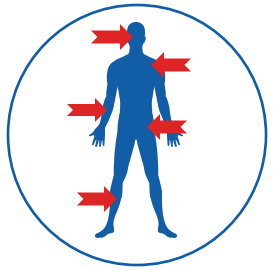
Module 1
What is myotonic dystrophy type 1 (DM1)?

Dyne | Medical Central

Module summary

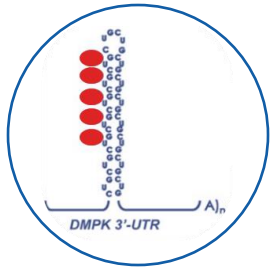


DM1 is a rare, progressive, genetic, neuromuscular disease with high morbidity and early mortality[1–5]

DM1 is a multi-system disease that presents with muscular and non-muscular symptoms[6]

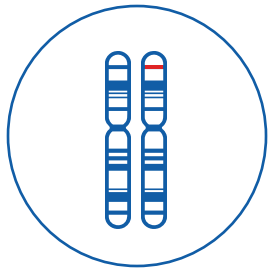
DM1 is caused by expansions in an unstable CTG repeat region in the *DMPK* gene[7]

In individuals with DM1, the DMPK gene contains ≥50 CTG repeats, compared with 5–34 in unaffected individuals[8]



Mutant *DMPK* mRNA forms a hairpin structure that sequesters MBNL proteins leading to spliceopathy[7]

Spliceopathy is the widespread disruption of RNA splicing[7,9]



DM1 is inherited in an autosomal dominant manner[10]

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]

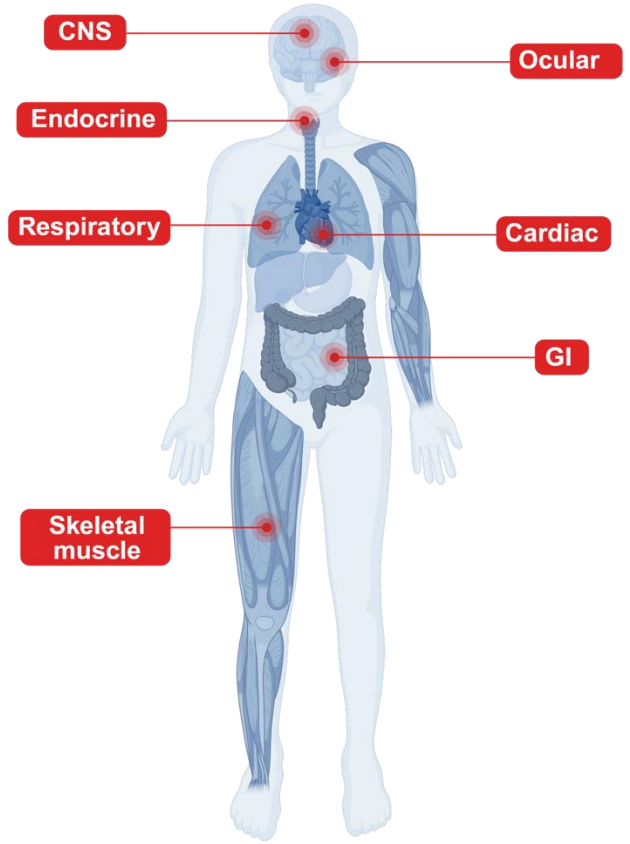
DM1 occurs in approximately 9.27 individuals per 100,000 worldwide[1]

CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica 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 disease[6]
  - 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, dystrophia myotonica 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?

1 Transcription

Pre-mRNA is produced, consisting of protein-coding exons interspersed with non-coding introns[1]

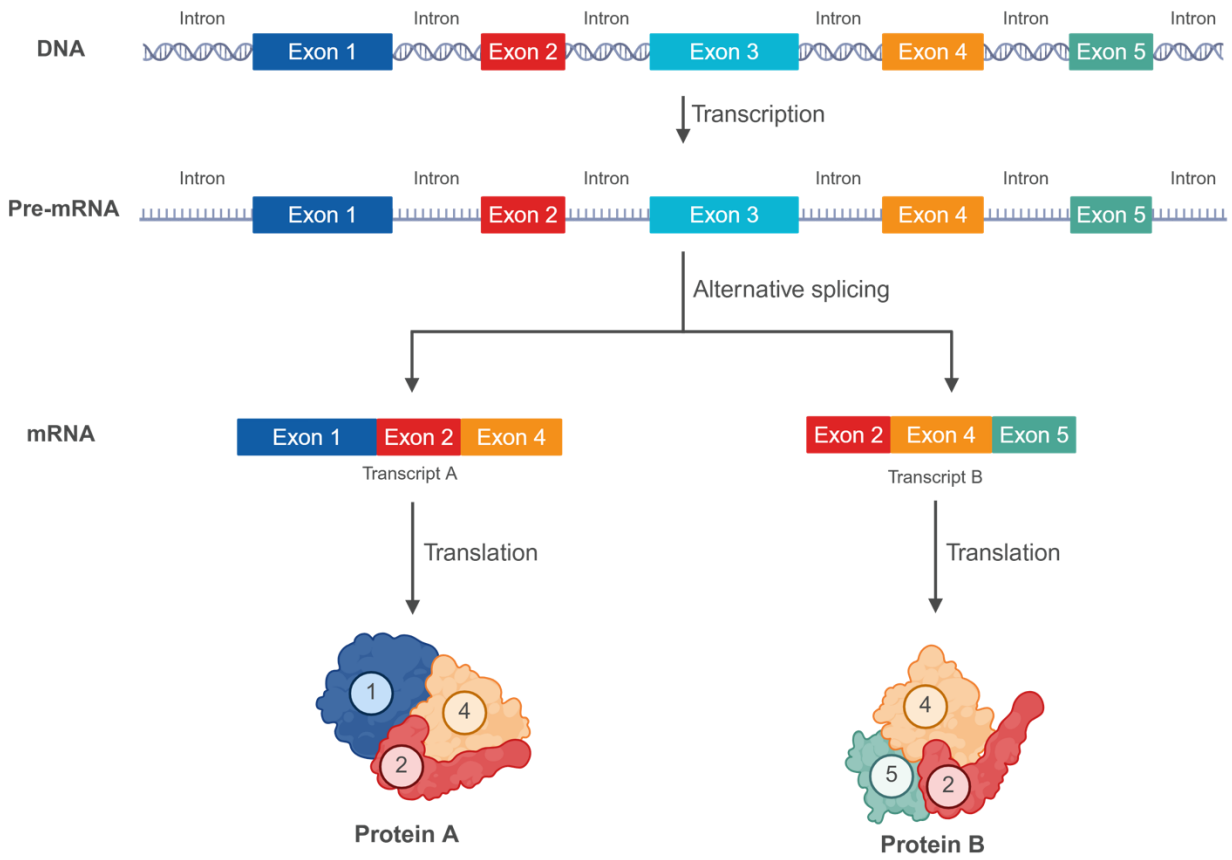
2 Splicing

Introns are removed, and exons are linked together to form mature mRNA[1]

Alternative splicing can produce different mature mRNAs from the same pre-mRNA, and therefore different proteins from the same gene.[1,2] More than 90% of human genes are alternatively spliced and most are dynamically regulated in a cell type- or developmental stage-specific manner[2]

3 Translation

Mature mRNA is exported to the cytoplasm, where the ribosome translates the mRNA reading frame into a functional protein[1]



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

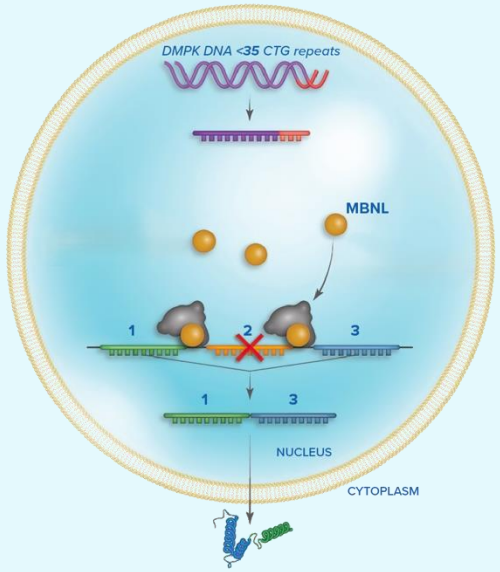
DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid.
Figure created in BioRender.[1,2]
Graphic shows a simplified representation of alternative splicing; for illustrative purposes only.
1. Alberts B, et al. *Mol Biol Cell.* 4th ed New York: Garland Science; 2002; 2. Choi S, et al. *Exp Mol Med.* 2023;55:755–766.

What is the mechanism of spliceopathy in DM1?

Unaffected individuals

***DMPK* gene contains 5–34 CTG repeats;**
35–49 repeats is considered 'premutation'[1]

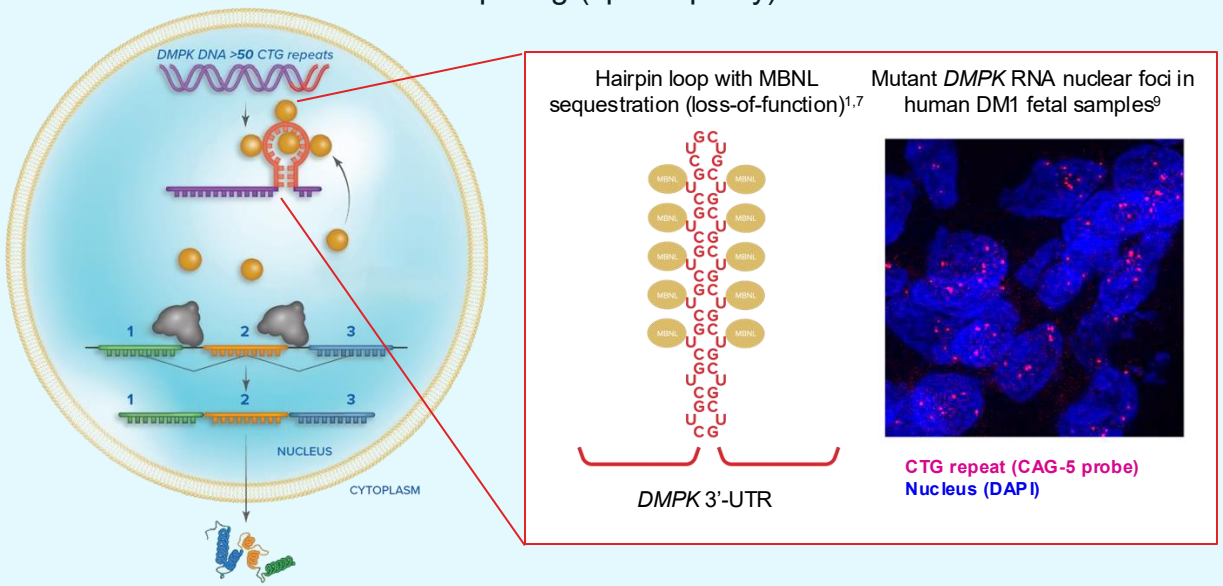
Under normal circumstances, the MBNL family of proteins are critical regulators of alternative splicing[2]



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, dystrophia myotonica 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.* 2025:22143602251365101. 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.

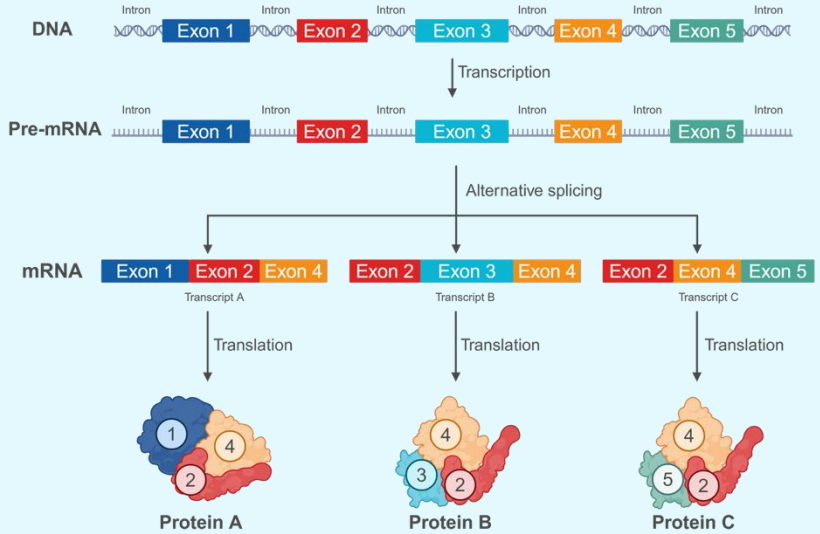
1. Chau A, Kalsotra A. *Dev Dyn.* 2015;244:377–390; 2. López-Martínez A, et al. *Genes (Basel).* 2020;11:1109; 3. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed).* 2020;35:185–206; 4. Thornton CA. *Neurol Clin.* 2014;32:705–719; 5. Davies BM, et al. *Proc Natl Acad Sci USA. 1997*;94:7388–7393; 6.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

Unaffected individuals

***DMPK* DNA** 5–34 CTG repeats in the 3' UTR[1]

MBNL proteins Normal function in regulating splicing[2]

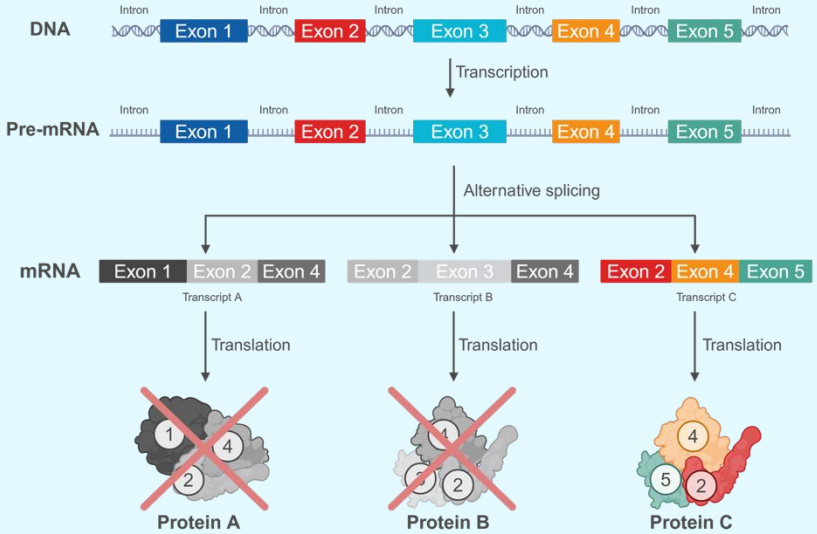


The alternative splicing of many genes is dynamically regulated in a cell type- or developmental stage-specific manner[3]

DM1 spliceopathy

***DMPK* DNA** 50 to >1000 CTG repeats in the 3' UTR[1]

MBNL proteins Sequestered in toxic *DMPK* RNA foci[2]



Spliceopathy in DM1 results in the abnormal persistence of fetal patterns of alternative splicing of hundreds of genes in adult tissues[1,4]

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

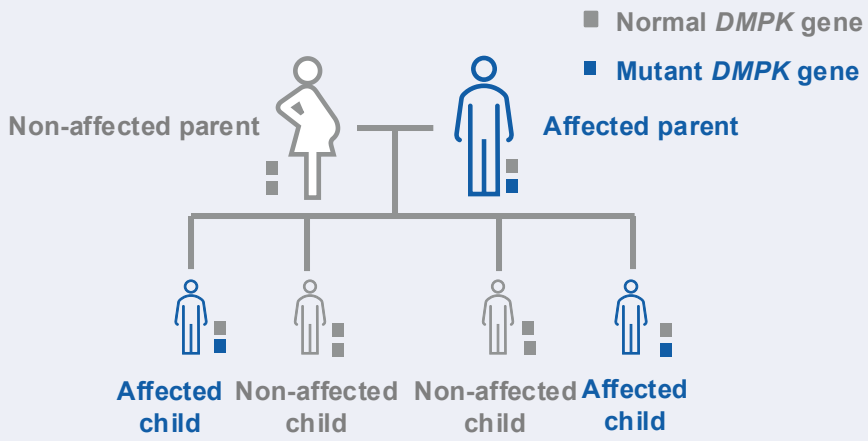
CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; DNA, deoxyribonucleic acid; MBNL, muscleblind-like; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid; UTR, untranslated region.
Figure created in BioRender.[3,5]
Graphic shows a simplified representation of alternative splicing; 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. Choi S, et al. *Exp Mol Med*. 2023;55:755–766; 4. Pascual-Gilabert M, et al. *Drug Discov Today*. 2021;26:1765–1772; 5. Alberts B, et al. *Mol Biol Cell*. 4th ed New York: Garland Science; 2002.

How is DM1 inherited?

DM1 is inherited in an autosomal dominant manner[1]

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 testing[2]



Offspring have a 50% chance of inheriting a mutant *DMPK* gene[1]

The expanded *DMPK* CTG region is highly unstable and increases in length during intergenerational transmission[3]

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 offspring[10]

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*, dystrophia myotonica 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. Thornton 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 20[1]

In individuals aged >40 years, the average repeat length in skeletal muscle is >4000 repeats, more than 3- to 25-fold larger than in blood[1]

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

CTG, cytosine–thymine–guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase gene.

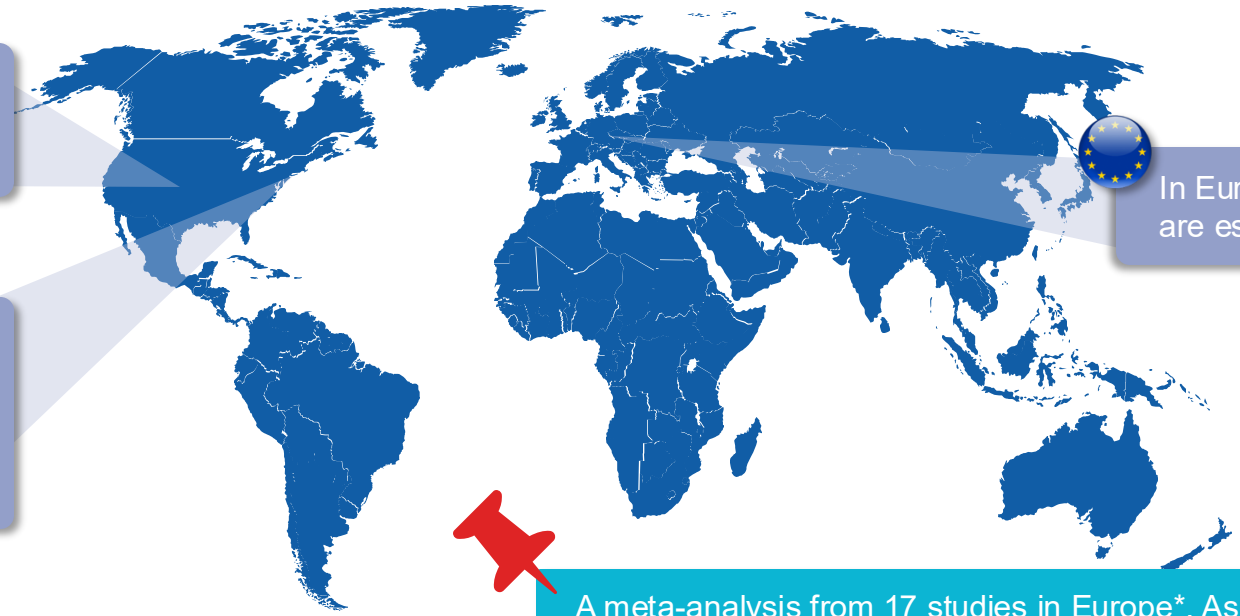
1. Thornton CA. *Neurol Clin.* 2014;32:705–719; 2. Thornton CA, et al. *Ann Neurol*. 1994;35:104–107; 3. Ashizawa T, et al. *Neurology.* 1993;43:2674–2678; 4. Nakamori M, et al. *Ann Neurol*. 2013;74:862–872.

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 individuals[1–5]

In the United States, ~40,000 individuals are estimated to be affected[1,6]

The genetic prevalence of DM1 among infants born in New York state with expansion of ≥50 CTG repeats was 1 in 2100 (or 4.8 per 10,000 births)[7]



In Europe, ~55,000 people are estimated to be affected[1]

A meta-analysis from 17 studies in Europe*, Asia, and Oceania reported a pooled estimated global prevalence of **9.27 cases per 100,000 individuals**, with estimates of individual studies ranging from 0.37 to 36.29 cases per 100,000[1]

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.