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Research Article

Research Advances in the Pathogenic Mechanisms of Charcot-Marie-Tooth Disease Type 2Z (CMT2Z)

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Abstract

Charcot-Marie-Tooth Disease Type 2Z (CMT2Z) is an inherited peripheral neurodegenerative disorder caused by mutations in the Microrchidia family CW-type zinc finger 2 (MORC2) gene. In recent years, the pathogenic mechanisms underlying CMT2Z have garnered increasing attention. Studies demonstrate that the MORC2 protein not only participates in DNA damage repair but also functions as a transcriptional regulator modulating epigenetic modifications. However, the precise mechanisms by which MORC2 mutations drive disease pathogenesis remain poorly understood, and the basis of clinical phenotypic heterogeneity is unclear. This review summarizes the CMT2Z genotype-phenotype spectrum, MORC2 physiological functions, and the mechanisms linking MORC2 dysfunction to CMT2Z, thereby providing a foundation for elucidating pathogenesis and developing targeted therapies.

Keywords: Charcot-Marie-Tooth Disease Type 2Z (CMT2Z), MORC2, HUSH complex, pathogenic mechanism

Introduction

Charcot-Marie-Tooth disease (CMT), also known as peroneal muscular atrophy, is a group of inherited neuromuscular disorders characterized by degenerative peripheral neuropathy, with an estimated prevalence of 1/2000-2500, making it one of the most common hereditary neuromuscular diseases worldwide [1]. Based on nerve conduction velocity and genetic patterns, CMT is classified into multiple subtypes. Among them, the axonal form CMT2 is pathologically characterized by peripheral axonal degeneration with normal or mildly slowed motor nerve conduction velocities. In recent years, CMT2Z, a crucial subtype of CMT2, has garnered increasing attention. CMT2Z is an autosomal dominant axonal neuropathy caused by mutations in the MORC2 gene, exhibiting complex clinical manifestations such as distal muscle weakness, sensory impairment, and, in some cases, central nervous system involvement [2].

CMT2Z was first reported in Spanish patients in 2016, and its pathogenesis is closely linked to MORC2 gene mutations [3]. The MORC2 gene encodes a protein containing an ATPase module, which is broadly involved in diverse biological processes, including DNA repair, transcriptional regulation, chromatin remodelling, and lipid homeostasis [4].

The dynamic expression of the MORC2 protein during nervous system development and maturation is critical for normal peripheral nerve function. To date, approximately 20 MORC2 mutations have been associated with CMT2Z, with p. Arg252Trp being the most prevalent mutation, typically presenting with juvenile or early-adult-onset distal muscle weakness and sensory deficits. Notably, certain MORC2 mutations may induce phenotypes resembling spinal muscular atrophy (SMA) or even involve central nervous system abnormalities, further highlighting the clinical heterogeneity of CMT2Z [5]. This phenotypic diversity suggests that MORC2 mutations may impact nervous system development and function through distinct molecular mechanisms.

Although CMT2Z shares clinical similarities with other axonal CMT subtypes, such as CMT2A, its pathogenesis and pathophysiological processes may be unique. Studies indicate that MORC2 mutations may disrupt gene expression regulation, DNA damage repair, and epigenetic silencing in neural cells, leading to axonal degeneration, impaired nerve conduction, and distal muscle weakness [4]. Therefore, elucidating the physiological roles of MORC2 and the effects of its mutations on the nervous system is essential for understanding the pathogenesis of CMT2Z and developing targeted therapeutic strategies. This article aims to synthesize current knowledge on the phenotypic spectrum of CMT2Z, MORC2 mutation profiles, and proposed pathogenic pathways underlying MORC2 dysfunction, thereby providing directions for future research into the disease mechanisms.

Advances in Genotype-Phenotype Correlations in CMT2Z

The phenotypic spectrum of CMT2Z varies across populations but shares common features. MORC2 mutations are the primary cause of CMT2Z, with reported mutations predominantly clustered within the ATPase module of the protein. Studies from different countries have identified multiple MORC2 mutations, including recurrent variants such as p.R252W and p.S87L, as well as novel mutations like p.C345Y and p.A369V, [6, 7] with de novo mutations frequently observed.

Phenotypic Spectrum in Spanish CMT2Z Cohorts

In addition to the initially reported p.S25L and p.R190W, Spanish researchers identified seven MORC2 missense mutations in 15 CMT2Z patients, including known variants (p.R252W, p.S87L, and p.Y394C) and novel mutations (p.R319C, p.A406V, p.D466G, and p.A152P). These mutations were primarily localized to the ATPase module, S5-transducer domain, and coiled-coil domain 1.

Based on phenotypes, patients were categorized into three groups: (1) scapuloperoneal variant (p.R252W, p.A406V, and p.D466G), characterized by asymmetric proximal upper limb weakness and neck flexor/extensor involvement with onset in adolescence; (2) neurodevelopmental variant (p.S87L and p.Y394C), featuring congenital hypotonia, delayed motor milestones, and central neurological abnormalities; and (3) classic CMT2 phenotype (p.R319C and p.A152P), marked by early distal lower limb weakness progressing to mild upper limb impairment [2].

These findings highlight that CMT2Z, despite its low incidence, exhibits marked individual heterogeneity characterized by diverse mutation loci and significant phenotypic variability. Clinical manifestations vary considerably in terms of age of onset (ranging from childhood to adulthood) and anatomical involvement (distal vs. proximal limbs, peripheral vs. central nervous systems), with some cases presenting central nervous system abnormalities. Notably, muscle weakness remains a unifying clinical feature across all subtypes.

CMT2Z Phenotypic Profiles in Korean and Japanese Cohorts

In studies of the CMT2Z phenotypic spectrum in Korea, screening was conducted using CMT2 families as the study cohort. Among 152 CMT2 families, 4 families (4 patients) were found to carry MORC2 mutations, with three mutation types identified: p.S25L, p.R70L, and p.R190W. The clinical genetics of Korean CMT2Z patients showed high similarity to the initially reported Spanish cases [3] in terms of allelic homogeneity and genotype-phenotype correlations, further confirming that MORC2 is the second most common causative gene for axonal CMT in Korea (second only to MFN2, the causative gene of CMT2A) [6].

Similarly, Japanese studies involving 434 patients identified MORC2 variants in 13 individuals (2.7% of CMT2 cases), with recurrent mutations (p.R190W and p.Q338R) and novel variants (p.C345Y, p.A369V, and p.Y332C) reported [8].

These results reinforce MORC2 as a major contributor to axonal CMT in East Asian populations, with high rates of de novo mutations and phenotypic variability mirroring Spanish cohorts.

Genotype-Phenotype Studies in Chinese CMT2Z Patients

In 2021, Chinese researchers screened 284 unrelated Chinese CMT2 families and identified four CMT2Z patients from four unrelated families, accounting for 1.4% of the cohort. MORC2 gene testing was performed on all patients, revealing mutation profiles for the four cases. Based on aggregated studies of global phenotypic spectra and case reports, among the mutations identified in the Chinese patients, p.D466G, p.S87L, and p.R252W were previously reported mutations, while p.C407Y was a novel mutation.

The four mutation loci identified in Chinese patients corresponded to markedly divergent phenotypes. Among these, the common p.R252W mutation was associated with typical axonal peripheral neuropathy. The p.S87L mutation caused severe spinal muscular atrophy (SMA)-like disease accompanied by cerebellar hypoplasia and intellectual disability, consistent with the "neurodevelopmental variant" observed in Spanish patients. The p.D466G mutation manifested as late-onset axonal CMT with hyperCKemia (elevated creatine kinase levels), while the novel p.C407Y mutation led to early-onset axonal sensorimotor neuropathy [9].

Summary of Advances in Genotype-Phenotype Studies

Through analyses of genotype-phenotype spectra across different countries and regions, we have determined that the prevalence of CMT2Z in Asian populations ranges from 1.4% to 2.7%, ranking it among the more frequent subtypes of CMT2. Studies from Korea and Japan indicate that its prevalence is second only to that of CMT2A (Table 1).

Table 1: Phenotype-Genotype Spectrum Across Different Countries (*indicates hotspot mutation genes).

Mutation	Domain location	Phenotypic Characteristics
Spain[2]		
p.S25L *	ATPase	Typical CMT2 phenotype
p.R190W *	ATPase	Scapuloperoneal variant
p.R252W *	ATPase	Scapuloperoneal variant
p.S87L *	ATPase	Neurodevelopmental abnormalities
p.Y394C	CC1	Neurodevelopmental abnormalities
p.R319C	CC1	Typical CMT2 phenotype
p.A406V	S5	Scapuloperoneal variant
p.D466G	S5	Scapuloperoneal variant
p.A152P	ATPase	Typical CMT2 phenotype
Korea[6]		
p.S25L *	ATPase	Typical CMT2 phenotype
p.R70L	ATPase	Axonal peripheral neuropathy
p.R190W *	ATPase	Scapuloperoneal variant, prominent lipid accumulation
Japan[8]		
p.R190W *	ATPase	Scapuloperoneal variant
p.Q338R	CC1	Early-onset axonal peripheral neuropathy
p.C345Y	CC1	Early-onset axonal peripheral neuropathy
p.A369V	CC1	Early-onset axonal peripheral neuropathy
p.Y332C	CC1	Undetermined
China[9]		
p.R252W *	ATPase	Axonal peripheral neuropathy
p.S87L *	ATPase	Spinal muscular atrophy (SMA)-like phenotype
p.D466G (de novo)	S5	Late-onset axonal CMT, elevated creatine kinase (CK) levels
p.C407Y	S5	Early-onset axonal motor and sensory neuropathy

The genotype-phenotype correlations in CMT2Z exhibit high heterogeneity, with mutations predominantly clustering in functionally critical domains. The clinical phenotypic spectrum spans from isolated peripheral neuropathy to complex neurodevelopmental abnormalities. As summarized in the table above, most mutations localize to the ATPase module, while others reside in the S5-transducer domain or coiled-coil domain 1 (CC1). These findings underscore the need to integrate CMT2Z phenotypes with the functional roles of distinct structural domains in experimental designs. Future studies should prioritize elucidating the mechanistic links between mutations in specific domains (e.g., ATPase, S5-transducer, or CC1) and their corresponding clinical manifestations. Additionally, research efforts should focus on recurrent hotspot mutations (e.g., p.S87L, p.R252W, p.S25L, and p.R190W), with particular emphasis on the classic CMT2Z phenotype associated with p.S25L and the severe neurodevelopmental phenotypes with central nervous system involvement linked to p.S87L.

Functional Roles of MORC2 Protein

The MORC2 gene is located at 22q12.2 and encodes MORC family CW-type zinc finger protein 2 (MORC2), a chromatin remodeling protein composed of 1032 amino acids that primarily localizes to the nucleus. MORC2 plays critical roles in DNA damage repair, [10] epigenetic transcriptional regulation, [11] and lipid homeostasis [12].

The MORC2 protein comprises four functional domains: a conserved ATPase domain, a CW (cysteine-tryptophan)-type zinc finger domain, a nuclear localization signal (NLS) domain (S5, CD), and a coiled-coil domain (CC1, CC2, CC3) (Figure 1).

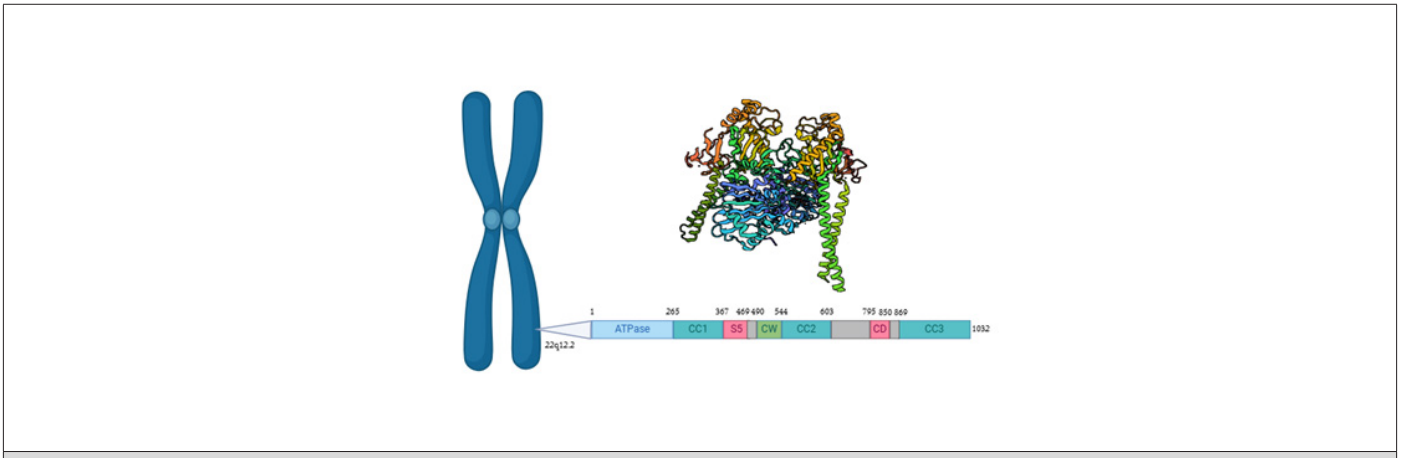

Figure 1: Schematic diagram of MORC2 gene localization and protein domains.

MORC2 is essential for nervous system development and axonal maintenance. Pathogenic mutations in MORC2 disrupt its normal functions, leading to neuropathy. These mutations predominantly impair ATPase activity, DNA damage repair capacity, and epigenetic regulation, which are considered central mechanisms underlying CMT2Z pathogenesis. Thus, understanding the physiological functions of MORC2 is critical for elucidating CMT2Z mechanisms.

Regulation of DNA Damage Repair

DNA damage is an inevitable cellular event, and failure to repair it promptly can result in genomic instability, degenerative disorders, or cancer. Cells activate a highly coordinated DNA damage response (DDR) network to detect and repair DNA lesions. Dynamic chromatin remodelling is indispensable during this process.

Recent studies have revealed that MORC2 interacts with poly (ADP-ribose) polymerase 1 (PARP1), a chromatin-associated enzyme responsible for synthesizing PAR polymers in mammalian cells during DDR. MORC2 directly binds to PARP1, and this interaction is enhanced following DNA damage. PARP1 mediates PARylation modification of MORC2 at its CW-type zinc finger domain, which enhances MORC2's ATPase activity and chromatin remodelling capacity, thereby promoting DNA repair.

Additionally, MORC2 stabilizes PARP1 by enhancing NAT10-mediated acetylation at lysine 949 (K949). This acetylation prevents ubiquitination and subsequent degradation of PARP1 at the same residue, ensuring its stability during DNA repair. Consequently, MORC2 mutations or deficiency impair PARP1 function, reducing DNA damage-induced PARP1 synthesis and compromising the recruitment of PARP1-dependent DNA repair factors, ultimately diminishing DNA repair efficiency [10].

In summary, MORC2 plays a pivotal role in DDR through its interaction with PARP1 and regulation of PARP1 stability. This discovery not only elucidates a novel function of MORC2 in DNA damage repair but also provides new insights into the accumulation of neuronal DNA damage in CMT2Z patients.

Transcriptional Silencing via Interaction with the HUSH Complex

Beyond DNA damage repair, MORC2 is critically involved in transcriptional and epigenetic regulation.

The Human Silencing Hub (HUSH) complex is a key chromatin regulatory machinery responsible for gene silencing. It consists of three core components: Transactivation suppressor (TASOR), M-phase phosphoprotein 8 (MPP8), and Periphilin. These proteins cooperatively silence intron less genomic elements derived from retro transposed RNAs, such as L1 retrotransposons. Periphilin, a critical HUSH subunit, specifically binds to RNA transcripts originating from target loci, initiating HUSH complex recruitment. Following RNA binding, the HUSH complex recruits two effector molecules: SETDB1, which deposits H3K9me3 histone marks at target sites, and MORC2, which mediates chromatin compaction [11] (Figure 2).

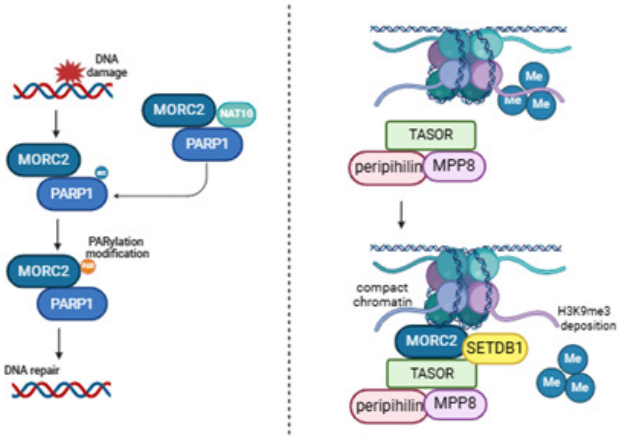

Figure 2: Left: Working model of MORC2-PARP1 interaction in DNA damage repair; Right: Schematic diagram of HUSH complex recruitment and transcriptional silencing mechanisms.

As a key effector of the HUSH complex, MORC2 maintains heterochromatic states to suppress aberrant transcription of endogenous retroviruses (ERVs) and retrotransposons such as long interspersed nuclear element-1 (LINE-1, L1). Excessive L1 transcription can disrupt cellular functions and genomic stability [13].

MORC2 Regulates Lipid Homeostasis

In the cytoplasm, MORC2 promotes lipogenesis, adipocyte differentiation, and lipid homeostasis by modulating the activity of ATP-citrate lyase (ACLY). MORC2 directly binds to ACLY's CoA-binding domain (residues 300-630), a region containing multiple phosphorylation sites (e.g., Ser454) critical for ACLY activation. Overexpression of MORC2 significantly enhances phosphorylation at ACLY Ser454 and boosts its enzymatic activity. Activated ACLY generates acetyl-CoA, which upregulates lipid synthesis enzymes, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). Conversely, knockdown of MORC2 reduces ACC phosphorylation and FAS protein levels, markedly inhibiting lipid accumulation. These findings highlight MORC2's pivotal role in metabolic regulation through ACLY-mediated mechanisms [12].

MORC2's central roles in DNA repair, epigenetic transcriptional silencing, and lipid homeostasis suggest that pathogenic mutations may drive neurodegeneration by compromising genomic stability, disrupting chromatin silencing, or damaging muscle tissues via dysregulated lipid metabolism. The following sections will delve into the molecular mechanisms linking MORC2 dysfunction to CMT2Z pathogenesis.

Mechanisms Underlying MORC2 Dysfunction in CMT2Z Pathogenesis

MORC2 Mutations Induce DNA Damage Accumulation Leading to Neuronal Apoptosis

Specific MORC2 mutations (e.g., p.S87L and p.R252W) reduce ATPase activity, impairing the protein's DNA damage repair function and triggering pathological cascades.

These mutations significantly decrease MORC2 protein synthesis and elevate levels of reactive oxygen species (ROS) and hydroxyl radicals. The accumulation of these free radicals induces DNA damage, leading to apoptosis in regions such as the cerebellum, spinal cord, and quadriceps muscles, thereby driving the onset and progression of CMT2Z. Restoring MORC2 or its ATPase function via gene therapy, or administering hydroxyl radical scavengers (e.g., nicaraven), can markedly reduce ROS levels, suppress apoptosis, and improve neurological and muscular function, offering novel therapeutic strategies for CMT2Z [14].

MORC2 Mutations Cause Overactivation of HUSH Complex-Mediated Transcriptional Silencing

Studies reveal that MORC2 mutations disrupt the normal function of its ATPase module, thereby dysregulating HUSH complex-mediated transcriptional silencing. Mutant MORC2 may aberrantly enhance HUSH complex activation via altered ATP binding and hydrolysis, leading to excessive suppression of specific genes critical for neurodevelopment.

In MORC2-knockout cellular models, mutant MORC2 amplifies the HUSH complex's epigenetic silencing effects, resulting in chromatin disorganization and abnormal repression of neuronal gene expression. A U.S. study demonstrated that mutations such as p. Glu27Lys and p. Arg132Cys most potently enhance HUSH complex activity and correlate with severe neurological phenotypes, including intellectual disability, developmental delay, and microcephaly [15].

Therapeutically, restoring MORC2 ATPase activity may reverse HUSH overactivation. Thus, gene therapy, HUSH complex modulators, or oxidative stress alleviation strategies represent potential in-

terventions. These findings deepen our understanding of MORC2's role in neurological disorders and provide new avenues for treating inherited neuropathies.

Emerging Insights into CMT2Z Pathogenic Mechanisms

A study by Central South University using patient-derived induced pluripotent stem cells (iPSCs) showed that the p.S87L mutation inhibits PI3K/Akt and MAPK/ERK signalling pathways, causing iPSC proliferation defects and G0/G1 phase arrest, potentially underlying SMA-like phenotypes. However, the precise mechanism linking p.S87L to these pathways (e.g., via epigenetic modifications or protein interactions) remains unclear [11].

Another study established a MORC2 p.S87L knock-in mouse model, revealing neuropathic phenotypes through electrophysiological, histological, and behavioural assays. Western blot analyses confirmed neuronal DNA damage and apoptosis as central pathological mechanisms,[16] highlighting the utility of animal models in validating disease mechanisms.

Discussion

By synthesizing global phenotypic data, we demonstrate that CMT2Z is the second most prevalent CMT2 subtype after CMT2A. Its severe and heterogeneous clinical manifestations stem from MORC2's multifunctionality, diverse mutation loci, and high de novo mutation rates. Continued clinical and statistical research on novel MORC2 mutations and their pathogenicity is imperative.

MORC2 mutations disrupt cellular processes such as gene expression regulation, DNA damage repair, and epigenetic silencing, collectively impairing neurological function. Future studies should integrate known MORC2 functions with mutation-specific structural domain effects to elucidate CMT2Z pathogenesis. Notably, no studies have yet explored the role of MORC2 in lipid homeostasis dysregulation in CMT2Z, representing a promising research direction.

CMT2Z pathogenesis involves mutation-specific domain dysfunction: ATPase domain mutations (e.g., p.R252W) primarily impair DNA repair, [14] while S5-transducer or CC1 domain mutations (e.g., p.S87L) disrupt HUSH complex signalling [15]. Structural biology approaches (e.g., cryo-EM analysis of mutant protein conformations) and cellular models are critical for dissecting these genotype-phenotype relationships.

Furthermore, identifying shared pathogenic mechanisms across mutations with overlapping phenotypes is essential. Current studies often focus on individual mutations, but the genetic and phenotypic heterogeneity of CMT2Z demands a broader approach. We propose starting with common phenotypes (e.g., distal weakness, central nervous system involvement) and systematically integrating multi-omics, electrophysiology, and functional assays to uncover convergent pathways. While identifying universal CMT2Z mechanisms remains challenging, this stepwise strategy will advance therapeutic development for this heterogeneous disorder.

Acknowledgement

None.

Conflict of Interest

None.

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