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DECODING MYOTONIC DYSTROPHY TYPE 1: INTEGRATIVE INSIGHTS INTO DISEASE ORIGINS, MOLECULAR PATHOGENESIS, DIAGNOSIS AND EMERGING THERAPEUTIC STRATEGIES

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Abstract

Background: *Myotonic Dystrophy Type 1 (DM1) (OMIM 160900) is a dominant autosomal, multisystem illness noticeable by many phenotypic expressions and a progressively worsening disease course. It is the most predominant muscular dystrophy between adults and is categorized by its miscellaneous symptoms and significant effect on value of life.*

Objective: *This review pursues to deliver a widespread summary of DM1, about its history, prevalence, causes, indications, pathogenesis, genetic underpinning, and present diagnostic and treatment methods.*

Methods: *A thorough literature review was performed, focused on historical progress, molecular mechanisms, medical symptoms, and therapeutic approaches linked with DM1. Data were gathered from several scholarly sources and original study papers.*

Results: *DM1 was firstly recognized in 1909 and has been linked with CTG repeat extensions in the DMPK gene since then. Epidemiologic research shows differing incidences of DM1 in various regions, with greater incidences in Europe than in Asia. The disorder is characterized by a variation of symptoms such as breathing difficulties, muscle weakness, hormonal imbalances, heart irregularities, and neurological difficulties. The central pathogenesis includes harmful RNA gain-of-function effects caused by prolonged CTG repeats. Although a cure is not available, supportive therapies and new gene treatments provide promise for alleviating symptoms and possibly fixing the root genetic issues.*

Conclusions: *DM1 continues to be a difficult condition due to its intricate pathophysiology. Progress in molecular genetics and treatment approaches, such as gene editing techniques, is setting the stage for enhanced management and possible future therapies.*

1. INTRODUCTION

1.1 Myotonic Dystrophy Type 1

Myotonic Dystrophy Type 1 (DM1), also called Batten disease, Steinert, and Gibb disease (OMIM 160900), is an autosomal, multisystemic, rare genetic disorder that has variable phenotypic characteristics and has a slowly progressive disease course. This condition is the most common muscular condition in adults, which carries significances of disabilities and a shortening of life span (Peter Harper, 2009).

DM1 is characterized by an extremely variable clinical presentation, which poses substantial challenges in patient management and the progress of clinical trials. The ailment can arise at any age, from infancy to late parenthood, with a varied range of onset forms. Symptoms can differ significantly in relations of severity and the specific organ systems exaggerated, often making the progression of the illness unpredictable. This inconsistency obscures the course of diagnosis, ongoing care, and therapies, while also offering difficulties in scheming clinical trials to evaluate possible therapeutic interferences (De Antonio *et al.*, 2016).

1.2 Current Challenges:

1. **Diagnosis and Misdiagnosis:** The clinical appearance of DM1 can diverge commonly and may copycat other neuromuscular syndromes, leading to postponements in diagnosis or misdiagnosis. Several health care workers lack consciousness of the sickness's wide-ranging symptoms, confounding appropriate diagnosis.
2. **Symptom Management:** DM1 displays with various indications, including muscle faintness, myotonia, cardiac arrhythmias, dysphagia, and endocrine dysfunction. Presently, there is no consistent treatment regimen, leading to unpredictable managing approaches.
3. **Genetic Counseling and Family Planning:** As a genetic disorder, DM1 advances significant worries about genetic counseling for exaggerated families. The expectation phenomenon, where indications worsen in sequential generations, obscures family planning and demands clear communication of dangers.
4. **Quality of Life and Mental Impact:** The long-lasting nature of DM1 can result to reduced excellence of life and increased societal loneliness. Mental problems, including nervousness and despair, are predominant but often ineffectively addressed in clinical situations.
5. **Research and Therapeutic Development:** There is an insistent need for besieged research to comprehend DM1's pathophysiology improved and to develop effective therapies. Existing treatments mostly address indications rather than adjusting disease development.
6. **Healthcare System Triangulation:** DM1 patients with often fight to navigate healthcare organizations due to the multidisciplinary nature of their attention. Coordination among consultants is crucial but often falls short, resulting in uneven attention.

2. Methodology

2.1 Literature Search Strategy

A thorough literature search was performed to collect related information on several aspects of DM1, including its history, symptoms, epidemiology, diagnostic approaches, pathophysiology, and possible treatment approaches. The search included a widespread range of databases, such as Google Scholar, PubMed, and Scopus, concentrating on articles available between 1909 and the present. Keywords used in the search included "*DMPK* gene," "CTG repeats," "Myotonic Dystrophy Type 1," "DM1," "genetic mutation," and "gene therapy." Both review papers and original research articles were included in the study.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria for the articles were:

- Peer-reviewed journal articles.
- Articles focusing on DM1, including its genetic basis, epidemiology, clinical manifestations, diagnosis, and treatment.
- Studies and reviews discussing gene therapy and advancements in DM1 treatment.

The exclusion criteria were:

- Non-peer-reviewed articles.
- Studies focusing on other forms of myotonic dystrophy or unrelated muscular dystrophies.
- Articles published in languages other than English, unless a reliable translation was available.

2.3 Data Extraction and Synthesis

Information was taken from the selected paper articles and categorized into definite themes corresponding to the several aspects of DM1. The themes involved:

- History and Evolution of DM1: Analysis of the historical background and discovery milestones of DM1.
- Epidemiology: Summarization of the frequency and distribution of DM1 across different geographical regions.
- Genetic and Molecular Basis: Detailed exploration of the genetic mutation (CTG repeats in the DMPK gene) responsible for DM1 and its pathogenic mechanisms.
- Clinical Manifestations: Compilation of the multisystemic symptoms associated with DM1, including cardiac, respiratory, endocrine, nervous system, and other complications.
- Diagnosis: Overview of the laboratory, electrophysiological, and molecular diagnostic techniques used in DM1 detection.
- Treatment and Management: Examination of current treatment strategies, supportive care, and the potential role of gene therapy in DM1.

2.5 Review and Interpretation

The extracted information was synthesized to deliver an inclusive overview of the present understanding of DM1, from its molecular foundations to medical management. The review also highlighted the gaps in knowledge and areas where further research is necessary, particularly in the development of gene therapy approaches.

2.6 Ethical Considerations

As this review article is based on previously published research, there were no direct ethical concerns. However, the review adheres to ethical standards in research, ensuring that all data and literature are appropriately cited and credited to the original authors.

3. Results and Discussion

3.1 History of Myotonic Dystrophy Type 1

DM1 is the classical form of Myotonic dystrophy (OMIM 160900), which was first described in 1909 (FE, 1909; PS Harper & Harper, 2001; Steinert, 1909).

In 1912, Curschmann discovered a high frequency of familial cataracts and introduced the term multisystemic disorder in 1936. Curschmann discovered the increased occurrence of familial cataracts in 1912 and gave the name multisystemic syndrome in 1936 (Curschmann, 1912, 1936)

In 1992, it was discovered that DM1 was caused by the expansion of CTG repeats in 3' untranslated region of the *DMPK* (*Dystrophia Myotonica Protein Kinase*) gene on chromosome 19 (Aslanidis *et al.*, 1992; Buxton *et al.*, 1992; Harley *et al.*, 1992; PS Harper & Harper, 2001). Table 1.1 shows the history of Myotonic Dystrophy Type 1.1.

Table 1.1: History of Myotonic Dystrophy Type 1

Year	Scientist Name	Information about DM1	References
1909	Hans Guatav Wilhem Steinert	First described	(FE, 1909; PS Harper & Harper, 2001; Steinert, 1909)
1912	Curschmann	Familial cataract discovery	(Curschmann, 1912, 1936)
1936	Curschmann	Term Multisystemic syndrome	(Curschmann, 1912, 1936)
1992	Aslanidis, Buxton, and Harley	Gene location with CTG mutation	(Aslanidis *et al.*, 1992; Buxton *et al.*, 1992; Harley *et al.*, 1992; PS Harper & Harper, 2001)

3.2 Epidemiology of DM1

In Asia, the frequency of DM1 is very low, (Hsiao *et al.*, 2003), whereas in Europe and New Zealand, its frequency is found to be 10 to 12/100,000 (Ford, Kidd, & Hammond-Tooke, 2006). Additionally, in Europe, it has a frequency of 10 to 12/100,000, which is cited by most of the authors (Hughes, Hicks, Nevin, & Patterson, 1996; Magee & Nevin, 2000; Norwood *et al.*, 2009; Siciliano *et al.*, 2001; Wheeler, Krym, & Thornton, 2007). It has a higher frequency of 18/100,000 in Croatia, as shown in Figure 1 (Medica, Markovi, & Peterlin, 1997).

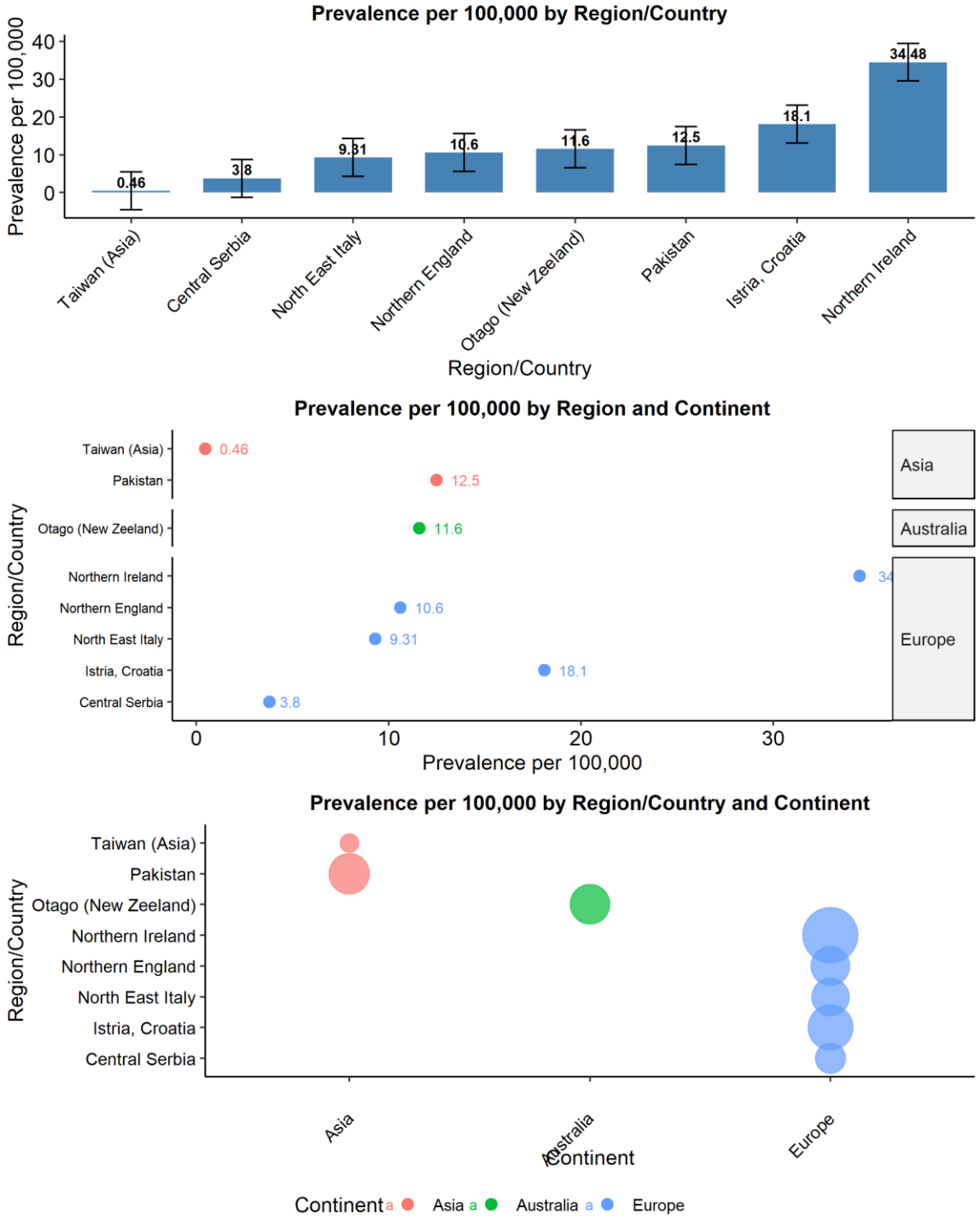


Figure 1: Prevalence by countries

Figure 1 represents the prevalence rates of DM1 across various geographical regions and countries. Prevalence, expressed as cases per 100,000 individuals, is presented alongside the year of publication for the source data and a corresponding reference. The regions include Vastra Gotland Region and Gothenburg in Western Sweden (both with 2017 data), Taiwan (2003), Otago, New Zealand (2006), Northern Ireland (1996), Northern England (2009), Northeast Italy (2001), Istria, Croatia (1997), Central Serbia (2005), and Pakistan (2020). Prevalence rates vary considerably, ranging from 0.46/100,000 in Taiwan (2003) to 18.1/100,000 in Istria, Croatia (1997). For Pakistan (2020), prevalence is listed as a "reference prevalence" of 1/8000 (Ford *et al.*, 2006; Hsiao *et al.*, 2003; Hughes *et al.*, 1996; Lindberg & Bjerkne, 2017; Medica *et al.*, 1997; Mladenović *et al.*, 2005; Norwood *et al.*, 2009; Shahzad *et al.*, 2020; Siciliano *et al.*, 2001).

3.3 Etiology of DM1

Myotonic dystrophy type 1 (DM1) is a hereditary condition passed down in an autosomal dominant pattern. It arises due to an expansion of CTG repeats within the 3' untranslated region of the DMPK gene. This mutation leads to the production of abnormal RNA, which accumulates in the cell nucleus as RNA foci. These foci interfere with the function of RNA-binding proteins, disrupting normal cell activities. This disruption contributes to various cellular abnormalities, which are responsible for the wide range of clinical features observed in DM1 (Querido, Gallardo, Beaudoin, Ménard, & Chartrand, 2011).

3.4 Symptoms/Complications of DM1

Slowly progressive distal muscle weakness, myotonia, and atrophy are the key symptoms, neck and face muscles are also involved. Dysphagia, nasal speech, and dysarthria are reported recurrently. The most prominent key symptom of DM1 is the early onset cataract with a frequency of 80 to 90 percent (when a patient is over 50 years of age, although they may appear earlier) (Gutiérrez *et al.*, 2019; Ikeda, Iwabe-Marchese, França Jr, Nucci, & Carvalho, 2016; Ivanovic, Meola, Vukojevic, & Peric, 2023). Symptoms which are related to the DM1 are described below;

3.4.1 Cardiac manifestations

In DM1, heart abnormalities are the most prominent and cause the deaths in one-third of the affected persons. Conduction abnormalities are seen commonly which is followed by atrioventricular arrhythmias. Among these supraventricular arrhythmias are found in 10 percent of the cases (Groh *et al.*, 2008; Petri, Vissing, Witting, Bundgaard, & Køber, 2012; Stojanovic *et al.*, 2013; Wahbi *et al.*, 2012).

3.4.2 Respiratory manifestations

Weakness of the respiratory muscles, and muscular dysfunction of upper airways are frequently observed leading to respiratory failure in the patients of DM1. These manifestations also bring cough effectiveness and respiratory clearance which results in pneumonia and recurrent lung infections. These involvements of the respiratory system and its frequent complications are key causes of death in patients of DM1 (Wahbi *et al.*, 2012).

3.4.3 Endocrine manifestations

Endocrine manifestations of DM1 include glucose intolerance, insulin resistance and type 2 diabetes mellitus along with erectile abnormalities and gonadal dysfunction in men are the most common endocrinological problems (Matsumura *et al.*, 2009). In 60 percent of the patients, dyslipidemia was found (Vujnic *et al.*, 2015). Involvement of pituitary glands, thyroid, adrenal, and parathyroid glands can also be found in DM1 patients (Dahlqvist, Ørngreen, Witting, & Vissing, 2015; Passeri *et al.*, 2013).

3.4.4 Nervous system complications

Abnormalities of the brain, including both structural and functional, are recurrent in the patients of DM1. Patients with congenital DM1 have a prominent intellectual disability with visualization defects and neurological impairments. Lethargy and extreme daytime sleepiness are the most common symptoms of the DM1 (Peric *et al.*, 2019; Romigi *et al.*, 2013)

Depression, frustration, social denial, and anxiety can also be seen (Minier, Lignier, Bouvet, Gallais, & Camart, 2018).

3.4.5 Other complications

Abdominal pain, constipation, gastrointestinal problems, diarrhea, dysphagia, cholecystitis, and occurrence of gallstones are frequently observed in the patients of DM1, especially with dysfunctions of smooth muscles (Fisette-Paulhus, Gagnon, Girard-Côté, & Morin, 2022).

Alopecia and involvement of skin are seen frequently in the congenital form of DM1 (Gadalla *et al.*, 2011).

The most prominent signs and symptoms of Myotonic Dystrophy Type 1 are shown in Figure 2.

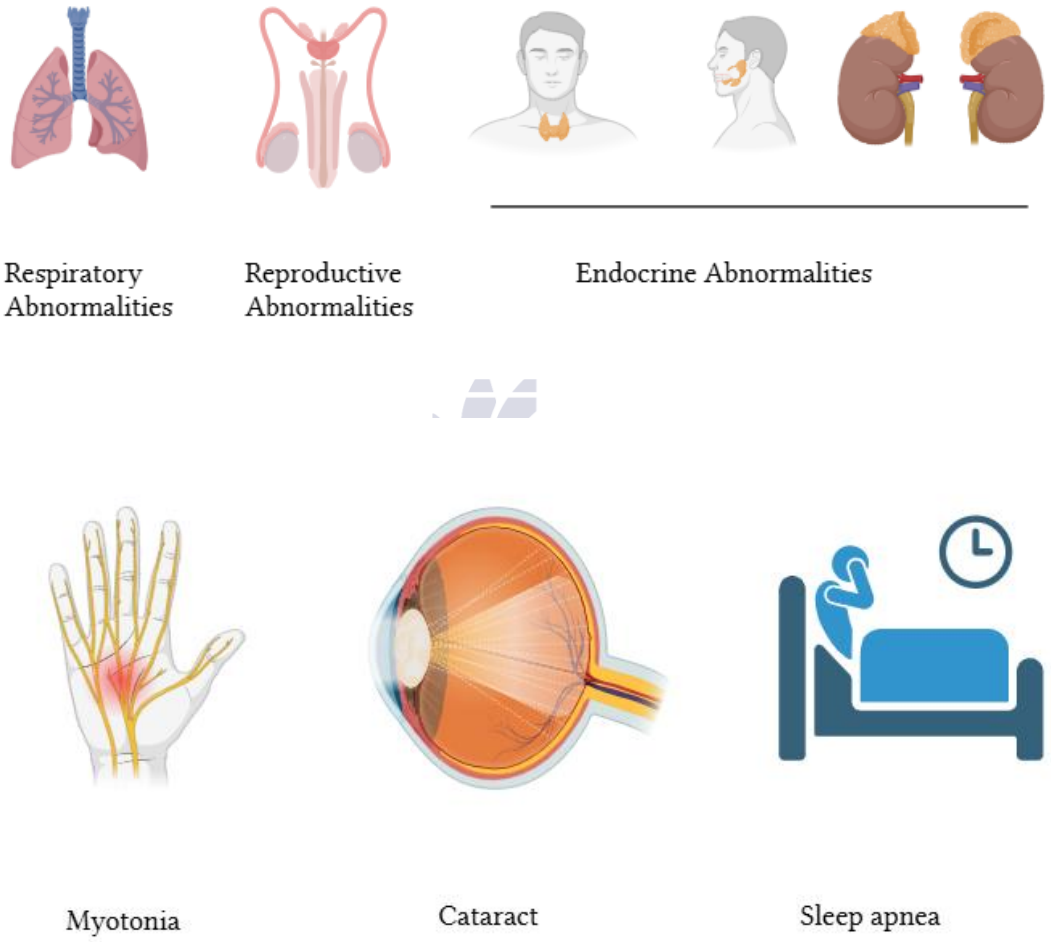


Figure 2: Common signs & symptoms

3.5 Transmission of DM1

Before 1997, it was believed that females carrying the DM gene were the only way by which DM1 could be transmitted from mother to offspring. It is now evident that the DM1 can also be passed down from the father, even though this phenomenon does not appear to be prevalent, as shown in Figure 3, because of molecular analysis's ability to show the DM1 expansion in presumed carriers (Bergoffen *et al.*, 1994; de Die-Smulders *et al.*, 1997; Nakagawa *et al.*, 1994; Ohya *et al.*, 1994).

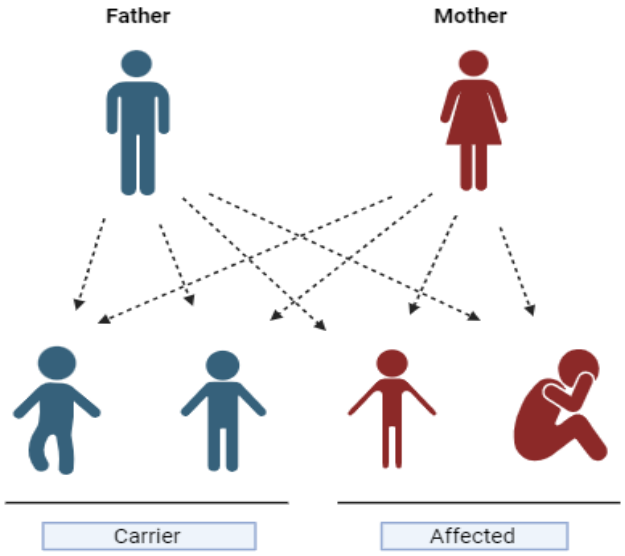


Figure 3: Transmission of DM1

3.6 Pathogenesis of DM1

Toxicity produced by the expansion of CTG repeats which is present in the 3' UTR of transcripts of the mutant *DMPK* gene is the primary phenomenon of the pathogenesis of DM1. It modifies downstream effectors functions and initiates dysregulations of the gene over modifications in the gene silencing, alternate splicing, transcription, translation, and polyadenylation (Batra *et al.*, 2014; Ebralidze, Wang, Petkova, Ebralidse, & Junghans, 2004; Huichalaf *et al.*, 2010; López-Martínez, Soblechero-Martín, de-la-Puente-Ovejero, Nogales-Gadea, & Arechavala-Gomeza, 2020; Rau *et al.*, 2011).

In DM1, the RBPs, which are RNA binding proteins, are the most studied families affected by the mutant *DMPK* transcript toxicity which are CUGBP-ETR-3-like and Muscle blind-like (CELF, MBNL) factors, these control the inclusion of alternative exons in various transcripts with respect to the tissues and developmental states indications and alterations in these will lead to the disease progression (Kalsotra *et al.*, 2008).

The Muscleblind like factors family consists of MBNL1, MBNL2, and MBNL 3 regulators of RNA metabolism, in which the expression levels are closely regulated by developmental stage in each tissue. The MBNL 1 and MBNL 2 are mostly expressed, whereas the MBNL 1 is the paralog which serves as the key function in most of the tissues, except the brain, where the MBNL 2 is mostly detected, and the MBNL 3 level of expression is more limited and is related to aging, regeneration, and muscle cell differentiation inhibition (Choi *et al.*, 2016; Fardaei *et al.*, 2002; Konieczny, Stepniak-Konieczna, & Sobczak, 2014; Lee *et al.*, 2010).

The family of CUGBP-ETR-3-like factors RNA binding proteins consists of six members, which are divided into two groups concerning their level of expression. Among these, CELF 1 and 2 are extremely expressed in many tissues, like, the heart, brain, and skeletal muscles, constituting the most and first studied group. Whereas the CELF 6 is present in neurons and can also be seen in testes and kidneys (Dasgupta & Ladd, 2012; Nasiri-Aghdam, Garcia-Garduño, & Jave-Suárez, 2021).

The alternate splicing is an RNA processing phenomenon that removes the intron between the splicing sites in pre-messenger RNAs to process the mRNAs. Spliceosome mediates this process and is highly regulated by the various motif sequences, in which RBP recognition takes place, which act as enhancers or repressors of respective splicing sites. This process contributes the proteomic variety by allowing a single gene to code for more than one messenger RNA and thus have multiple functions to play

(Greenberg & Soreq, 2013; Pan, Shai, Lee, Frey, & Blencowe, 2008).

The last step in the maturation of RNA is the polyadenylation, and it comprises the cleavage of nascent pre-messenger RNA 3' end and polyadenylation tail addition at the site of cleavage, which performs the key function in RNA stability, its efficiency of translation, and mRNA localization. And if more than one polyadenylation site is owned by the gene, then the usage difference of those sites is known as the alternative polyadenylation (Proudfoot, 2011; Yeh & Yong, 2016).

The alternate splicing and the alternative polyadenylation processes have been described to be altered and perform a key role in the pathogenesis of DM1 (Batra *et al.*, 2014).

3.7 *Dystrophia Myotonica Protein Kinase (DMPK)* Gene Physiology

The *DMPK* gene encodes threonine/serine protein kinase, which is critical for various physiological and developmental functions (Harmon, Harmon, Larsen, Paulson, & Perryman, 2008; Llagostera *et al.*, 2007; Pantic *et al.*, 2013; Reddy *et al.*, 1996; Schulz, McIntosh, Kasten, Wieringa, & Epstein, 2003).

The key functions of the protein of *DMPK* in the normal tissues are in the heart and skeletal muscles. Regulation of calcium ion homeostasis in myotubes is the main function of the *DMPK* protein. (Benders, Groenen, Oerlemans, Veerkamp, & Wieringa, 1997), gating sodium ion channels inside the tissues of skeletal muscles (Mounsey, Mistry, Ai, Reddy, & Moorman, 2000). Myotube formation from the myoblast cells is promoted (Bush, Taft, Meixell, & Perryman, 1996)Atrioventricular conduction facilitation and membrane-bound cardiac beta-adrenergic receptors protection are involved are other activities performed by the *DMPK* gene (Berul *et al.*, 1999; Llagostera *et al.*, 2012).

3.8 DM1 and CTG triplets

Individuals with

1. The number of CTG repeats <39 is unaffected and considered normal.
2. The number of CTG repeats between 50 to 99 is said to be pre-mutation, and in most patients, cataracts develop.
3. The number of CTG repeats between 100 to 200 has mild or moderate muscular weakness.
4. Patients with several CTG repeats between 200 to 1000 are said to be adult-onset/juvenile DM1.
5. And the number of CTG repeats between 1000-6000 progresses the congenital or classical form of DM1 (Arsenault *et al.*, 2006; Salehi *et al.*, 2007). As mentioned in Table 1.2.

Table 1.2 Table showing the number of CTG repeats with DM1 types

No of CTG repeats	Disease cadre
<39	Unaffected/normal
50-99	Pre-mutation
100-200	Mild/Moderate
200-1000	Adult onset/Juvenile
1000-6000	Congenital/Classical

3.9 Types/Forms of DM1

DM1 can be categorized into the four forms, which depend upon the time of onset of symptoms.

1. Classical form or congenital form, its symptoms usually shows at birth or first year after birth, and patient represents generalize weakness of muscles, mental retardation and conditions of autism (EKSTRÖM, HAKENÄS-PLATE, Tulinius, & Wentz, 2009).
2. Childhood type, in this type of DM1 patient shows the symptoms between the ages of 1 year to 10 years, and this form is more severe than the classic form (EKSTRÖM *et al.*, 2009).
3. The adult classical type of DM1 occurs between the ages of 10 to about 40 years, and patients exhibit lethargy, cognitive impairment, progressive weakness of muscles, and myotonia (Thornton, 2014)
4. Mild or late-onset type, in this type of DM1, symptoms may occur from the 20 but usually after the 40 to 50 years age and represent minor symptoms like cataracts or muscular

weakness (Meola & Cardani, 2015a; Thornton, 2014; Turner & Hilton-Jones, 2014)

3.10 Genetics and clinical differences between DM1 and DM2

Both DM1 and DM2 are autosomal myopathic syndromes and are characterized by myotonia, myopathies, and multisystemic organ involvement (Meola & Cardani, 2015b).

Despite phenotype resemblances, Myotonic dystrophy comprises two heritarily separate disorders and requires different diagnostic and management policies.

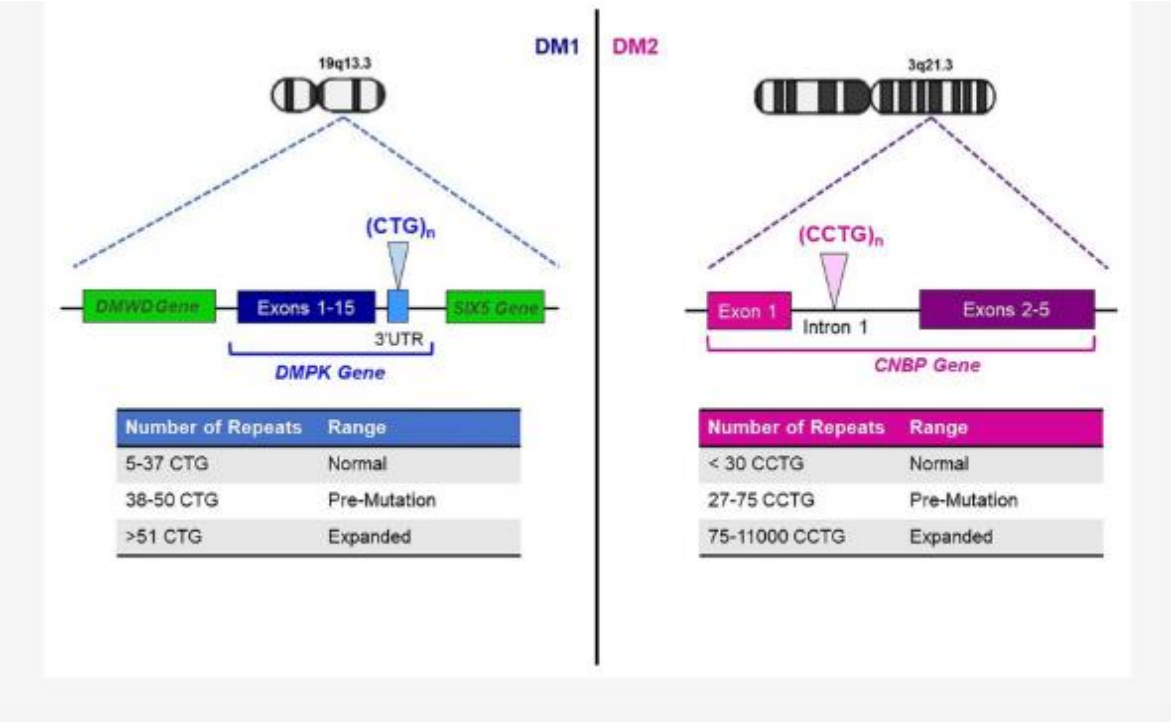
The number of CTG repeats expansion on the *DMPK* gene (MIM *605377) at 3'UTR on chromosome 19q13.3 causes the DM1 or myotonic dystrophy type 1, whereas a (CCTG)n expansion in the first intron of the CNBP gene (MIM *116955) on chromosome 3q21.3 causes myotonic dystrophy type 2 (Liquori *et al.*, 2001; Mahadevan *et al.*, 1992).

The number of CTG repeats in DM1 patients ranges from 51 to various thousands, with disruptions of the CTG array, which is reported in approximately 3-5% of patients with DM1 (Botta *et al.*, 2017; Braida *et al.*, 2010; Musova *et al.*, 2009).

The length of CTG repeats between 38 to 50 is considered a pre-mutation allele, and it shows increased variability, which leads to a higher pathogenic repetition of expansion. (Meola & Cardani, 2015b; Bjarne Udd & Krahe, 2012).

In addition to the number of CTG repeats, the number of CCTG repeats in the CNBP gene is part of complex phenomena which have polymorphic sections in numbers of (TG) (TCTG) (CCTG) (NCTG) (CCTG) configuration (Bachinski *et al.*, 2009).

Healthy individuals contain alleles with less than 30 repeats, while in DM2, these alleles contain 75-11000 CCTG repeats. (Bjarne Udd & Krahe, 2012). The Genetics and differentiation of DM1 and DM2 are shown in Figure 4.



Number of Repeats	Range
5-37 CTG	Normal
38-50 CTG	Pre-Mutation
>51 CTG	Expanded

Number of Repeats	Range
< 30 CCTG	Normal
27-75 CCTG	Pre-Mutation
75-11000 CCTG	Expanded

Figure 4: Genetics and differentiation of DM1 and DM2 (Liquori *et al.*, 2001; Mahadevan *et al.*, 1992)

3.11 Lab Diagnosis of DM1

3.11.1 Blood tests

In patients with DM1, the level of creatinine kinase is moderately raised. Common findings are the higher amount of liver enzymes in especially gamma-glutamyl transferase, as IgG hypogammaglobulinemia, the reasons are unknown (B Udd *et al.*, 2011).

3.11.2 Electrophysiological studies

These studies are used before the development of molecular testing of DM1, and in this, Electromyography is used with the combination of myopathic changes and myotonia for DM1 diagnosis (Aldehag, Jonsson, & Ansved, 2005).

3.11.3 Muscle histopathology

This type of study is not performed because of the availability of molecular testing for DM1. However, the histological structures may include the prominent internal nuclei, which are generally represented as a "Row" of nuclei, ring fibers, variable myofiber size, and myofiber atrophy type 1. In the late stage of DM1, fibrosis may be found, and fatty acid replacement may be found (Meola & Cardani, 2015a).

3.11.4 Molecular testing

PCR or the Southern blot is used for the confirmation of DM1 diagnosis, and molecular testing is preferred for DM1 diagnosis. DNA fragments with repeats of 5 to 125 can be detected by PCR.

Patients of DM1 with two alleles of *DMPK* contain a decreased CTG repeats number and on the gel, two bands appear in patients of DM1 having an increased number of CTG repeats, like more than 125, or patients with an equal number of CTG repeats having two *DMPK* alleles, then only one band appears on the gel. In this situation, a Southern blot is used to confirm to diagnosis of DM1. On the southern blot, the expansion of *DMPK* alleles may show as a smear representing different sizes of fragments due to the somatic heterogeneity.

Presently, a Southern blot of white blood cells' genomic DNA is the standard method of detection for the alleles of *DMPK* with CTG repeats up to 100 (Kamsteeg *et al.*, 2012).

3.12 Treatment of Myotonic Dystrophy Type 1

Currently, there is no effective treatment available for DM1, but supportive treatment can be given to patients depending on their symptoms (López-Morató, Brook, & Wojciechowska, 2018).

For patients experiencing symptoms of myotonia, anti-myotonic drugs such as sodium channel blockers may be recommended. Medications like phenytoin, propafenone, mexiletine, procainamide, quinine, flecainide, and carbamazepine have been shown to alleviate the complications associated with myotonia (Logigian *et al.*, 2010).

DM1 patients must be observed for head drop, foot drop, falls, ptosis, dysphagia, dyspnoea, figure flexure weakness, and dysarthria. A regular exercise program for fitness of heart and weight control is advised; though, there is not much evidence to conclude that exercise can preserve the strength of muscles (Smith & Gutmann, 2016).

Therapeutic strategies for symptoms like muscular weakness include cervical collars, physical therapy, occupational therapy, orthotics, speech or swallow evaluation, and assistive devices such as a wheelchair or walker are used when needed.

For the patients of DM1 who have weakness of respiratory muscles, BiPAP (Bilevel positive airway pressure) is used. Methylphenidate (Puymirat, Bouchard, & Mathieu, 2012) Or Modafinil can be used for Ehlers-Danlos disorders (Meola & Cardani, 2015a; Thornton, 2014; Turner & Hilton-Jones, 2010).

Antiarrhythmic medicines like sodium channel blockers, especially Class 1 drugs, should be used with care because these drugs may be pro-arrhythmic. For patients who have cardiac conduction abnormalities, cardiac block either second-degree or third-degree, cardiac arrhythmias, or tachycardia, a pacemaker and implantable defibrillator should be suggested (Epstein *et al.*, 2013; Groh *et al.*, 2008; Verhaert, Richards, Rafael-Fortney, & Raman, 2011).

Patients with erectile dysfunction, testicular failure, or infertility should be referred to specialists. In erectile dysfunction, drugs may be helpful for men. Women with infertility, menstruation issues, and dysmenorrhea should be referred to obstetrics and gynaecology.

Muscular weakness and myotonia may lead to intestinal dysmotility, dysphagia, and aspiration. Drugs such as erythromycin or metoclopramide can be used to reduce the complications of hypomotility. For constipation, certain dietary modifications like fluids, fibres, or laxatives should be used.

Cholestyramine can progress to incontinence, diarrhoea, and pain. When this cholestyramine fails, drugs such as norfloxacin can be used to

treat the overgrowth of bacteria (Turner & Hilton-Jones, 2010). The list of medical conditions with their therapeutic strategies is given in Table 1.3 and Figure 5.

Table 1.3 Conditions with therapeutic strategies

Conditions	Therapeutic strategies	References
Myotonia	Phenytoin, propafenone, mexiletine, procainamide, quinine, flecainide, and carbamazepine	(Logigian *et al.*, 2010)
Head drop, foot drop, falls, ptosis, dysphagia, dyspnoea, figure flexure weakness, and dysarthria	Regular exercise program for the fitness of the heart and weight control	(Smith & Gutmann, 2016)
Muscular weakness	Cervical collars, physical therapy, occupational therapy, orthotics, speech or swallow evaluation, and assistive devices such as wheelchairs, walkers	(Meola & Cardani, 2015a; Thornton, 2014; Turner & Hilton-Jones, 2010)
Weakness of the respiratory muscles	BiPAP (Bilevel positive airway pressure)	(Meola & Cardani, 2015a; Thornton, 2014; Turner & Hilton-Jones, 2010)
Ehlers-Danlos disorders	Methylphenidate, Modafinil	(Meola & Cardani, 2015a; Thornton, 2014; Turner & Hilton-Jones, 2010)
Cardiac conduction abnormalities, cardiac block, either second-degree or third-degree, cardiac arrhythmias, or tachycardia	Sodium channel blockers, especially Class 1 drugs, pacemakers, and implantable defibrillators	(Epstein *et al.*, 2013; Groh *et al.*, 2008; Verhaert *et al.*, 2011)
Erectile dysfunction, testicular failure, or infertility	Refer to the specialists	(Turner & Hilton-Jones, 2010)
Intestinal dysmotility, dysphagia, and aspiration	Erythromycin or metoclopramide	(Turner & Hilton-Jones, 2010)
Incontinence, diarrhoea, and pain	Norfloxacin	(Turner & Hilton-Jones, 2010)

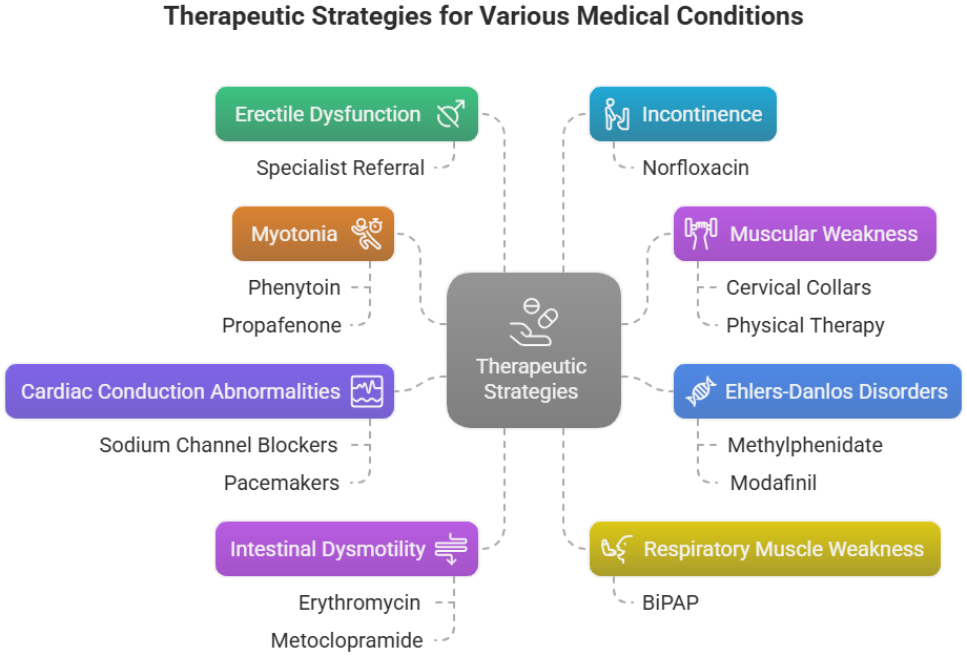


Figure 5: Therapeutic Strategies for DM1

3.13 Future prospects of DM1 therapeutics

CRISPR (clustered regularly interspaced short palindromic repeats) technology has advanced into a versatile tool for both editing and regulating gene expression in a sequence-specific manner. In the context of DM1 syndrome models, it has been specifically adapted to address the underlying genetic abnormalities. This includes targeting and removing expanded DNA sequences, inhibiting their transcription to prevent the production of harmful RNA, and facilitating the degradation of toxic RNA molecules. These tailored modifications aim to directly treat the root cause of DM1 by addressing the genetic and molecular disruptions associated with the condition (Marsh, Hanson, Wood, Varela, & Roberts, 2020; Scrudato *et al.*, 2019).

4. Conclusion

Myotonic Dystrophy Type 1 (DM1) is a complicated, multisystem condition that continues to be one of the most common types of adult-onset muscular dystrophy. The illness results from an increase in CTG repeats within the DMPK gene, causing extensive cellular impairment via a toxic RNA gain-of-function mechanism. This molecular pathology supports the varied and frequently serious clinical symptoms seen in DM1, including muscle weakness and myotonia as well as complications in the cardiac, respiratory, endocrine, and nervous systems. The multisystemic aspects of DM1 create considerable management challenges, requiring a multidisciplinary care approach that tackles the diverse symptoms and complications. The differences in the prevalence of DM1 across various regions imply that genetic and environmental influences play a role, with some populations showing increased disease rates. Distinguishing between DM1 and DM2, while difficult because of shared clinical characteristics, is essential for precise diagnosis and suitable treatment. Improvements in molecular diagnostics, especially through PCR and Southern blotting, have greatly enhanced the precision and rapidity of DM1 diagnosis, decreasing the dependence on more invasive methods such as muscle biopsy.

Even with considerable progress in comprehending the molecular and clinical features of DM1, the treatment still primarily focuses on alleviating symptoms, as there's no available cure at this time. Management approaches aim to reduce symptoms and avert complications, especially in the cardiac and respiratory systems, which are the primary reasons for morbidity and mortality in DM1

patients. The advancement of gene therapies, particularly those utilizing CRISPR techniques, provides hopeful opportunities for future treatments by potentially addressing the root genetic cause of the condition. These new treatments have the capacity to not only relieve symptoms but also alter the progression of the disease, providing optimism for patients and their loved ones.

In summary, although considerable advancements have occurred in comprehending and treating DM1, continued research is essential to fully grasp the disease's complexity and create effective treatments. Maintaining emphasis on the molecular mechanisms of DM1, alongside progress in genetic therapies, will probably lead to more precise and effective treatments, thereby enhancing outcomes and quality of life for individuals impacted by this challenging condition

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Author Contributions

All authors contributed equally to this study.

Conflict of Interest

All authors declare no conflict of interest Data Availability Data presented in this study will be available on a fair request to the corresponding author

Data Availability

Data presented in this study will be available on a fair request to the corresponding author

Ethics Approval

Not applicable to this paper

All writers equally contributed to this research study.

Novelty Statement: This review distinctively produces over a century of systematic and clinical information on Myotonic Dystrophy Type 1 (DM1), offering a combined perspective that extents from the disorder's historical roots to the latest developments in molecular diagnostics and gene-based treatments. By highlighting current understandings into the RNA-mediated pathogenesis and assessing cutting-edge therapeutic progresses, including gene editing and antisense technologies, this work offers a timely and inclusive reference that links foundational considerate with modern control approaches for DM1.

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