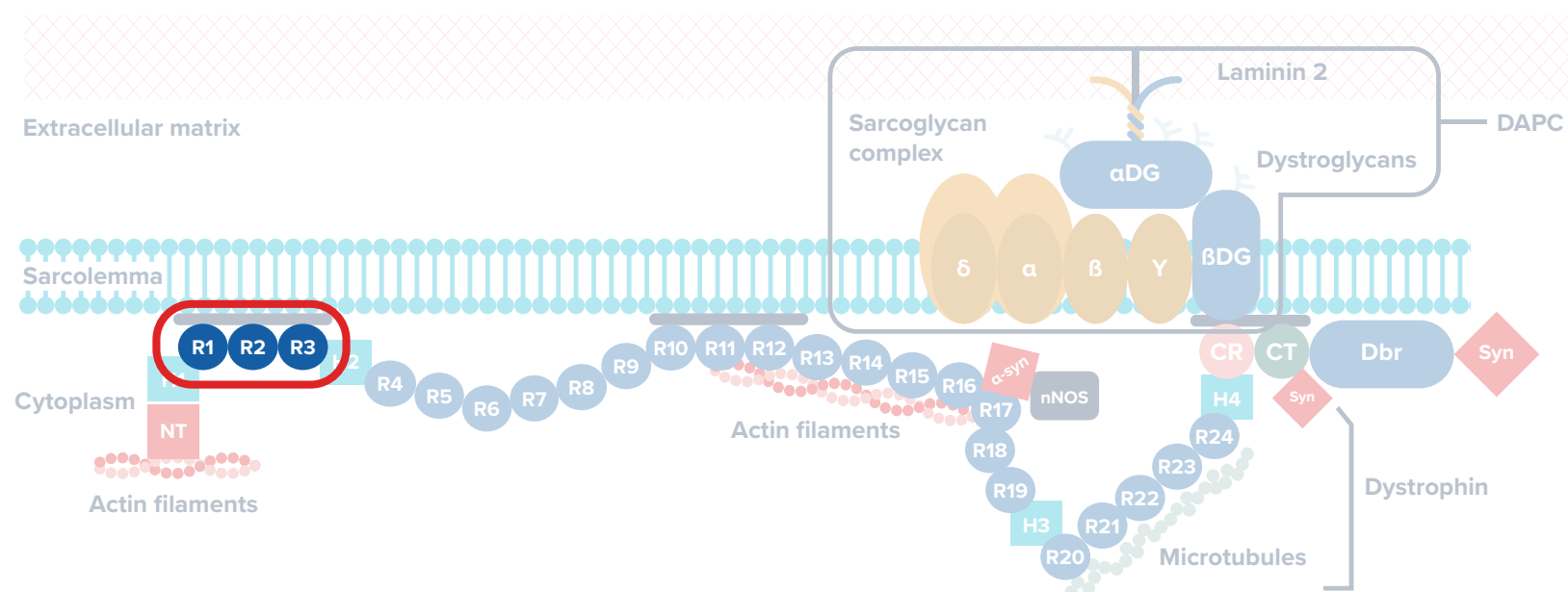
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Domains of the **dystrophin** protein perform a variety of structural and signaling functions in the cell.¹ **Tap the circles to explore.**



Sarcolemma-binding domain

Exons 10–16 encode the R1–R3 subdomain, one of four subdomains (R1–R3, R10–R12, cysteine-rich domain and C-terminus) that have been shown to anchor dystrophin to the sarcolemma in the skeletal muscle of *mdx* (i.e., dystrophin deficient) mice.^{2,3}



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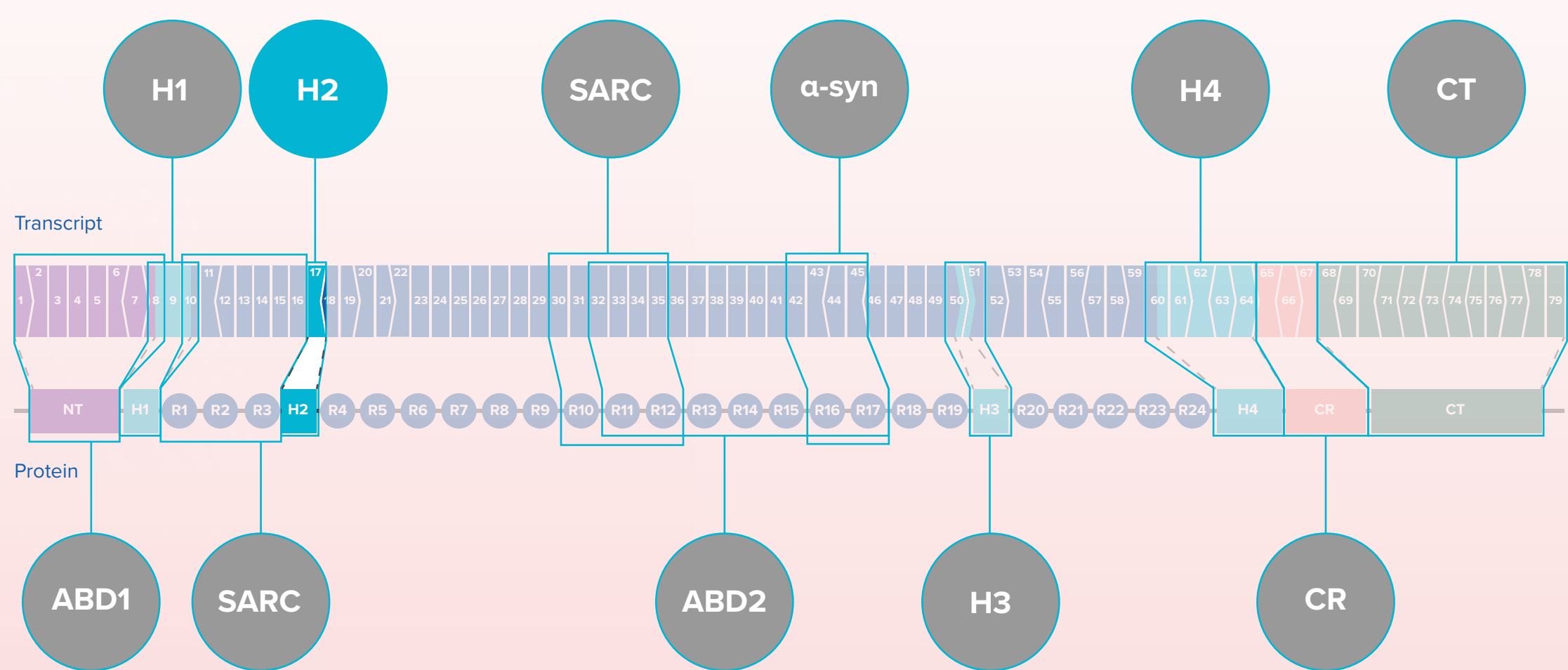
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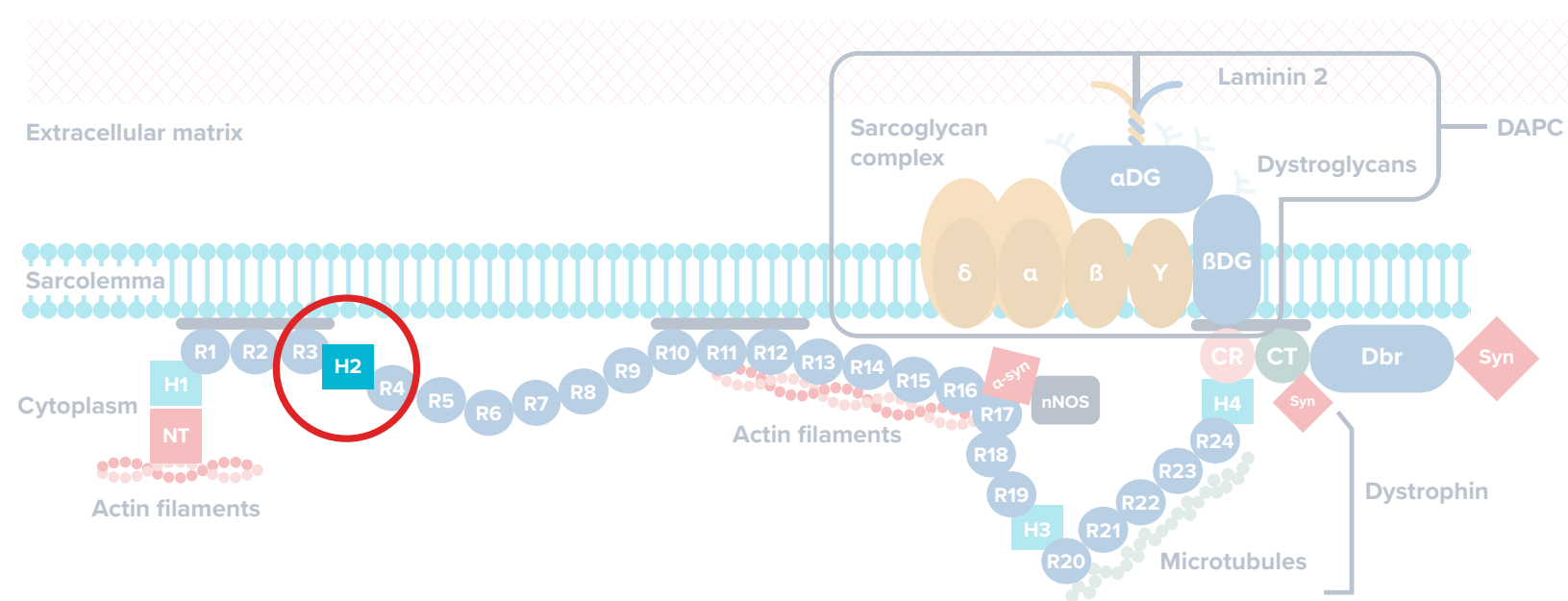
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Hinge region 2

Exon 17 encodes hinge region 2 (H2), one of the four short, proline-rich hinge regions that give dystrophin flexibility.^{1,2}



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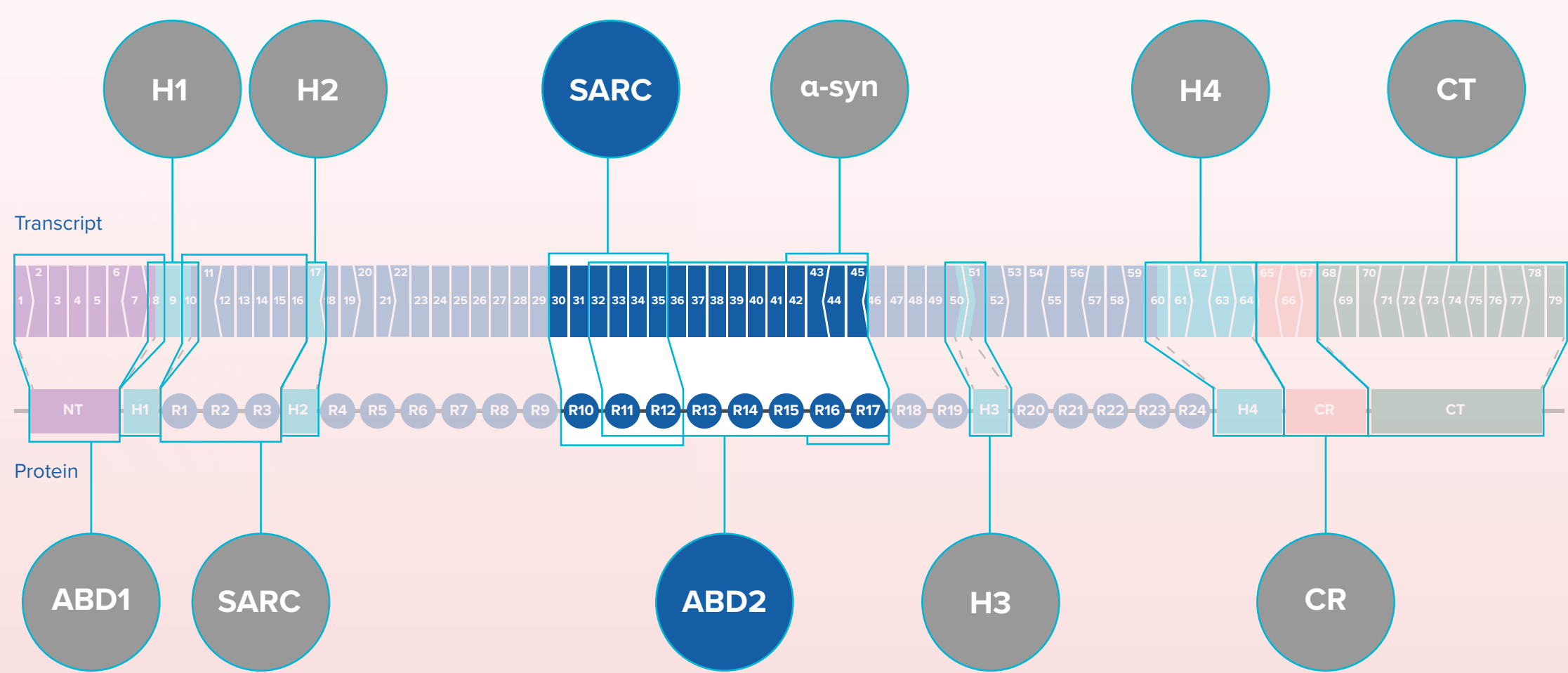
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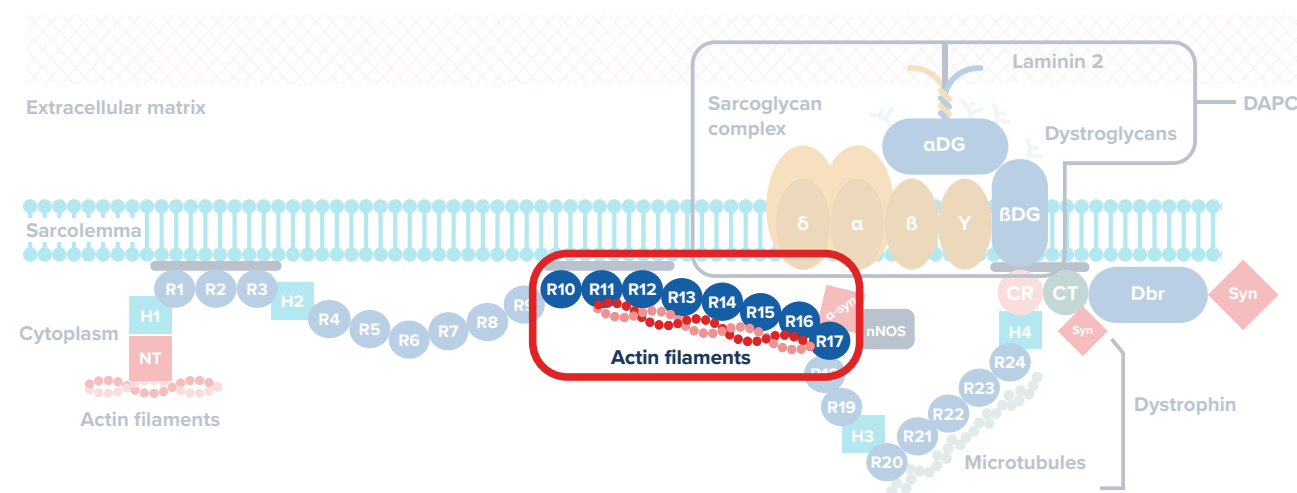
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Sarcolemma-binding domain and actin binding domain 2

Exons 32–45 encode a section of the rod domain that contains a second actin-binding domain (ABD2).^{1,2} It binds to actin filaments, linking dystrophin to the subsarcolemmal actin network.¹ While the role of ABD2 remains to be fully understood, dystrophin constructs lacking the central DMD region, including ABD2, have resulted in only a partial rescue of the dystrophic phenotype in *mdx* (i.e., dystrophin-deficient) mice.³

Exons in this region (exons 30–35) also encode one of four subdomains (R1–R3, R10–R12, cysteine-rich domain and C-terminus) that have been shown to anchor dystrophin to the sarcolemma in the skeletal muscle of *mdx* (i.e., dystrophin deficient) mice. The R10–R12 subdomain has no membrane-binding activity in cardiac muscle cells, suggesting a different functional role for dystrophin in the heart compared with skeletal muscle.⁴



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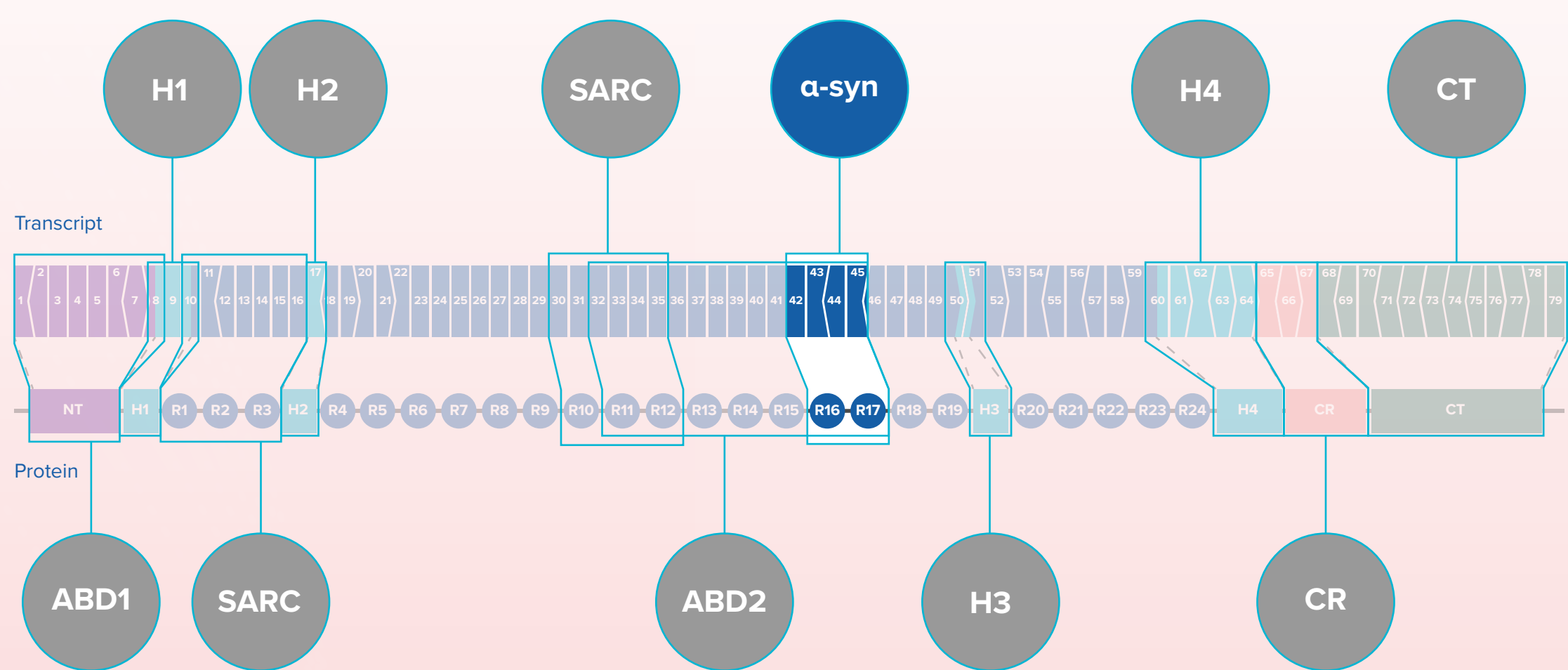
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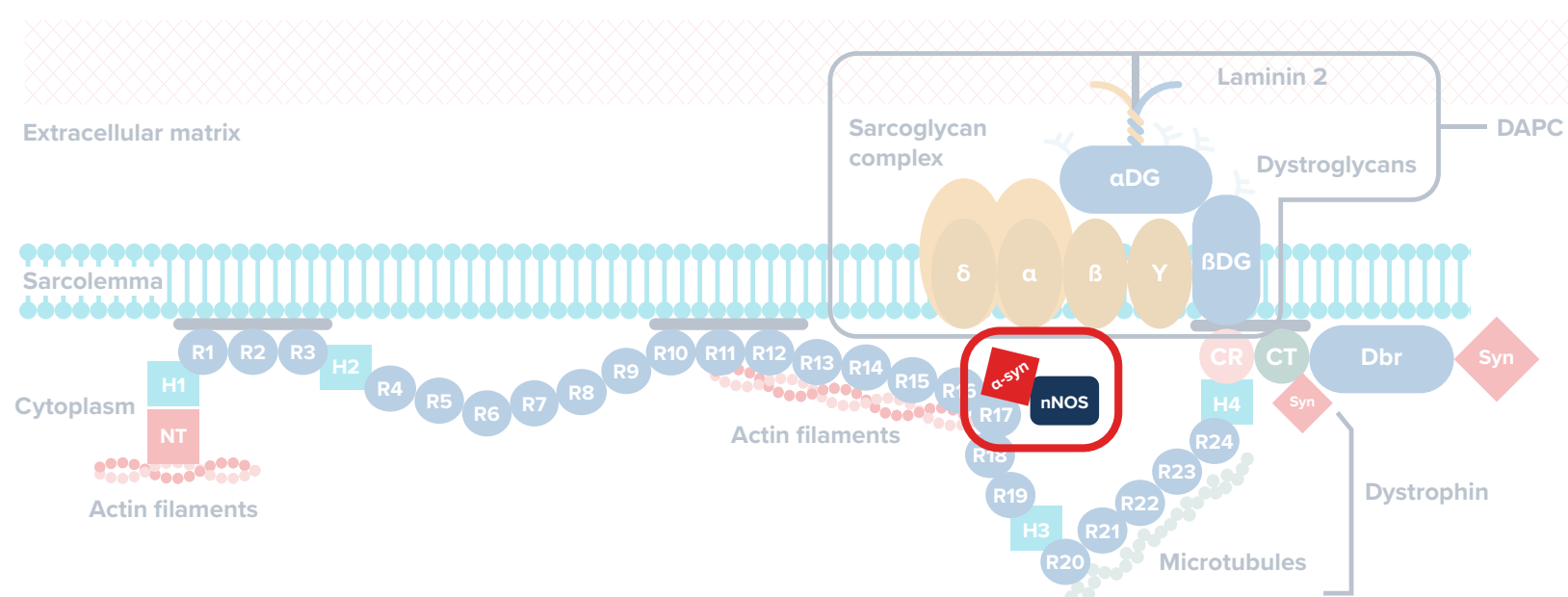
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α-syntrophin-binding domain

Exons 42–45 encode the binding site for α-syntrophin, which facilitates the interaction between neuronal nitric oxide synthase (nNOS).^{1–3} nNOS anchored at the sarcolemma produces nitric oxide during physical activity, which signals blood vessels to dilate to increase blood flow to provide sufficient oxygen and nutrition to muscle cells.¹



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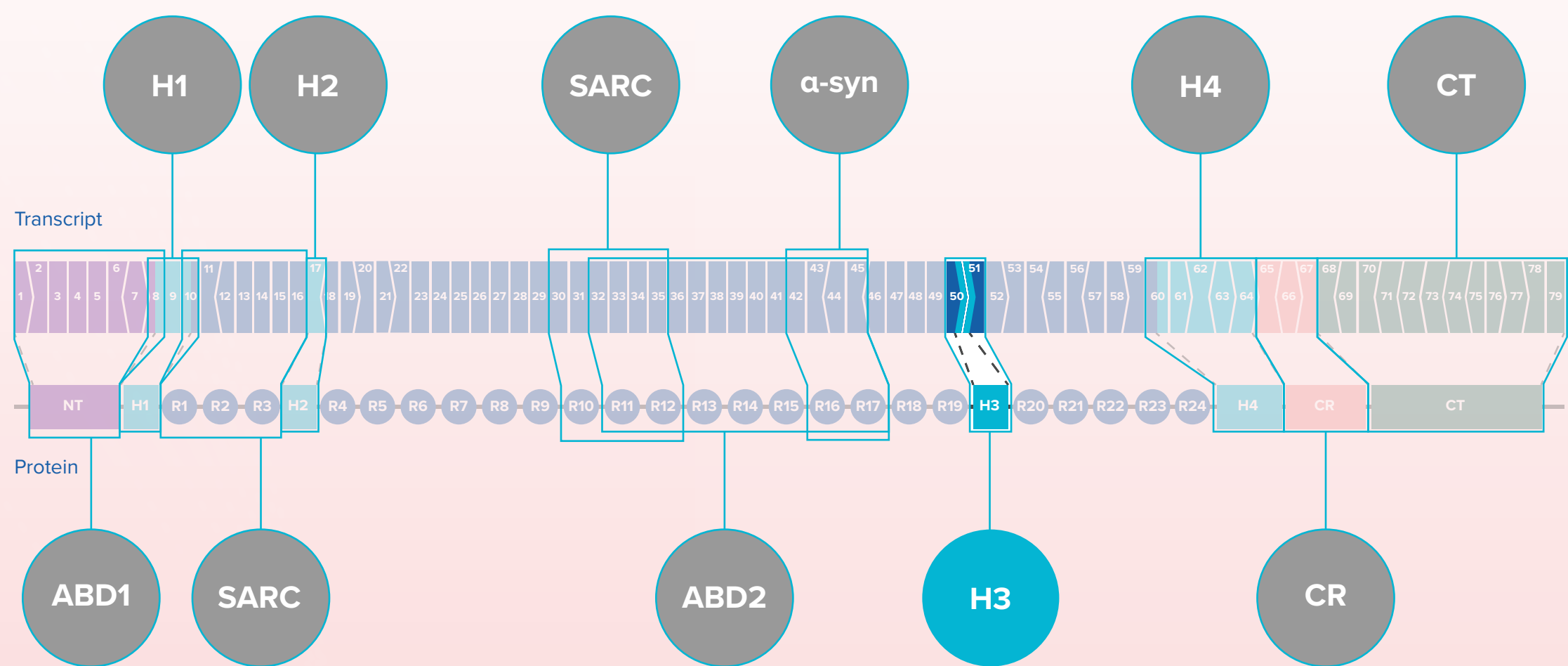
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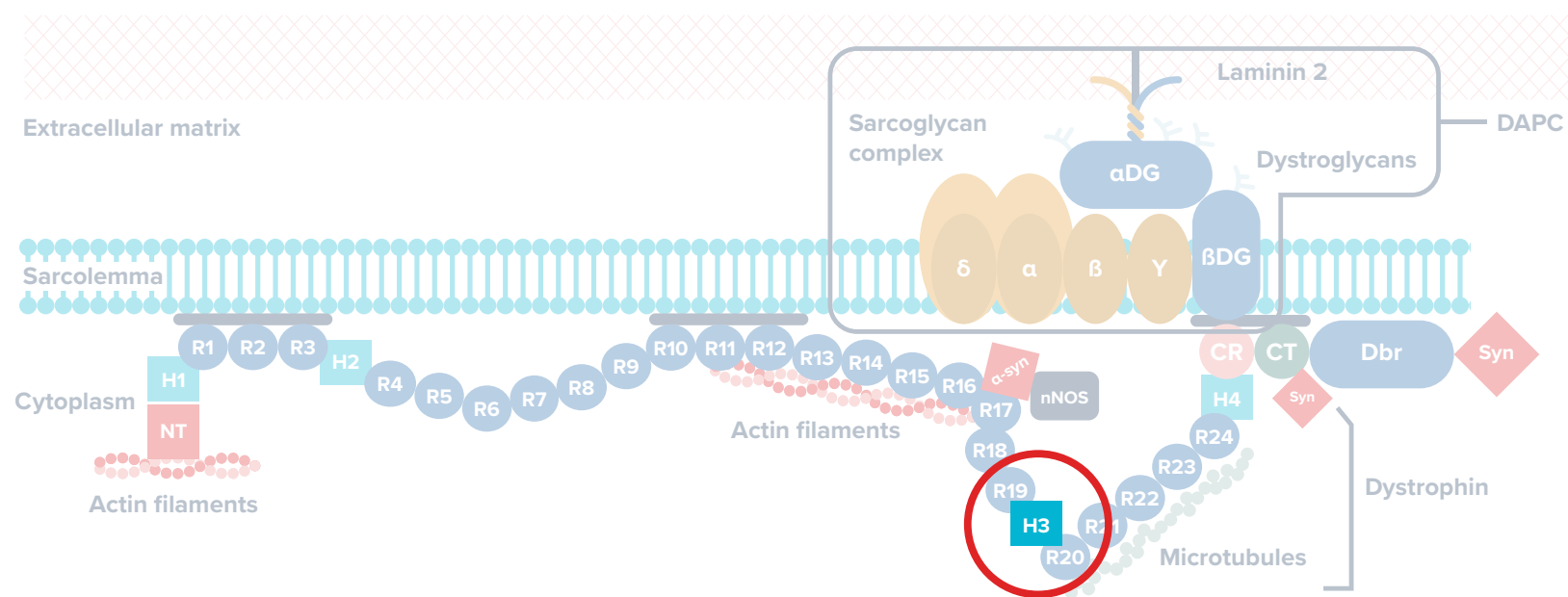
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Hinge region 3

Exons 50–51 encode hinge region 3 (H3), one of the four short, proline-rich hinge regions that give dystrophin flexibility.^{1,2} Dystrophin constructs containing hinge 2 (H2), but lacking H3, appear to induce ringed fibers, which are indicative of chronic strain injury at the myotendinous junction, in the muscles of *mdx* (i.e., dystrophin-deficient) mice.³



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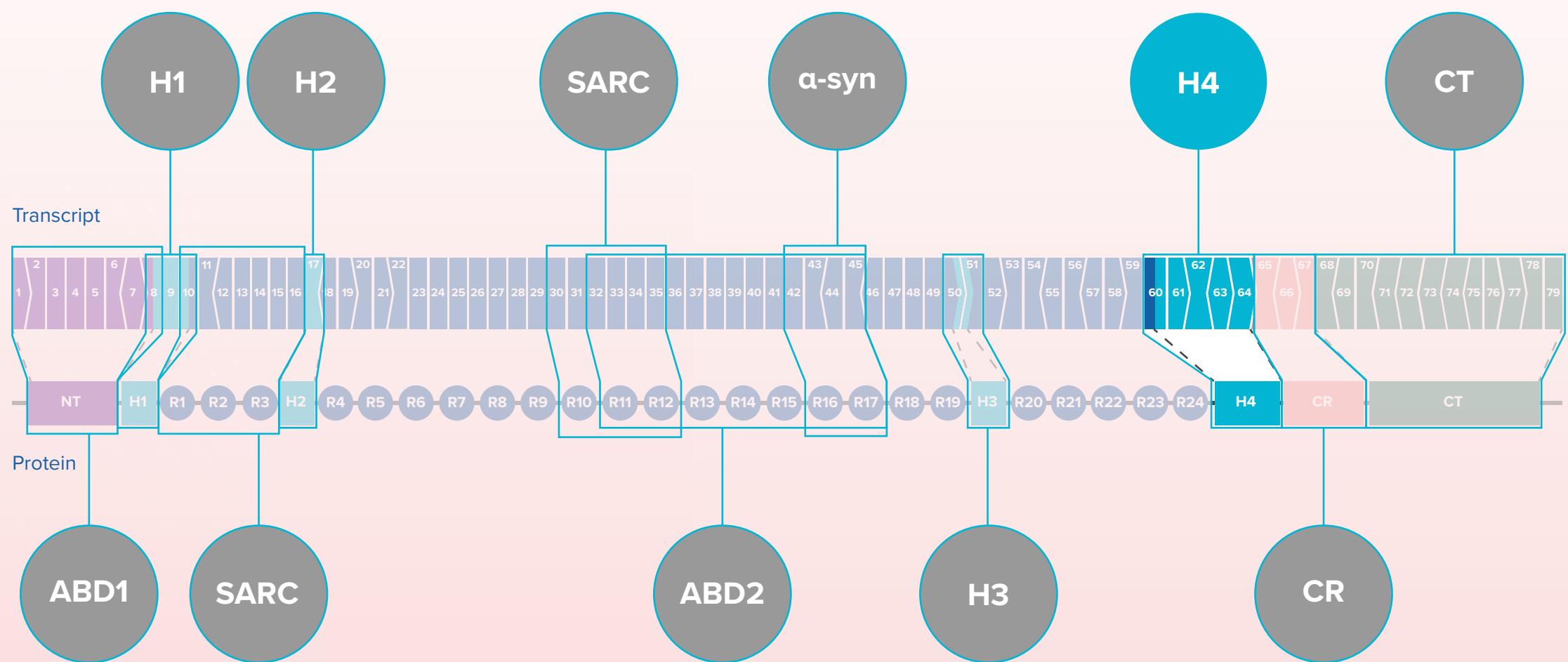
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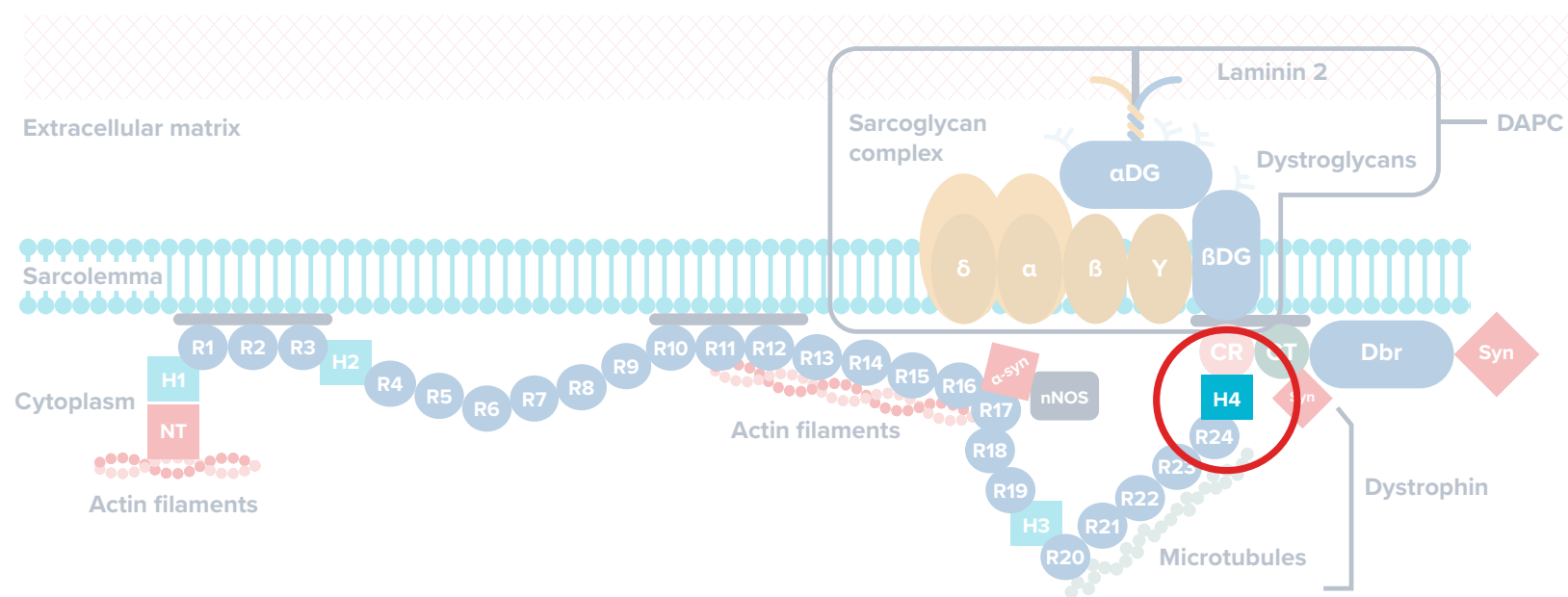
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Hinge region 4

Exons 60–64 encode hinge region 4 (H4), one of the four short, proline-rich hinge regions that give dystrophin flexibility.^{1,2} In addition to this role, H4 has a WW (two tryptophan residues) domain that aids the binding of dystrophin to β -dystroglycan.¹ H4 is essential for dystrophin function as removal has been shown to impair the anchoring of dystrophin to the sarcolemma in *mdx* (i.e., dystrophin-deficient) mice.³



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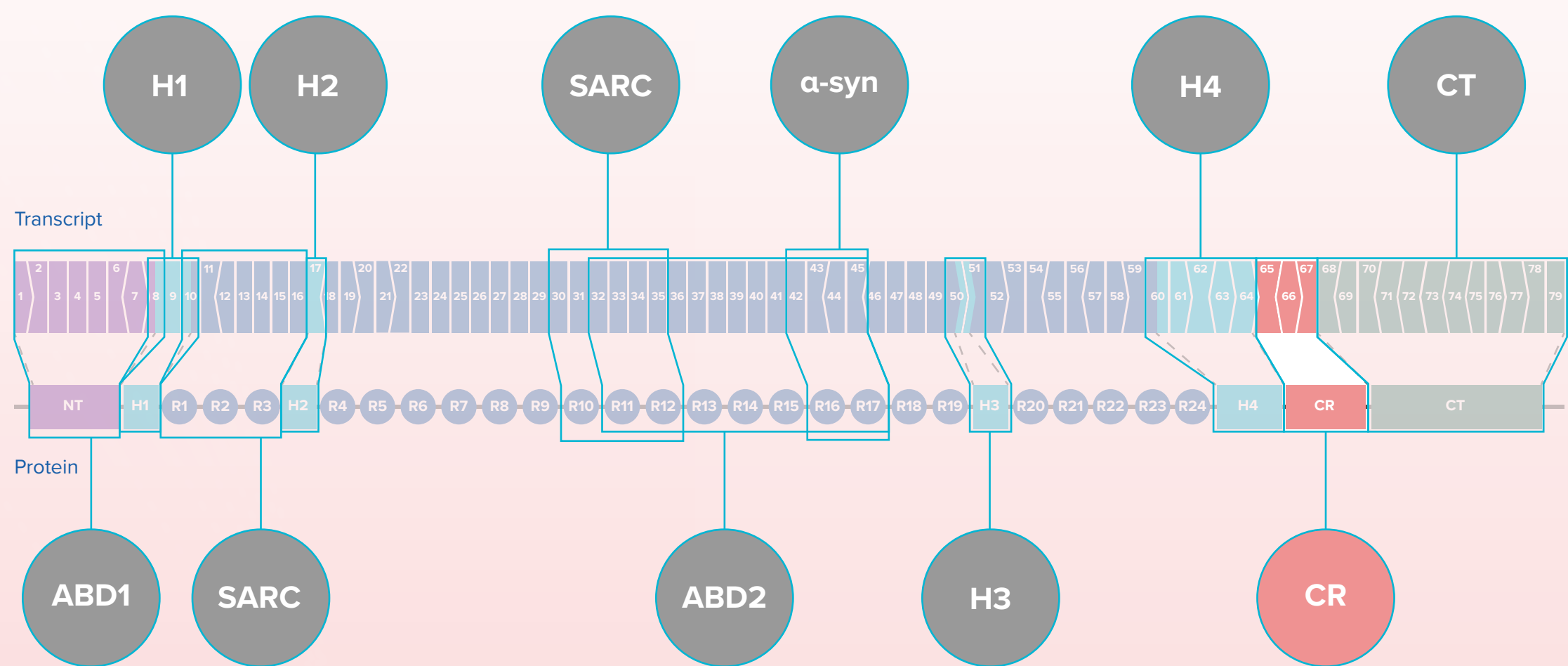
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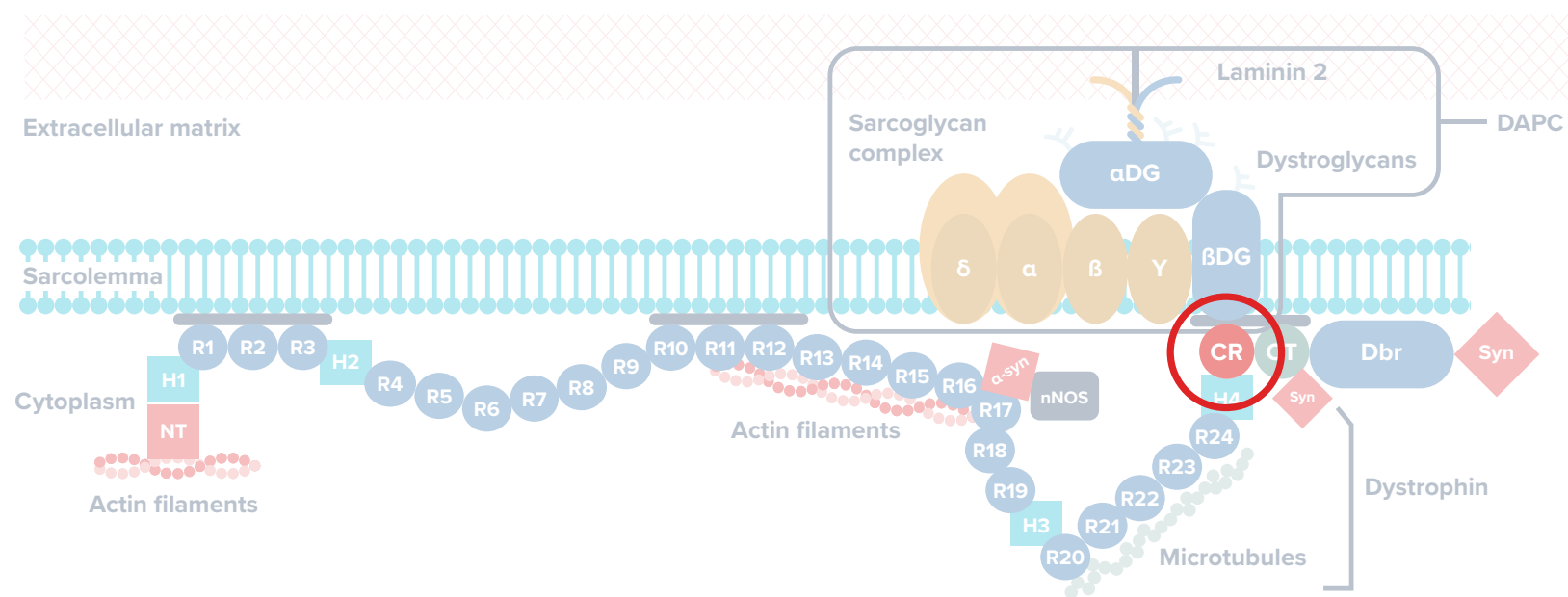
Understanding dystrophin in DMD

Domains of the **dystrophin** protein perform a variety of structural and signaling functions in the cell.¹ **Tap the circles to explore.**



Cysteine-rich domain

Exons 65–67 encode the cysteine-rich domain.^{1,2} Together, the cysteine-rich domain and the WW (two tryptophan residues) domain of H4 act as the binding site for β -dystroglycan.¹ This interaction anchors dystrophin to the sarcolemma.¹ Patients lacking the cysteine-rich domain consistently present with severe muscular dystrophy.³



BACK TO TOPIC
SELECTION

ABD, actin-binding domain; **CR**, cysteine rich; **CT**, C-terminus (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; **Sarc**, sarcolemma; **Syn**, syntrophin; **WW**, two tryptophan residues.

First image references: Gao QQ, et al. *Compr Physiol*. 2015;5(3):1223–39, Roberts RG, et al. *Genomics*. 1993;16(2):536–8, Zhang Y, et al. *Physiol Rev*. 2018;98(3):1205–40, Adams ME, et al. *Hum Mol Genet*. 2018;27(17):2978–85, Zhao J, et al. *Hum Mol Genet*. 2016;25(17):3647–53, and Constantin B. *Biochim Biophys Acta*. 2014;1838(2):635–42.

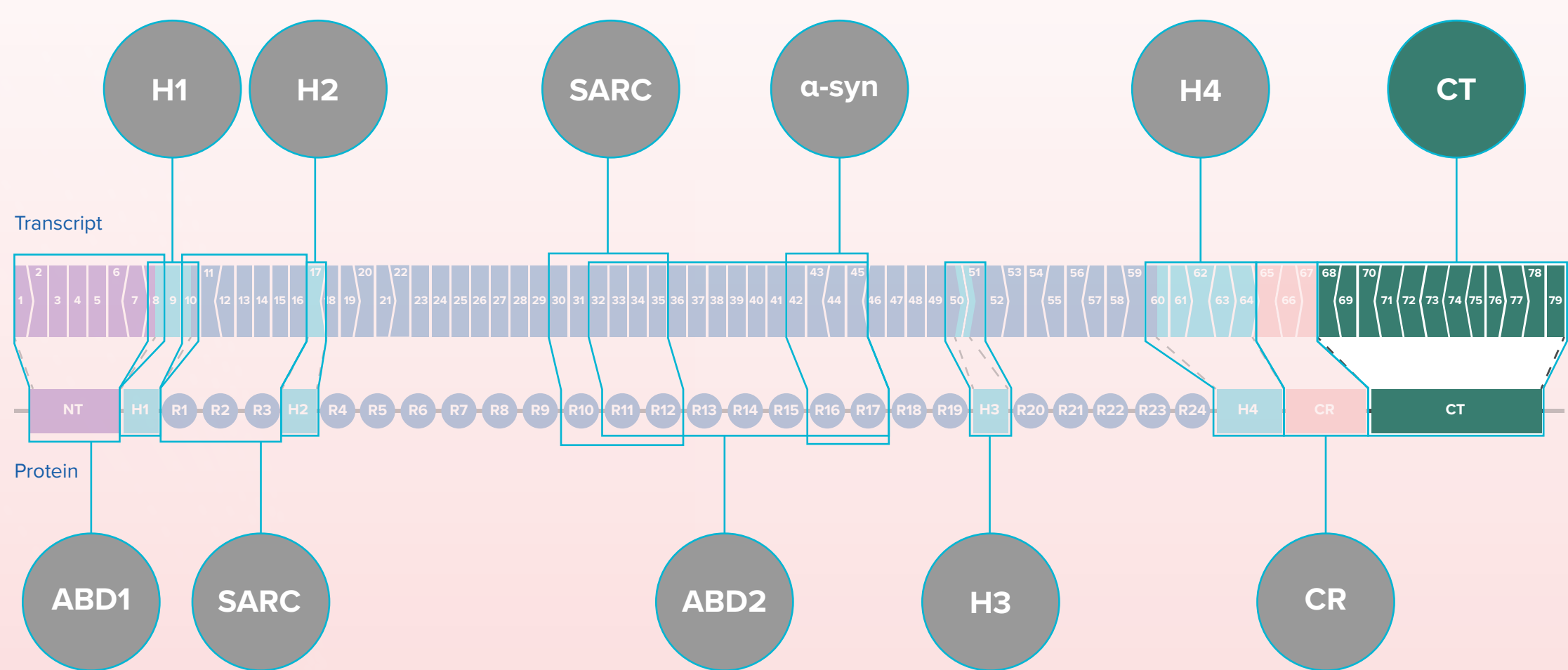
Second image references: Gao QQ, McNally EM. *Compr Physiol*. 2015;5(3):1223–39, Zhao J, et al. *Hum Mol Genet*. 2016;25(17):3647–53, and Adams ME, et al. *Hum Mol Genet*. 2018;27(17):2978–85. Image used with permission of The Author, from Zhao J, et al. *Hum Mol Genet*. 2016;25:3647–3653; permission conveyed through Copyright Clearance Center, Inc.

References: 1. Gao QQ, et al. *Compr Physiol*. 2015;5(3):1223–39; 2. Roberts RG, et al. *Genomics*. 1993;16(2):536–8; 3. Bies RD, et al. *J Clin Invest*. 1992;90(2):666–72.



Understanding dystrophin in DMD

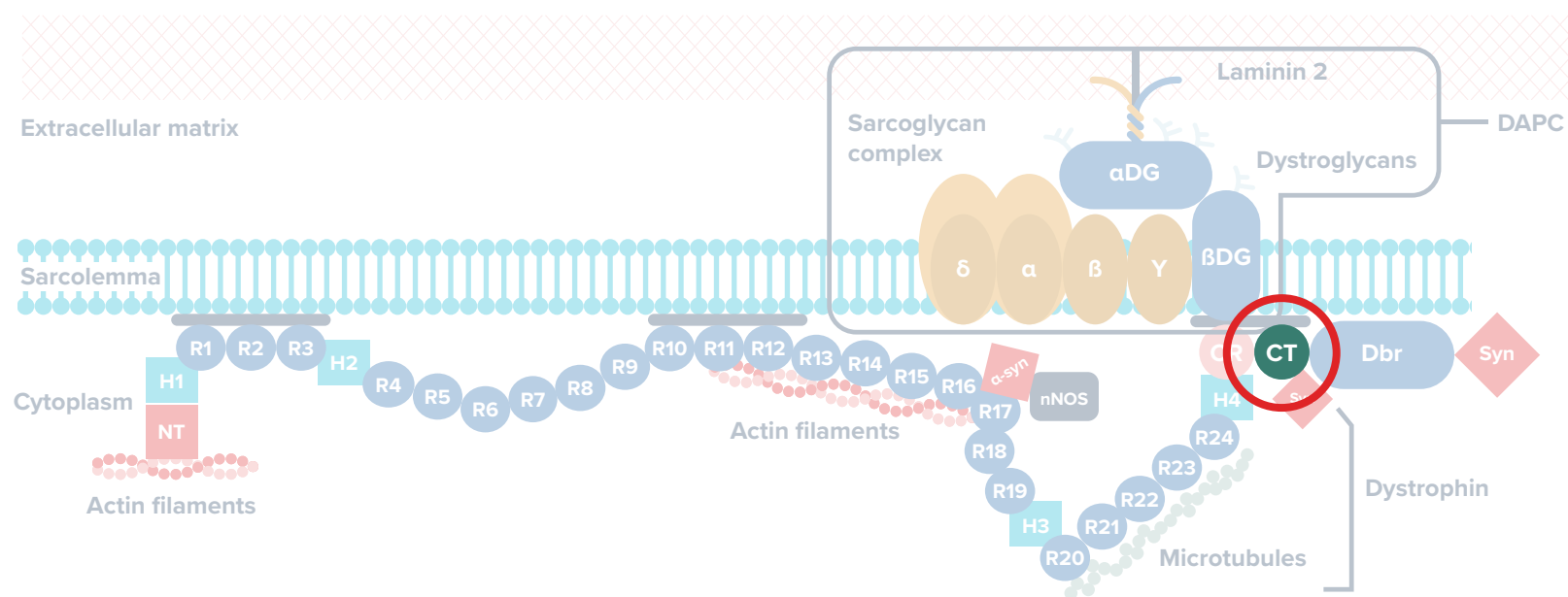
Domains of the **dystrophin** protein perform a variety of structural and signaling functions in the cell.¹ **Tap the circles to explore.**



C-terminus

Exons 68–79 encode the C-terminus, which anchors dystrophin to the sarcolemma, and provides binding sites for dystrobrevin and syntrophin, mediating their sarcolemma localization.^{1–3} Dystrobrevin plays a role in maintaining the structural integrity of the cell and associates with syntrophin, which is involved in numerous cell signaling pathways.^{1,4}

The role of the C-terminus is not well understood; however, dystrophin constructs lacking the C-terminus, but retaining the cysteine-rich domain, appear functional in *u-dko* (i.e., dystrophin- and utrophin-deficient) mice.⁵



**BACK TO TOPIC
SELECTION**

ABD, actin-binding domain; **CR**, cysteine rich; **CT**, C-terminus (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; **Sarc**, sarcolemma; **Syn**, syntrophin.

First image references: Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39, Roberts RG, et al. *Genomics.* 1993;16(2):536–8, Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40, Adams ME, et al. *Hum Mol Genet.* 2018;27(17):2978–85, Zhao J, et al. *Hum Mol Genet.* 2016;25(17):3647–53, and Constantin B. *Biochim Biophys Acta.* 2014;1838(2):635–42.

Second image references: Gao QQ, McNally EM. *Compr Physiol.* 2015;5(3):1223–39, Zhao J, et al. *Hum Mol Genet.* 2016;25(17):3647–53, and Adams ME, et al. *Hum Mol Genet.* 2018;27(17):2978–85. 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.

References: 1. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 2. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 3. Zhao J, et al. *Hum Mol Genet.* 2016;25(17):3647–53, 4. Constantin B. *Biochim Biophys Acta.* 2014;1838(2):635–42; 5. Yue Y, et al. *Mol Ther.* 2006;14(1):79–87.



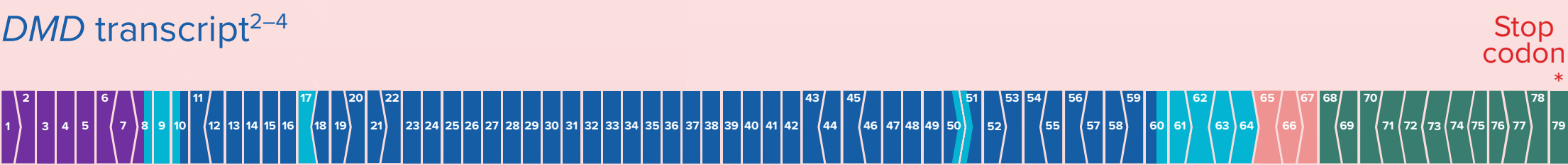
Understanding dystrophin in DMD

Mutations in the *DMD* gene

DMD is caused by mutations in the *DMD* gene that result in reduced production or absence of functional dystrophin protein, either by disrupting the reading frame or by a nonsense mutation that generates a premature stop codon^{1,2}

Most patients with DMD have large deletions (~68%) or duplications (~11%) spanning one or more exons, but smaller mutations are also seen (~20%).²

In contrast, patients with the milder disease phenotype, known as Becker muscular dystrophy (BMD), generally have mutations that maintain the open reading frame (i.e., in-frame mutations).²



See examples of these types of mutations

Frameshift mutation

Nonsense mutation

In-frame mutation

NEXT >

BMD, Becker muscular dystrophy; **DMD**, Duchenne muscular dystrophy.

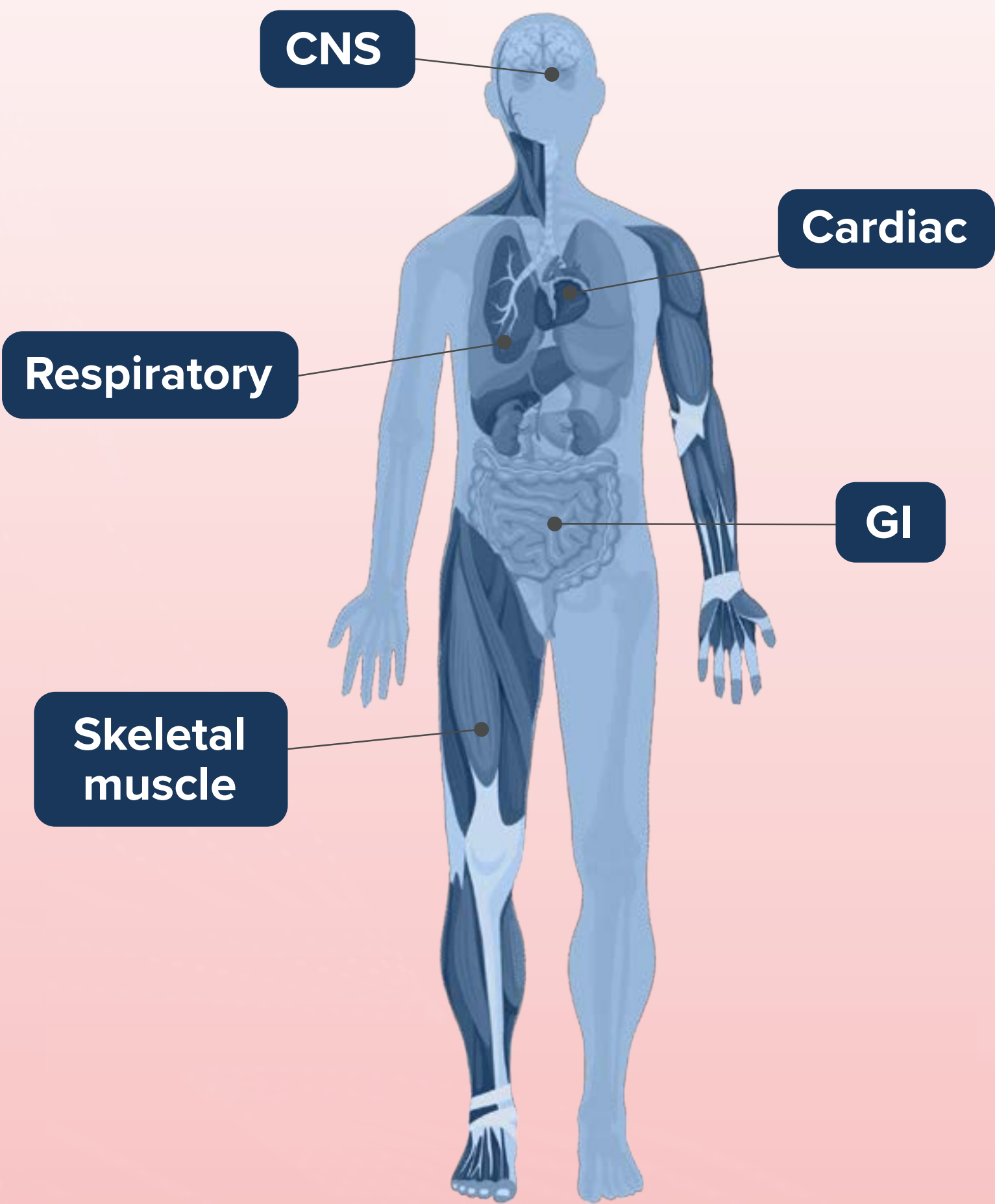
References: 1. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther.* 2017;17(2):225–36;
2. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8;
4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.



Understanding dystrophin in DMD

The impact of a lack of functional dystrophin for patients with DMD

Dystrophin deficiency manifests in a multisystemic manner, affecting skeletal, smooth, and cardiac muscle, as well as the CNS.¹



Dystrophin-producing investigational therapies aim to achieve broad distribution of dystrophin protein that includes key domains and maintains similar properties to dystrophin produced in healthy individuals with the goal of enabling functional improvement in people living with DMD.^{2–7}

BACK TO TOPIC
SELECTION

CNS, central nervous system; **DMD**, Duchenne muscular dystrophy; **GI**, gastrointestinal.

References: 1. Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473(12):1813–39; 2. Waldrop MA, et al. *J Neuromuscul Dis.* 2020;7(3):217–29; 3. Nakamura A, et al. *J Hum Genet.* 2017;62(4):459–63; 4. Tasfaout H, et al. *Nature.* 2024;632(8023):192–200; 5. Albin S, et al. *Int J Mol Sci.* 2023;24(14):11421; 6. Ramos JN, et al. *Mol Ther.* 2019;27(3):623–35; 7. Duan D. *Systemic Mol Ther.* 2018;26(10):2337–56.



Understanding dystrophin in DMD

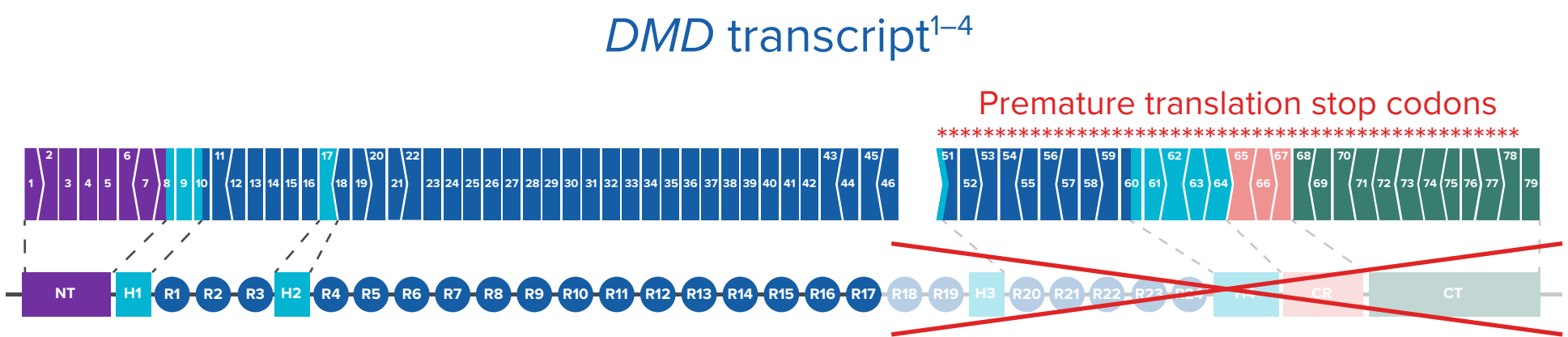
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Most patients with DMD have large deletions (~68%) or duplications (~11%) spanning one or more exons, but smaller mutations are also seen (~20%).²

Frameshift mutation

In this example, deletion of exons 47–50 leads to premature protein synthesis termination. While exon deletions can occur anywhere in the gene, exons 45–55 are the most common deletional hot spot.¹



Truncated dystrophin protein^{1–3}

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

References: 1. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 2. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

BMD, Becker muscular dystrophy; **DMD**, Duchenne muscular dystrophy.

References: 1. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther.* 2017;17(2):225–36; 2. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

Understanding dystrophin in DMD

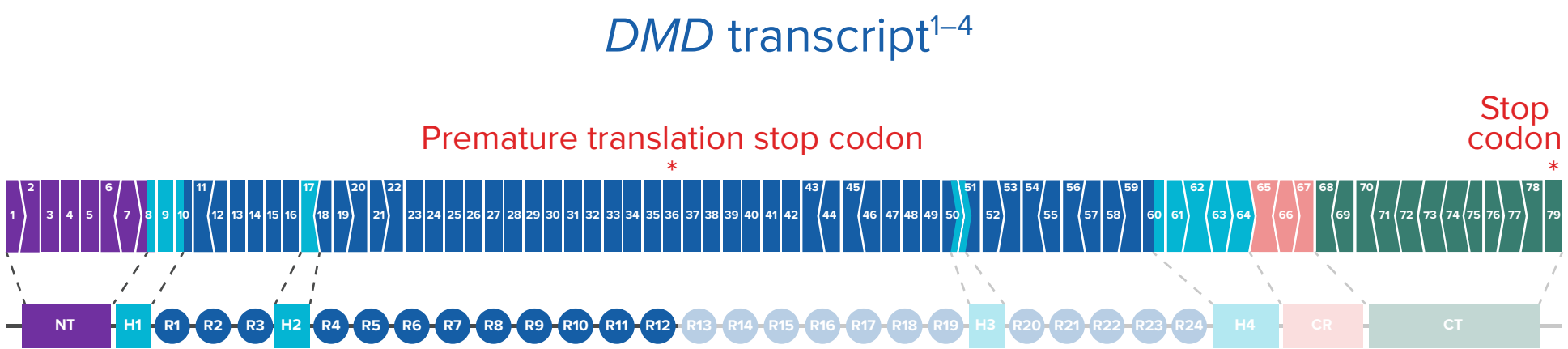
Mutations in the *DMD* gene

DMD is caused by mutations in the DMD gene that result in reduced production or absence of functional dystrophin protein, either by disrupting the reading frame or by a nonsense mutation that generates a premature stop codon^{1,2}

Most patients with DMD have large deletions (~68%) or duplications (~11%) spanning one or more exons, but smaller mutations are also seen (~20%).²

Nonsense mutation

In this example, a point mutation changes an amino acid codon to a stop codon, ending translation prematurely and leading to a truncated dystrophin protein.¹ Truncated *DMD* genes with this mutation are unstable and subject to degradation resulting in little to no dystrophin protein.²



Truncated dystrophin protein^{1–3}

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

References: 1. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 2. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

BMD, Becker muscular dystrophy; **DMD**, Duchenne muscular dystrophy.

References: 1. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther.* 2017;17(2):225–36; 2. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

Understanding dystrophin in DMD

Mutations in the *DMD* gene

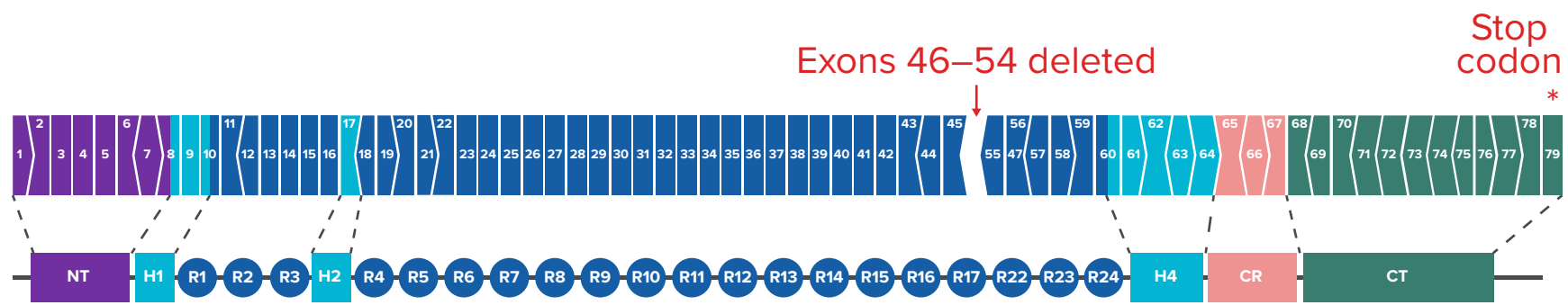
DMD is caused by mutations in the DMD gene that result in reduced production or absence of functional dystrophin protein, either by disrupting the reading frame or by a nonsense mutation that generates a premature stop codon^{1,2}

Most patients with DMD have large deletions (~68%) or duplications (~11%) spanning one or more exons, but smaller mutations are also seen (~20%).²

In-frame mutation

In this example, deletion of exons 46–54 does not disrupt the reading frame, and translation can continue past the deletion. This yields an internally shortened dystrophin protein that retains many functional domains, including the N- and C-terminal domains, which play an important role in connecting the actin cytoskeleton to the extracellular matrix.¹

DMD transcript^{1–4}



Internally shortened dystrophin protein^{1–3}

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

References: 1. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 2. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

BMD, Becker muscular dystrophy; **DMD**, Duchenne muscular dystrophy.

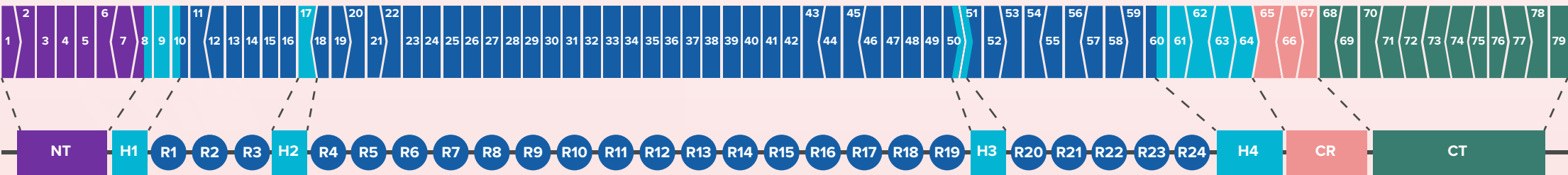
References: 1. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther.* 2017;17(2):225–36; 2. Aartsma-Rus A, et al. *J Med Genet.* 2016;53(3):145–51; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40.

Understanding dystrophin in DMD

Features of exon skipping-produced dystrophin and micro-dystrophin

The full-length dystrophin is a large protein which, as an integral part of the DAPC, provides support to the cell during contraction and forms scaffolding for a number of signaling molecules.^{1,2}

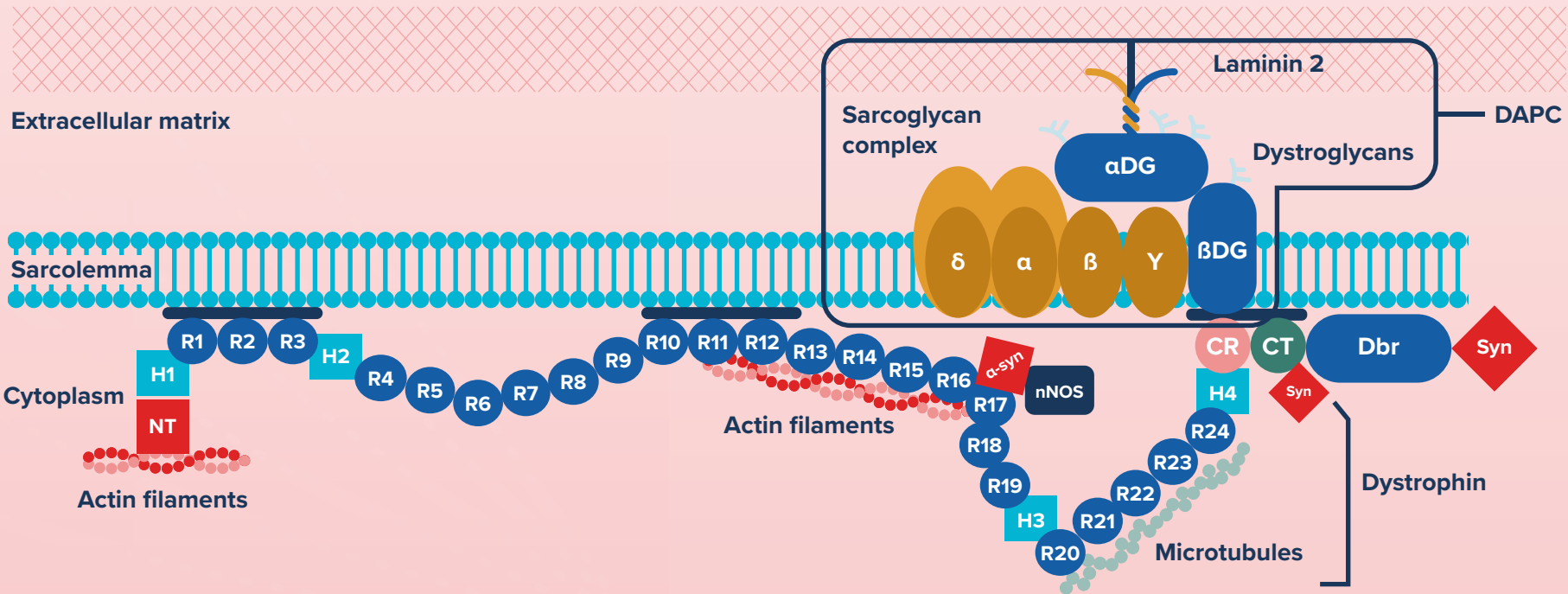
DMD transcript^{3,4}



Full-length dystrophin protein¹⁻³

Protein size: 427 kDa

Full-length dystrophin as part of the DAPC^{1,5,6}



Compared with micro-dystrophin, exon skipping-produced dystrophin is closer in size to full-length dystrophin.

Tap the buttons to explore:^{2,7-9}

Exon skipping-produced dystrophin

Micro-dystrophin

BACK TO TOPIC SELECTION

CR, cysteine rich; **CT**, C-terminus (carboxy-terminus); **DAPC**, dystrophin-associated protein complex; **Dbr**, dystrobrevin; **DG**, dystroglycan; **DMD**, Duchenne muscular dystrophy; **H**, hinge; **kDa**, kilodalton; **nNOS**, neuronal nitric oxide synthase; **NT**, N-terminus; **R**, spectrin-like repeat; **Syn**, syntrophin.

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References: 1. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 2. Elangkovan N, Dickson G. *J Neuromuscul Dis.* 2021;8(S2):S303–S316; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40; 5. Zhao J, et al. *Hum Mol Genet.* 2016;25(17):3647–53; 6. Adams ME, et al. *Hum Mol Genet.* 2018;27(17):2978–85; 7. Nakamura A. et al. *J Hum Genet.* 2017;62(10):871–76; 8. Nicolas A, et al. *Hum Mol Genet.* 2015;24(5):1267–79; 9. FDA. News release. <https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gene-therapy-patients-duchenne-muscular-dystrophy>. Accessed January 14, 2025.



Features of exon skipping-produced dystrophin and micro-dystrophin

DMD transcript^{3,4}

F

Exon skipping-produced dystrophin protein^{2,3,5-8}

References: 1. Nakamura A, et al. *J Hum Genet.* 2017;62(4):459–63; 2. Nakamura A. et al. *J Hum Genet.* 2017;62(10):871–6; 3. Roberts RG, et al. *Genomics.* 1993;16(2):536–8; 4. Zhang Y, et al. *Physiol Rev.* 2018;98(3):1205–40; 5. Gao QQ, et al. *Compr Physiol.* 2015;5(3):1223–39; 6. Nicolas A, et al. *Hum Mol Genet.* 2015;24(5):1267–79; 7. Adams ME, et al. *Hum Mol Genet.* 2018;27(17):2978–85; 8. Zhao J, et al. *Hum Mol Genet.* 2016;25(17):3647–53; 9. Elangkovan N, Dickson G. *J Neuromuscul Dis.* 2021;8(s2):S303–16; 10. Bladen CL, et al. *Hum Mutat.* 2015;36(4):395–402.

Features of exon skipping-produced dystrophin and micro-dystrophin

DMD transcript^{3,4}

Construct encoding gene therapy-produced micro-dystrophin³⁻⁵



Protein size: 138 kDa

This image represents only one micro-dystrophin construct. Different constructs are in preclinical and clinical development.

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

References: 1. Tasfaout H, et al. *Nature*. 2024;632(8023):192–200; 2. England SB, et al. *Nature*. 1990;343(6254):180–2; 3. Roberts RG, et al. *Genomics*. 1993;16(2):536–8; 4. Chamberlain JS, et al. *Hum Gene Ther*. 2023;34(9–10):404–15; 5. Zhang Y, et al. *Physiol Rev*. 2018;98(3):1205–40; 6. Gao QQ, et al. *Compr Physiol*. 2015;5(3):1223–39; 7. Nicolas A, et al. *Hum Mol Genet*. 2015;24(5):1267–79; 8. Adams ME, et al. *Hum Mol Genet*. 2018;27(17):2978–85; 9. Zhao J, et al. *Hum Mol Genet*. 2016;25(17):3647–53; 10. FDA. News release. <https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gene-therapy-patients-duchenne-muscular-dystrophy>. Accessed January 14, 2025.

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