

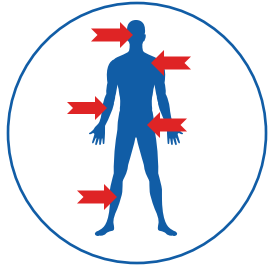


Module 1

What is myotonic dystrophy type 1 (DM1)?

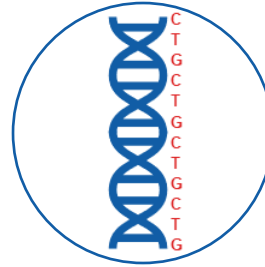


Module summary



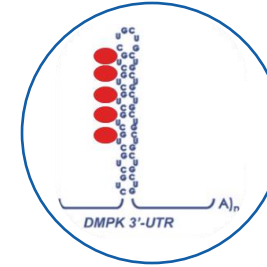
DM1 is a rare, progressive, genetic, neuromuscular disease with high morbidity and early mortality^{1–5}

DM1 is a multi-system disease that presents with muscular and non-muscular symptoms⁶



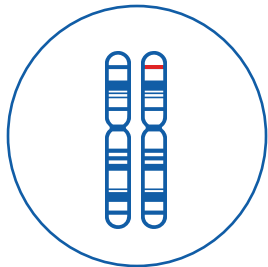
DM1 is caused by expansions in an unstable CTG repeat region in the *DMPK* gene⁷

*In individuals with DM1, the *DMPK* gene contains ≥ 50 CTG repeats, compared with 5–34 in unaffected individuals⁸*



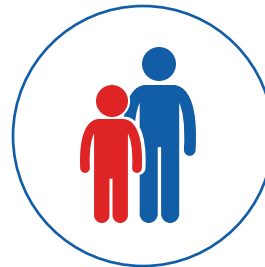
Mutant *DMPK* mRNA forms a hairpin structure that sequesters MBNL proteins leading to spliceopathy⁷

Spliceopathy is the widespread disruption of RNA splicing^{7,9}



DM1 is inherited in an autosomal dominant manner¹⁰

Intergenerational transmission can lead to increased expansion length, causing earlier onset and increasing disease severity^{6,11}



CTG repeat length varies between different tissues and increases with age^{6,12,13}

This contributes to the progressive and heterogeneous nature of DM1^{6,12,13}



DM1 is the most common adult-onset muscular dystrophy^{1,14}

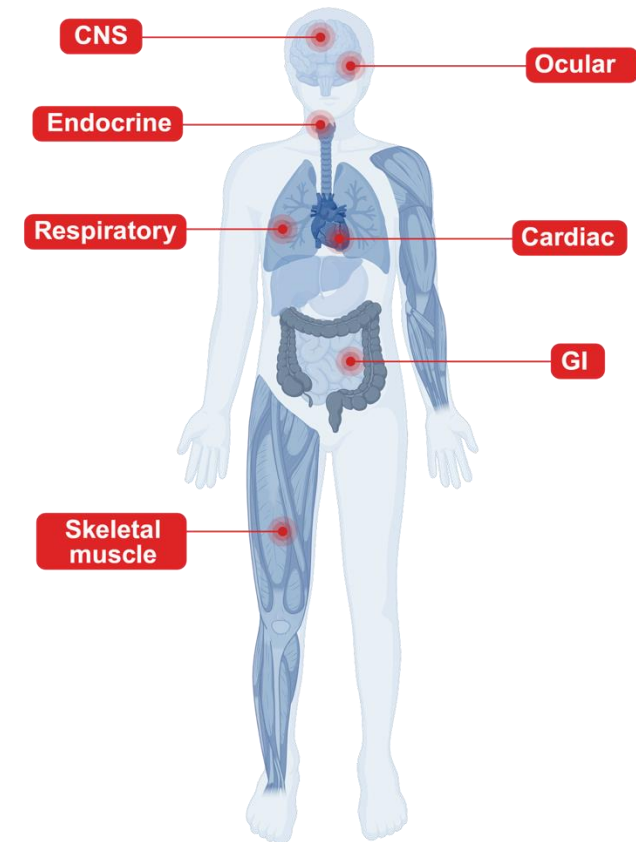
DM1 occurs in approximately 9.27 individuals per 100,000 worldwide¹

CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophin myotonia protein kinase; MBNL, muscleblind-like; mRNA, messenger ribonucleic acid.

1. Liao Q, et al. *Neuroepidemiology*. 2022;56:163–73; 2. Mathieu J, et al. *Neurology*. 1999;52:1658–1662; 3. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 4. Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464; 5. Wenninger S, et al. *Front Neurol*. 2018;9:303; 6. Thornton CA. *Neurol Clin*. 2014;32:705–719; 7. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 8. Chau A, Kalsotra A. *Dev Dyn*. 2015;244:377–390; 9. Pascual-Gilabert M, et al. *Drug Discov Today*. 2021;26:1765–1772; 10. Myotonic Dystrophy Support Group. Accessed May 6, 2025. <https://www.myotonicdystrophysupportgroup.org/how-is-myotonic-dystrophy-inherited/>; 11. Harper PS, et al. *Am J Hum Genet*. 1992;51:10–16; 12. Thornton CA, et al. *Ann Neurol*. 1994;35:104–107; 13. Ashizawa T, et al. *Neurology*. 1993;43:2674–2678; 14. Savic-Pavicevic D, et al. *BioMed Res Int*. 2013;2013:391821.

What is DM1?

- DM1 is a rare, progressive, genetic, neuromuscular disease with high morbidity and early mortality^{1–5}
- DM1 is caused by expansions in an unstable CTG repeat region in the *DMPK* gene, leading to a widespread disruption of RNA splicing, known as spliceopathy, which drives the multi-system manifestations of the disease⁶
 - Muscular symptoms involve skeletal, cardiac, and smooth muscles, and non-muscular symptoms mainly affect the CNS, but can also include cataracts, male infertility, endocrine abnormalities, and a higher incidence of cancer^{4,5,7,8}



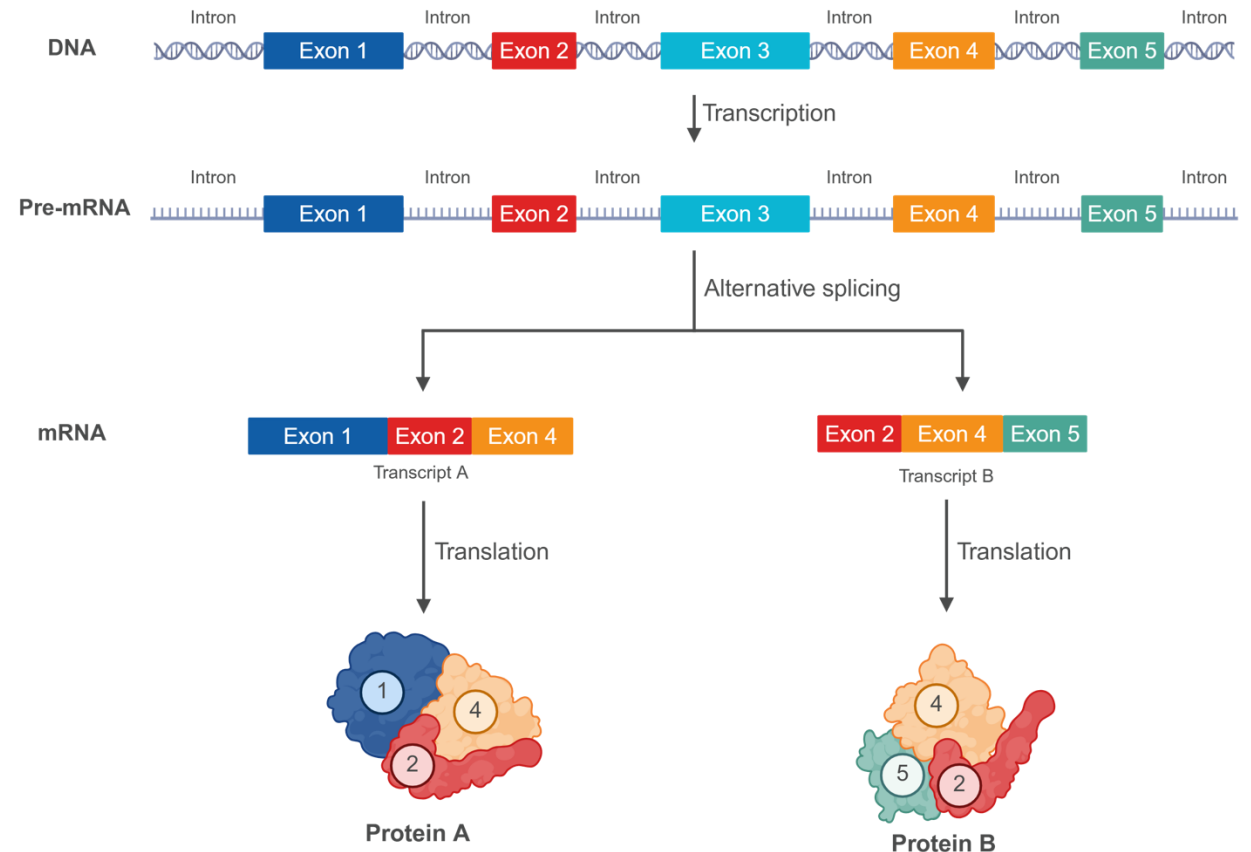
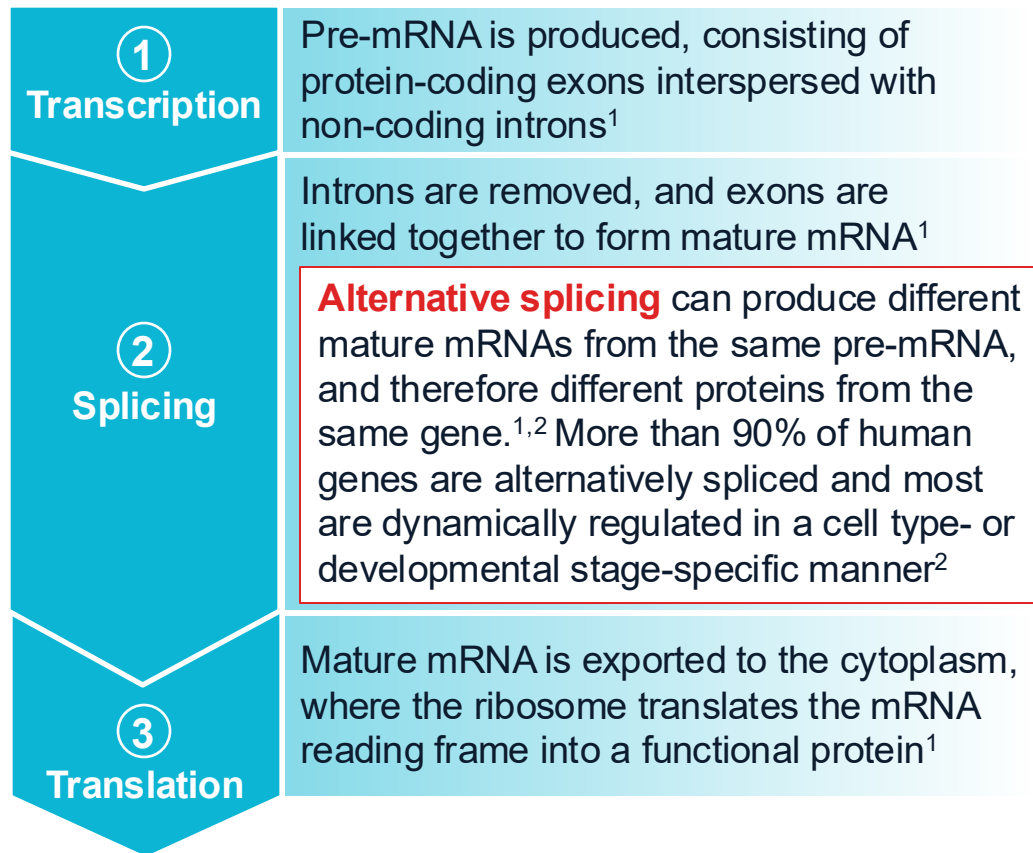
DM1 is a rare neuromuscular disorder with multi-systemic involvement, caused by widespread spliceopathy^{1,3,6,7}

CNS, central nervous system; CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophin myotonia protein kinase; GI, gastrointestinal.

Figure created in BioRender.

1. Liao Q, et al. *Neuroepidemiology*. 2022;56:163–173; 2. Mathieu J, et al. *Neurology*. 1999;52:1658–1662; 3. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 4. Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464; 5. Wenninger S, et al. *Front Neurol*. 2018;9:303; 6. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 7. Thornton CA. *Neurol Clin*. 2014;32:705–719; 8. Kim WB, et al. *Korean J Urol*. 2012;53:134–136.

What happens during RNA splicing?



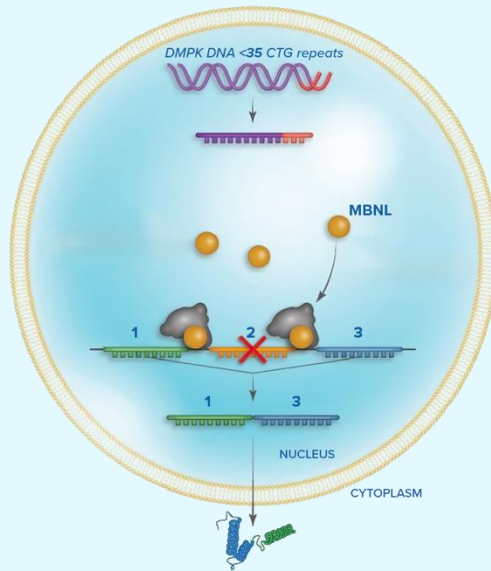
Splicing removes introns to produce mature mRNA ready for translation; many genes are alternatively spliced to produce different mature mRNAs^{1,2}

What is the mechanism of spliceopathy in DM1?

Unaffected individuals

***DMPK* gene contains 5–34 CTG repeats; 35–49 repeats is considered ‘premutation’¹**

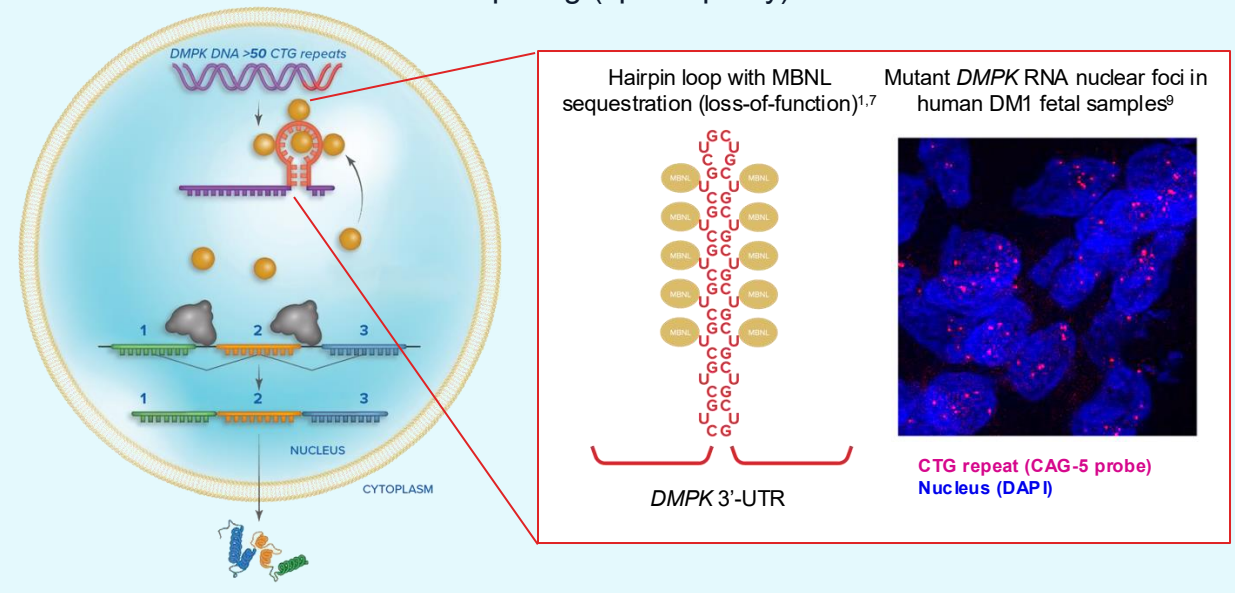
Under normal circumstances, the MBNL family of proteins are critical regulators of alternative splicing²



DM1 spliceopathy

***DMPK* gene contains ≥ 50 CTG repeats, and can have >1000 ^{1,3,4}**

Mutant *DMPK* mRNA forms a stable hairpin structure that sequesters members of the MBNL family of proteins into toxic nuclear foci, leading to widespread dysregulation of RNA splicing (spliceopathy)^{1,2,5–8}

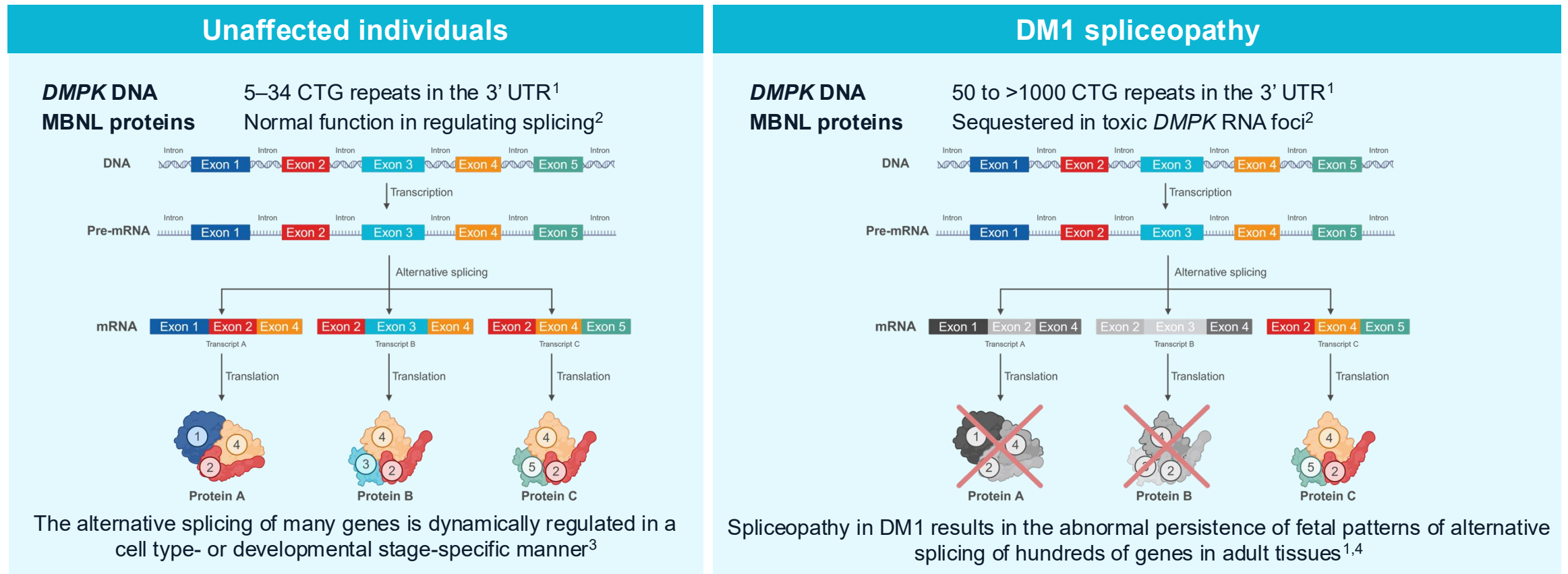


mRNA transcribed from the mutated *DMPK* gene forms stable hairpin loops that sequester MBNL proteins and form nuclear foci^{1,5,6,8}

CAG, cytosine-adenine-guanine; CTG, cytosine-thymine-guanine; DAPI, 4',6-diamidino-2-phenylindole; DMPK, dystrophin myotonic protein kinase; DM1, myotonic dystrophy type 1; MBNL, muscleblind-like; mRNA, messenger ribonucleic acid; UTR, untranslated region. Image of nuclear foci from Michel L, et al. *PLoS One* 2015;10:e0137620, licensed under a CC-BY 4.0 Creative Commons license; doi:10.1371/journal.pone.0137620. Spliceopathy images used with permission of Sage Publications, from Berglund JA, et al. *J Neuromuscul Dis.* 2025;22:143602251365101. Epub ahead of print; permission conveyed through Copyright Clearance Center, Inc. Images show a simplified representation of spliceopathy in individuals with DM1 and unaffected individuals; for illustrative purposes only.

1. Chau A, Kalsotra A. *Dev Dyn.* 2015;244:377–390; 2. López-Martínez A, et al. *Genes (Basel).* 2020;11:1109; 3. Gutiérrez-Gutiérrez G, et al. *Neurologia (Engl Ed).* 2020;35:185–206; 4. Thornton CA. *Neurol Clin.* 2014;32:705–719; 5. Davies BM, et al. *Proc Natl Acad Sci USA.* 1997;94:7388–7393; 6. Napierala M, Krzyzosiak WJ. *J Biol Chem.* 1997;272:1079–1085; 7. Misra C, et al. *Adv Neurobiol.* 2018;20:213–238; 8. Pascual-Gilbert M, et al. *Drug Discov Today.* 2021;26:1765–1772; 9. Michel L, et al. *PLoS One* 2015;10:e0137620.

What is the mechanism of spliceopathy in DM1?

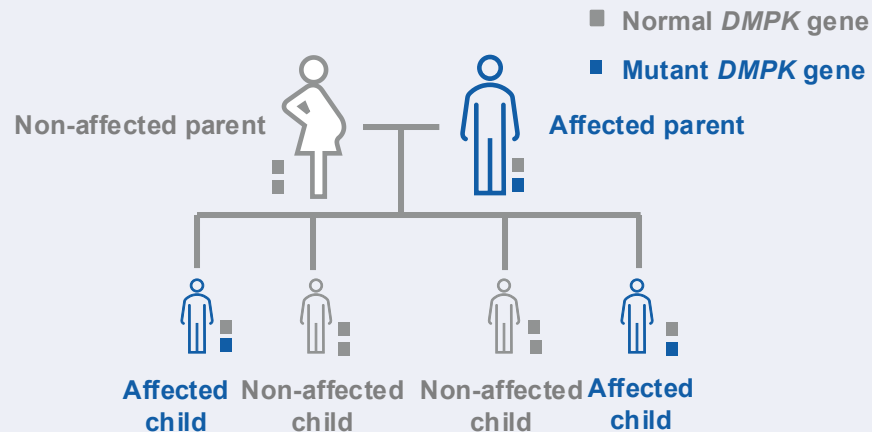


Sequestered MBNL proteins cannot perform their normal function in splicing, so the expression of many genes throughout the body is dysregulated^{1,2,4}

How is DM1 inherited?

DM1 is inherited in an autosomal dominant manner¹

Genetic counselling is recommended for those exhibiting clinical signs of DM1 and for at-risk family members to enable them to make an informed decision on proceeding with genetic testing²



Offspring have a 50% chance of inheriting a mutant *DMPK* gene¹

The expanded *DMPK* CTG region is highly unstable and increases in length during intergenerational transmission³

This phenomenon is known as anticipation – increasing disease severity and earlier age of onset in successive generations.⁴ The direction and size of intergenerational change in CTG expansion depend on both parental repeats and the sex of the transmitting parent^{5–8}



Longer CTG repeats are generally inherited from mothers, contributing to congenital DM1^{6,9,10}



Juvenile, adult, and late-onset forms of DM1 are generally transmitted by fathers^{6,9}



Individuals with 35–49 repeats are asymptomatic, but may transmit longer CTG expansions to their offspring¹⁰

On average, the CTG expansion increases by >200 repeats during intergenerational transmission^{3,11}

DM1 is inherited in an autosomal dominant manner.¹ Intergenerational transmission can lead to increased expansion length, causing earlier onset and increasing disease severity^{3,4}

CTG, cytosine–thymine–guanine; DM1, myotonic dystrophy type 1; *DMPK*, dystrophin myotonia protein kinase gene.

1. Myotonic Dystrophy Support Group. Accessed May 6, 2025. <https://www.myotonicdystrophysupportgroup.org/how-is-myotonic-dystrophy-inherited/>; 2. Savic Pavicevic D, et al. *BioMed Res Int*. 2013;2013:391821;

3. Thomson CA. *Neurol Clin*. 2014;32:705–719; 4. Harper PS, et al. *Am J Hum Genet*. 1992;51:10–16; 5. Rakocevic-Stojanovic V, et al. *Eu J Neurol*. 2004;12:235–237; 6. Martorell L, et al. *Prenat Diagn*. 2007;27:68–72;

7. Brunner HG, et al. *Am J Hum Genet*. 1993;53:1016–1023; 8. Lavedan C, et al. *Am J Hum Genet*. 1993;52:875–883; 9. De Temmerman N, et al. *Am J Hum Genet*. 2004;75:325–329; 10. Gutierrez Gutierrez G, et al. *Med Clin (Barc)*.

2020;153:82.e1–82.e17; 11. Redman JB, et al. *JAMA*. 1993;269:1960–1965.

What is the impact of somatic mosaicism in DM1?

- Instability of the expanded *DMPK* CTG region leads to variable repeat length in different tissues, a concept known as somatic mosaicism^{1–3}
- Somatic mosaicism in DM1 is tissue specific, age dependent, and biased toward further expansion during aging, contributing to the progressive and heterogeneous nature of the disease^{1–3}



In DM1, greater expansion of CTG repeat lengths are seen in non-dividing cells (e.g. skeletal muscle, heart, brain) than in proliferating cells of the hematopoietic system^{1–4}



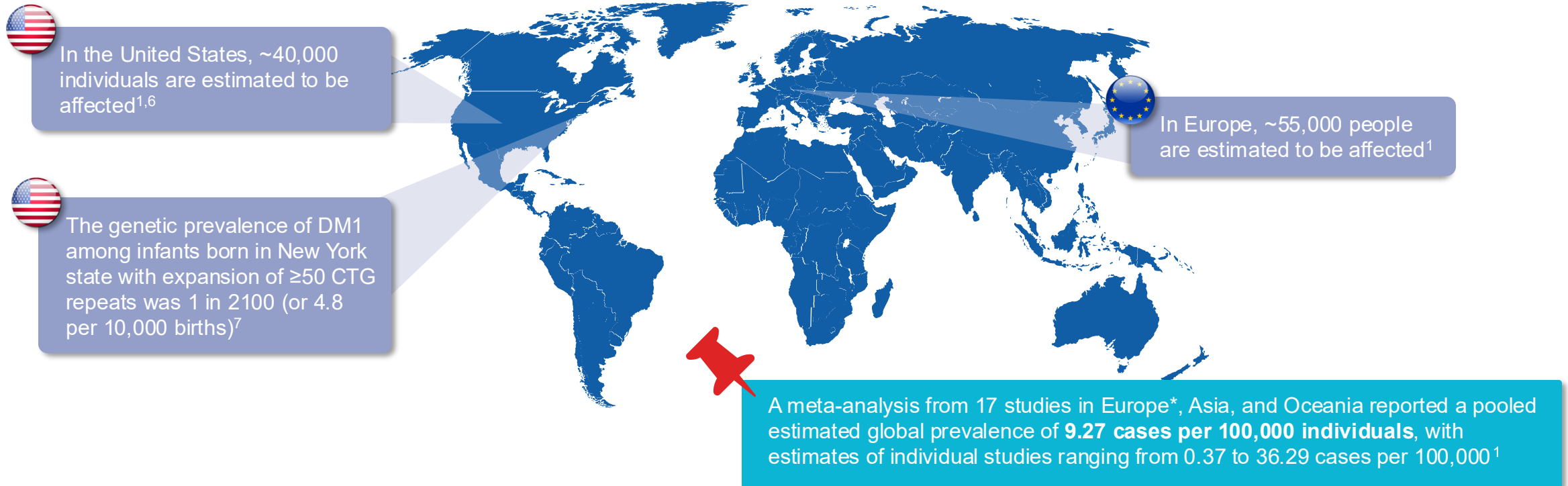
CTG repeats in skeletal muscle of individuals with DM1 expand to >2000 repeats by age 20¹

In individuals aged >40 years, the average repeat length in skeletal muscle is >4000 repeats, more than 3- to 25-fold larger than in blood¹

CTG repeat length varies between different tissues and increases with age, contributing to the progressive and heterogeneous nature of DM1^{1–3}

What is the prevalence of DM1?

- Prevalence estimates for DM1 can vary greatly between different countries and ethnic groups, and a true estimate is difficult to achieve due to a significant delay in diagnosis for many individuals¹⁻⁵



DM1 is the most common adult-onset muscular dystrophy, occurring in approximately 9.27 individuals per 100,000 worldwide^{1,8}

*Includes studies from Southwestern Norway, Northern Spain, Serbia, Western Sweden, Republic of Ireland, Rome (Italy), Finland, Northern England, Belgrade (Serbia), Northern Ireland, Italy, Western Sweden, and Istra (Croatia).

CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1.

1. Liao Q, et al. *Neuroepidemiology*. 2022;56:163–173; 2. Yotova V, et al. *Hum Genet*. 2005;117:177–187; 3. Ashizawa T, Epstein HF. *Lancet*. 1991;338:642–643; 4. Hsiao KM, et al. *Neuroepidemiology*. 2003;22:283–289;

5. Hilbert JE, et al. *J Neurol*. 2013;260:2497–504; 6. Ashizawa T, et al. *Neurol Clin Pract*. 2018;8:507–520; 7. Johnson NE, et al. *Neurology*. 2021;96:e1045–e1053; 8. Savic-Pavicevic D, et al. *BioMed Res Int*. 2013;2013:391821.