What is a **spliceopathy?**

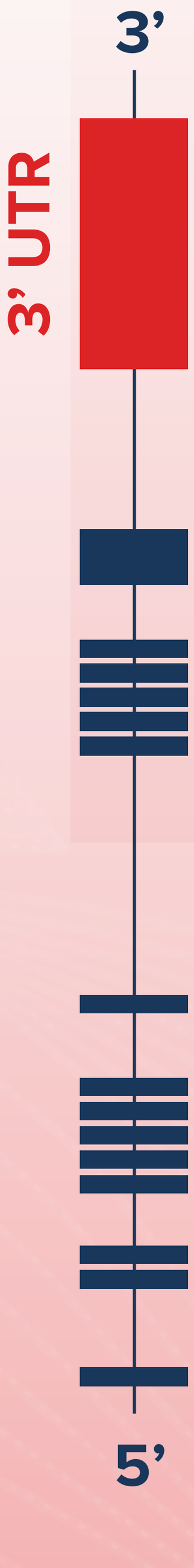
Click on the button below to learn what a spliceopathy is, and how it leads to the clinical manifestations of DM1.

START HERE

What is a **spliceopathy?**

The *DMPK* gene

DM1 is a multisystemic, progressive disease caused by an expansion of a CTG trinucleotide repeat in the 3’ UTR of the *DMPK* gene.[1–5]



CTG, cytosine, thymine, guanosine; **DM1,** myotonic dystrophy type 1; ***DMPK,*** dystrophia myotonica protein kinase; **UTR,** untranslated region.

References: 1. Thornton CA. *Neurol Clin* 2014;32:705–719; 2. Gutiérrez Gutiérrez G, et al. *Neurologia (Engl Ed)* 2020;35:185–206; 3. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390; 4. Hamshere MG, et al. *Proc Natl Acad Sci USA* 1997;94:7394–7399; 5. NCBI. DMPK. Available at: https://www.ncbi.nlm.nih.gov/gene/1760 (accessed August 2024).

What is a **spliceopathy?**

The *DMPK* gene

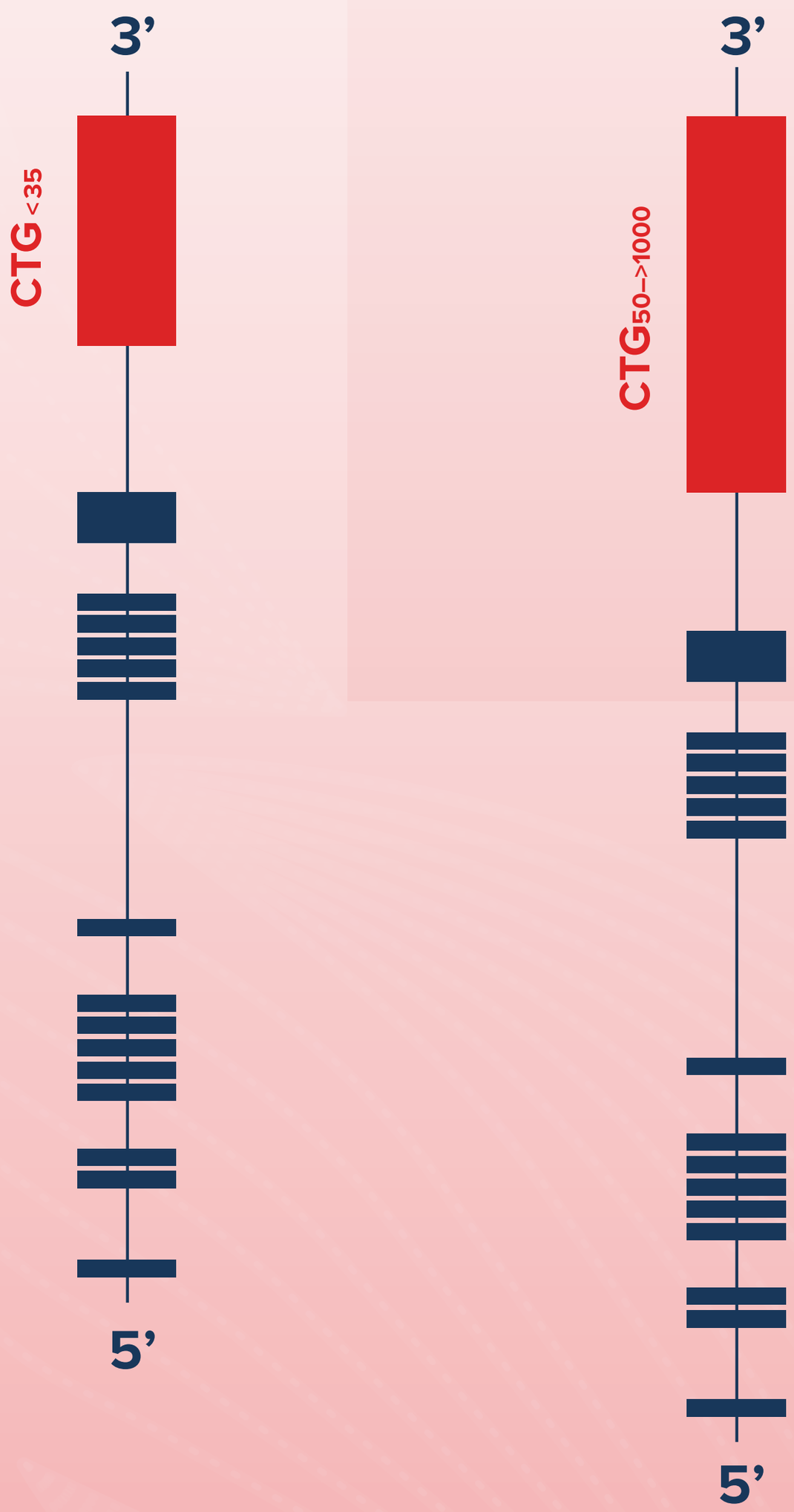
DM1 is a multisystemic, progressive disease caused by an expansion of a CTG trinucleotide repeat in the 3’ UTR of the *DMPK* gene.[1–5]

DMPK in unaffected individuals[1–5]

In unaffected individuals, the *DMPK* gene contains **5–34** CTG repeats in the 3’ UTR.[a]

DMPK in individuals with DM1[1–5]

In individuals with DM1, the *DMPK* gene contains **50 to >1000** CTG repeats.

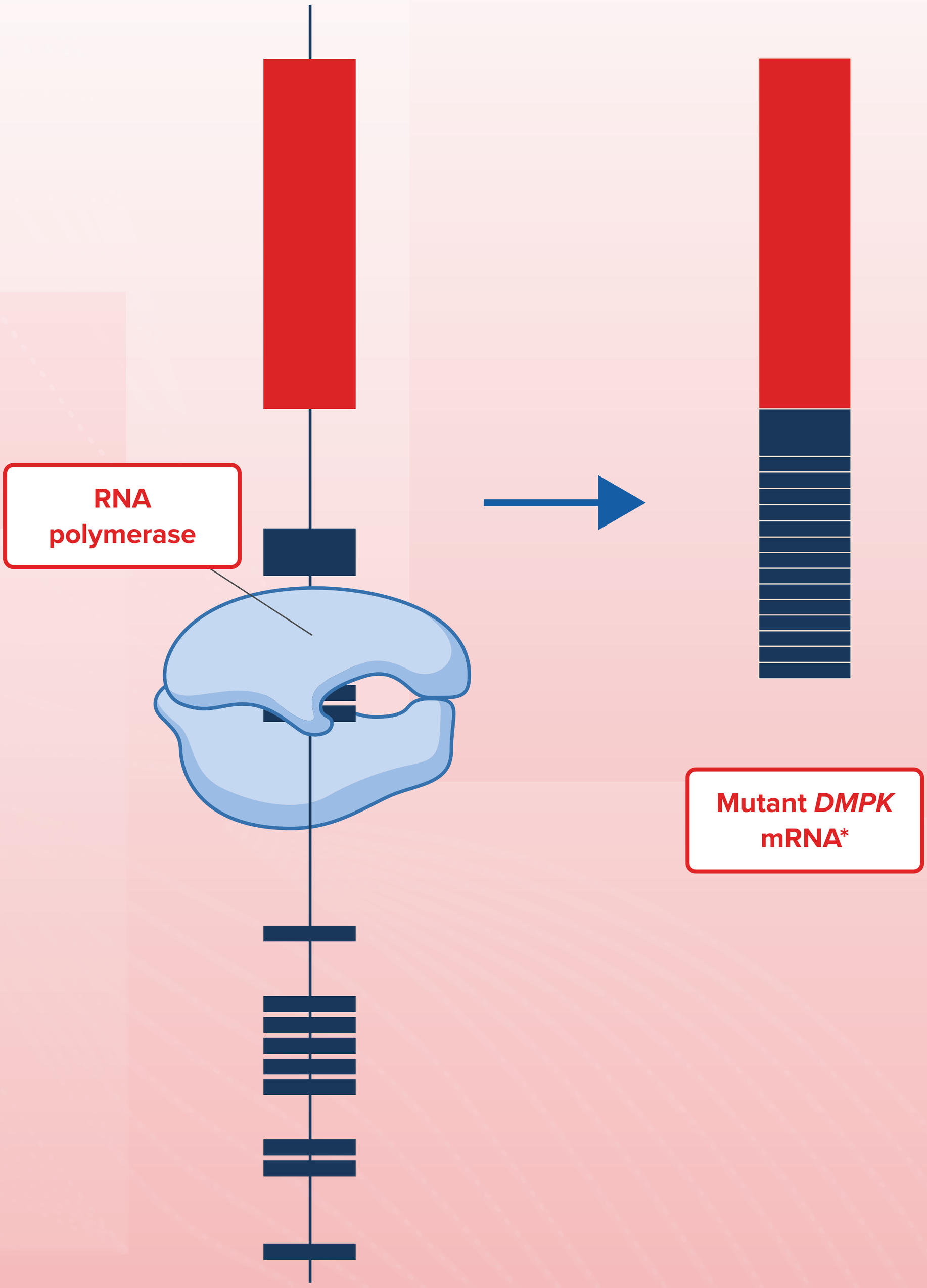


[a] **Individuals with premutation *DMPK* (35–49 repeats) are asymptomatic, but can transmit a greater number of repeats to their offspring who may reach the mutation range (>1000 repeats).[2]**

References: 1. Thornton CA. *Neurol Clin* 2014;32:705–719; 2. Gutiérrez Gutiérrez G, et al. *Neurologia (Engl Ed)* 2020;35:185–206; 3. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390; 4. Hamshere MG, et al. *Proc Natl Acad Sci USA* 1997;94:7394–7399; 5. NCBI. DMPK. Available at: https://www.ncbi.nlm.nih.gov/gene/1760 (accessed August 2024).

What is a
spliceopathy?

Transcription of the *DMPK* gene[1–3]



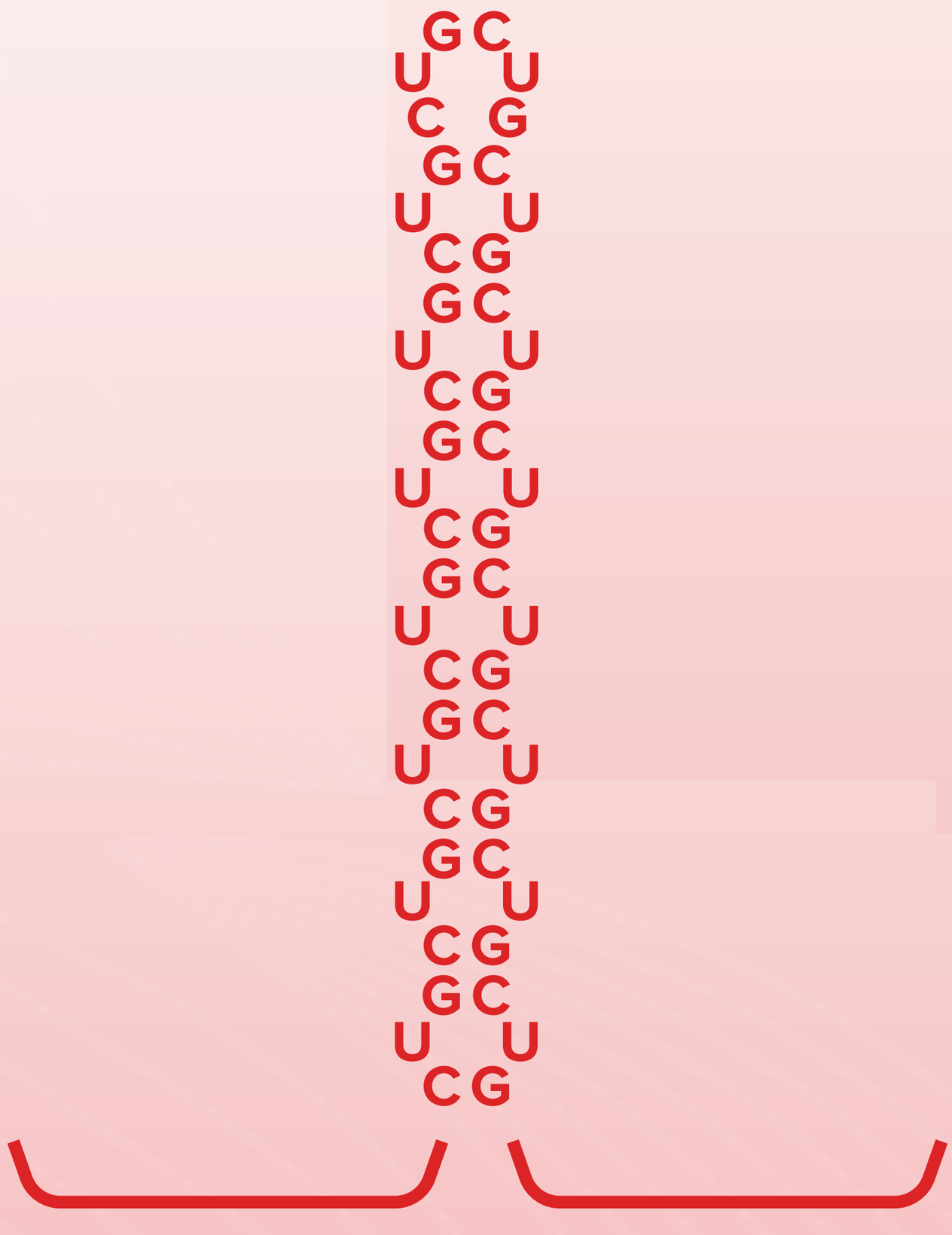
*Step depicting the processing of pre-mRNA to mRNA not shown here.

References: 1. Hamshere MG, et al. *Proc Natl Acad Sci USA* 1997;94:7394–7399; 2. NCBI. DMPK. Available at: https://www.ncbi.nlm.nih.gov/gene/1760 (accessed August 2024); 3. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390.

What is a **spliceopathy?**

The stable hairpin loop

Expanded CUG repeat in mRNA transcribed from the mutated *DMPK* gene forms stable hairpin loops.[1,2]



Mutant *DMPK* mRNA 3’-UTR

CUG, cytosine, uracil, guanosine.

References:
1. Napierala M, Krzyzosiak WJ. *J Biol Chem* 1997;272:1079–1085;
2. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390.

What is a
spliceopathy?

The stable hairpin loop

The stable hairpin loops sequester members of the MBNL family of proteins, critical regulators of alternative splicing, leading to the formation of toxic nuclear foci.[1,2]

MBNL, muscleblind like splicing regulator.

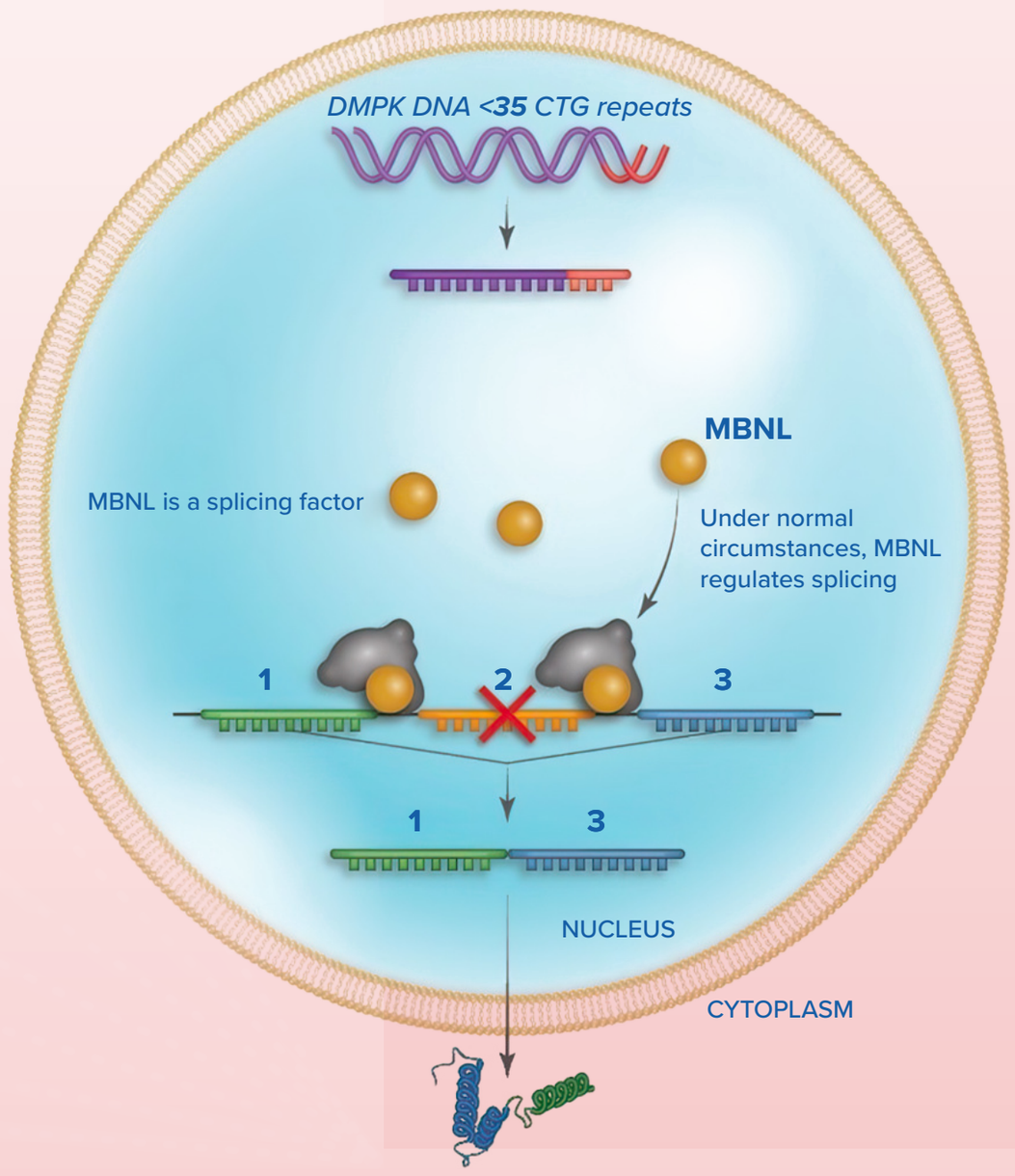
References:
1. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
2. Misra C, et al. *Adv Neurobiol* 2018;20:213–238.

What is a **spliceopathy?**

How splicing is affected in DM1

Sequestration of MBNL proteins into nuclear foci reduces the pool of free, unbound MBNL, leading to a loss of function and widespread dysregulation of hundreds of transcripts in DM1. This aberrant splicing pattern is known as spliceopathy.[1–3]

Unaffected individuals



Normal splicing leads to
appropriate protein synthesis

Splicing: Non-coding introns are removed from pre-mRNA, linking the coding exons together to form mature mRNA transcripts[4]

Alternative splicing (ie, splicing in different ways) can produce different mature mRNAs from the same pre-mRNA[4]

Image used with permission of Sage Publications, from Berglund JA, et al. *J Neuromuscul Dis.* 2025:22143602251365101. Epub ahead of print; permission conveyed through Copyright Clearance Center.

References:
1. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
2. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
3. Wang ET, et al. *Cell* 2012;150:710–724;
4. Choi S, et al. *Exp Mol Med* 2023;55:755–766.

What is a **spliceopathy?**

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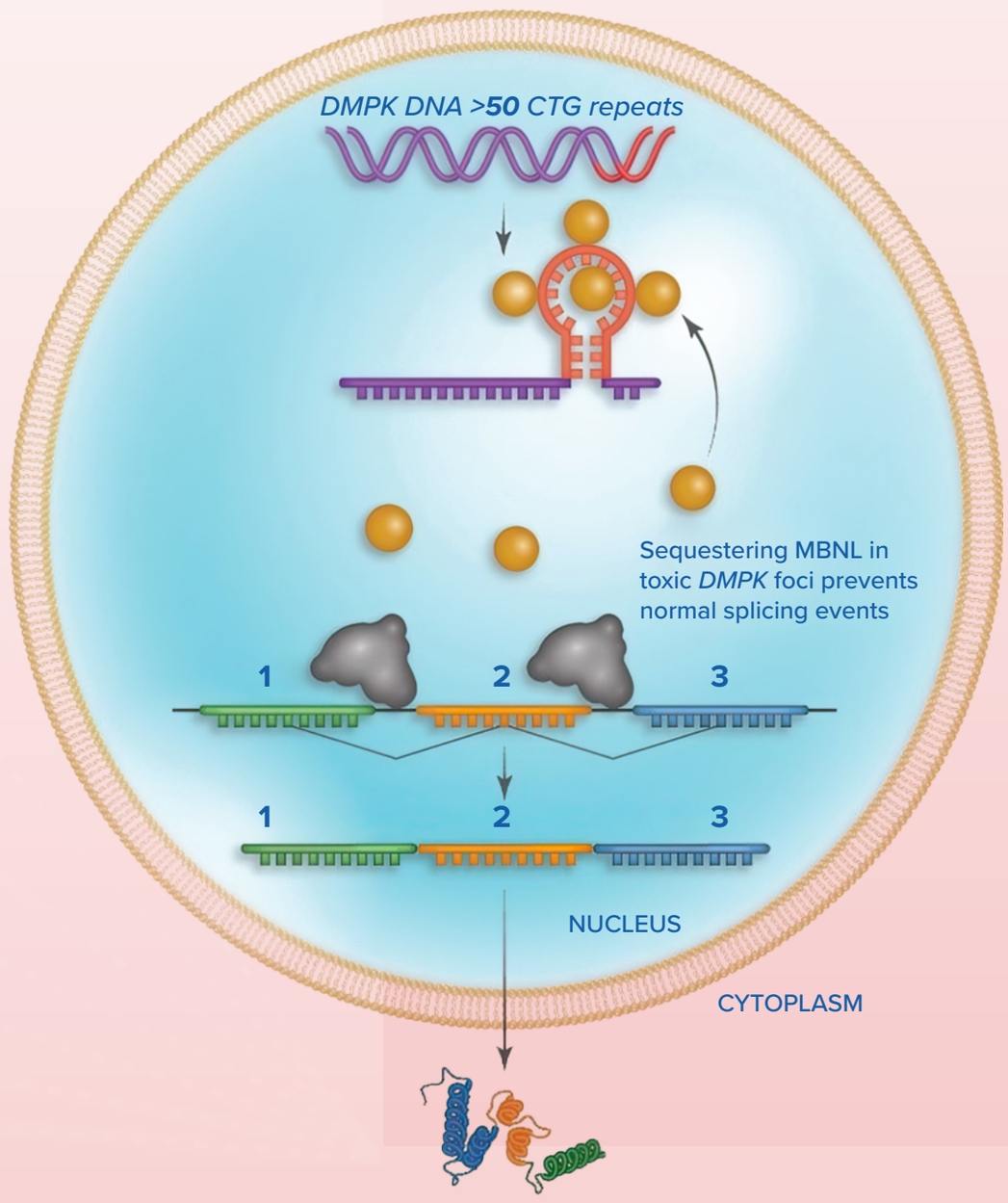
Individuals with DM1



Disrupted splicing **impairs** normal **protein synthesis**

This representation of mis-splicing has been simplified.

Image used with permission of Sage Publications, from Berglund JA, et al. *J Neuromuscul Dis.* 2025:22143602251365101. Epub ahead of print; permission conveyed through Copyright Clearance Center.

References:
1. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
2. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
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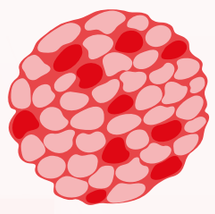
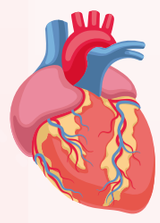
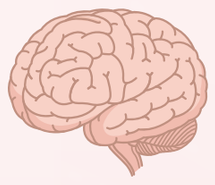
4. Choi S, et al. *Exp Mol Med* 2023;55:755–766.

What is a **spliceopathy?**

Mis-splicing of genes in DM1

In DM1, developmentally regulated events switch from adult to embryonic splicing patterns. These embryonic isoforms can't meet adult tissue needs, leading to defects that contribute to disease pathogenesis.[1] As genes altered by mis-splicing in DM1 are found in multiple tissues,[2] individuals experience a spectrum of clinical manifestations.

Myotonia and muscle weakness[2] 	*CLCN1* *BIN1* *TNNT3* *MTMR1* *NFIX* *DTNA* *CACNA1S* *DMD* *ATP5MC2* *NEB* *PKM2* *RyR1* *CAPN3* *NCOR2* *SOS1* *MBNL1* *ATP2A1*
Cardiac conduction complications[2] 	*ATP2A2* *LDB3* *SCN5A* *TNNT2* *TTN* *MYOM1* *ALPK3* *RBFOX2* *ZASP/LDB*
Cognitive impairment[2,3] 	*MAPT* *NMDAR1* *MBNL1* *MBNL2* *APP* *GRIP1*
Metabolic complications[2] 	*INSR* *PKM2*

This is not a complete list of genes that are mis-spliced in DM1.

See the Module 3 digital handout to explore the multisystem clinical manifestations of DM1

Click on the buttons below to find out how mis-splicing affects two key genes in DM1

CLCN1 ***BIN1***

References:
1. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
2. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
3. Otero BA, et al. *Cell Rep* 2021;34:108634.

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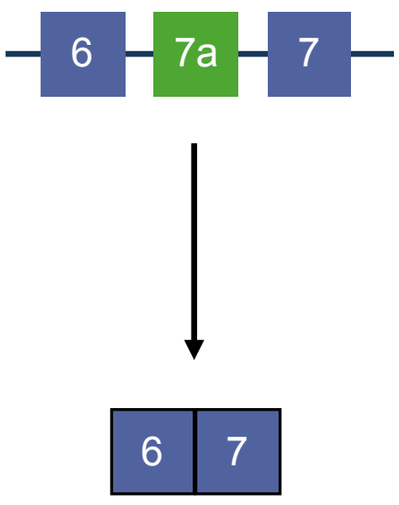
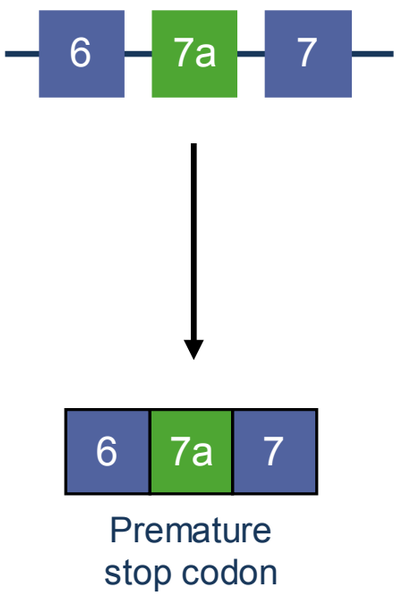
CLCN1

Mis-splicing of *CLCN1* results in the degradation of the transcript due to the presence of a premature stop codon in the spliced-in exon 7a. Decrease in functional CLCN1 protein results in myotonia in DM1.[1–3]

Unaffected individuals



Individuals with DM1



References:
1. Charlet-B N, et al. *Mol Cell* 2002;10:45–53; 2. Mankodi A, et al. *Mol Cell* 2002;10:35–44;
3. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390.

CLCN1 **BIN1**

References:
1. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
2. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
3. Otero BA, et al. *Cell Rep* 2021;34:108634.

What is a
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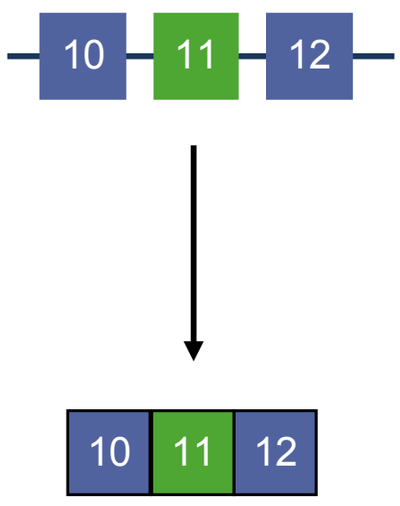
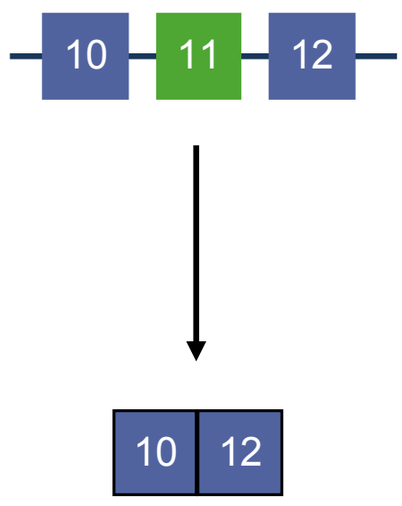
BIN1

Mis-splicing of *BIN1* results in the exclusion of exon 11 and expression of an isoform of BIN1 protein that cannot bind phosphoinositides and tubulate membranes. This causes disruption of T-tubule biogenesis and muscle weakness in DM1[1,2]

Unaffected individuals



Individuals with DM1



Reference:
1. Fugier C, et al. *Nat Med* 2011;17:720–725; 2. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390.

CLCN1 **BIN1**

References:
1. Chau A, Kalsotra A. *Dev Dyn* 2015;244:377–390;
2. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
3. Otero BA, et al. *Cell Rep* 2021;34:108634.

Date of preparation: July 2026. MED-00699.