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Review of 40 genes causing congenital myasthenic syndromes

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Congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders characterized by compromised neuromuscular signal transmission due to pathogenic germline variants in genes expressed at the neuromuscular junction (NMJ). A total of 40 genes have been reported in CMS (*AGRN, ALG14, ALG2, CHAT, CHD8, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, COL13A1, COLQ, DES, DOK7, DPAGT1, GFPT1, GMPPB, LAMA5, LAMB2, LRP4, MACF1, MUSK, MYO9A, PLEC, PREPL, PTPN11, PURA, RAPSN, RPH3A, SCN4A, SLC18A3, SLC25A1, SLC5A7, SNAP25, SYT2, TEFM, TOR1AIP1, UNC13A, UNC50* and *VAMP1*). The 40 genes are putatively classified into 13 subtypes by pathomechanical, clinical, and therapeutic features. A unique feature shared by recently identified genes is that CMS is concomitantly recognized in other mostly severer diseases. For example, four recently identified genes exhibit the following phenotypes: *PURA*-CMS, developmental delay; *TEFM*-CMS, mitochondrial disease; *PTPN11*-CMS, Noonan syndrome/Leopard syndrome; and *DES*-CMS, desmin myopathy. Conversely, these diseases are not always associated with CMS, although genetic and/or environmental factors that determine the involvement of the NMJ remain to be identified. In this review, particular emphasis will be placed on five recently identified genes (*MACF1, TEFM, PTPN11, DES* and *UNC50*).

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INTRODUCTION

CMS are caused by pathogenic germline variants in genes expressed at the neuromuscular junction (NMJ), and are characterized by defective neuromuscular signal transduction [1, 2]. Pathogenic variants have been identified in 40 genes (*AGRN, ALG14, ALG2, CHAT, CHD8, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, COL13A1, COLQ, DES, DOK7, DPAGT1, GFPT1, GMPPB, LAMA5, LAMB2, LRP4, MACF1, MUSK, MYO9A, PLEC, PREPL, PTPN11, PURA, RAPSN, RPH3A, SCN4A, SLC18A3, SLC25A1, SLC5A7, SNAP25, SYT2, TEFM, TOR1AIP1, UNC13A, UNC50* and *VAMP1*) (Fig. 1). The causative genes have been classified into three categories of presynaptic, synaptic, and postsynaptic CMS. To delineate clinical, pathomechanical, and therapeutic features of CMS, we classified the 40 genes into 13 subtypes (Tables 1 and 2). We extensively reviewed 35 genes causing CMS in 2023 [1]. In addition to the epidemiology, inheritance, and therapeutic features of CMS, five recently identified genes in CMS (*MACF1, TEFM, PTPN11, DES* and *UNC50*) will be introduced in detail in this review.

EPIDEMIOLOGY

The prevalences of CMS per million in total population are 1.8 (18/10,000,000) in Brazil [3], 1.8 (64/35,500,000) in Spain [4], 3.1 (28/9,000,000) in Austria [5], and 3.2 (37/11,900,000) in Belgium [6], which gives rise to the weighted average of 2.2 per million in total population. Similarly, the prevalences of CMS per million under age 18 years are 9.2 (123/13,900,000) in UK [7], 22.2 (8/360,000) in Slovenia [8] and 10.5 (28/2,670,000) in Austria [5], and the weighted average becomes 9.7 per million under age 18 years.

INHERITANCE

All except for the following five forms of CMS are caused by loss-of-function variants with autosomal recessive inheritance (Table 2). Autosomal dominant inheritance or hemiallelic de novo variant is observed in slow-channel CMS (SCCMS) [1], *PURA*-CMS [9], *PTPN11*-CMS [10], *SNAP25*-CMS [11, 12] and some [13–15] but not all [16–18] patients of *SYT2*-CMS. SCCMS is caused by a missense variant that prolongs the channel openings of acetylcholine receptors (AChRs), and 50% abnormal AChRs are sufficient to cause SCCMS [1]. *PURA*-CMS and *PTPN11*-CMS are associated with developmental delay and are likely to be caused by loss-of-function of *PURA* [9] and gain-of-function of *PTPN11* [10], respectively. Both *SNAP25*-CMS [11, 12] and *SYT2*-CMS [13–18] show LEMS-like CMS, and are likely to be caused by dominant negative effects.

THERAPEUTIC FEATURES

Therapeutic agents for CMS include cholinesterase inhibitors (ChEIs) (pyridostigmine and neostigmine), β-adrenergic agents (ephedrine, salbutamol, and albuterol), amifampridine (3,4-diaminopyridine), quinidine, fluoxetine, and acetazolamide (Table 2) [19, 20].

ChEIs block both acetylcholinesterase and butyrylcholinesterase, and prolong the dwell time of acetylcholine released from the nerve terminal, thereby make acetylcholine receptor open for a prolonged time. ChEIs are effective in most but not all forms of CMS. ChEIs are contraindicated for *COLQ*-CMS [21–23] and *LAMB2*-CMS [24], because respiratory arrest may occur in some patients. Similarly, ChEIs are ineffective or worsen symptoms in patients with SCCMS, *AGRN*-CMS, *LRP4*-CMS and *MUSK*-CMS [25–27]. The reason for the

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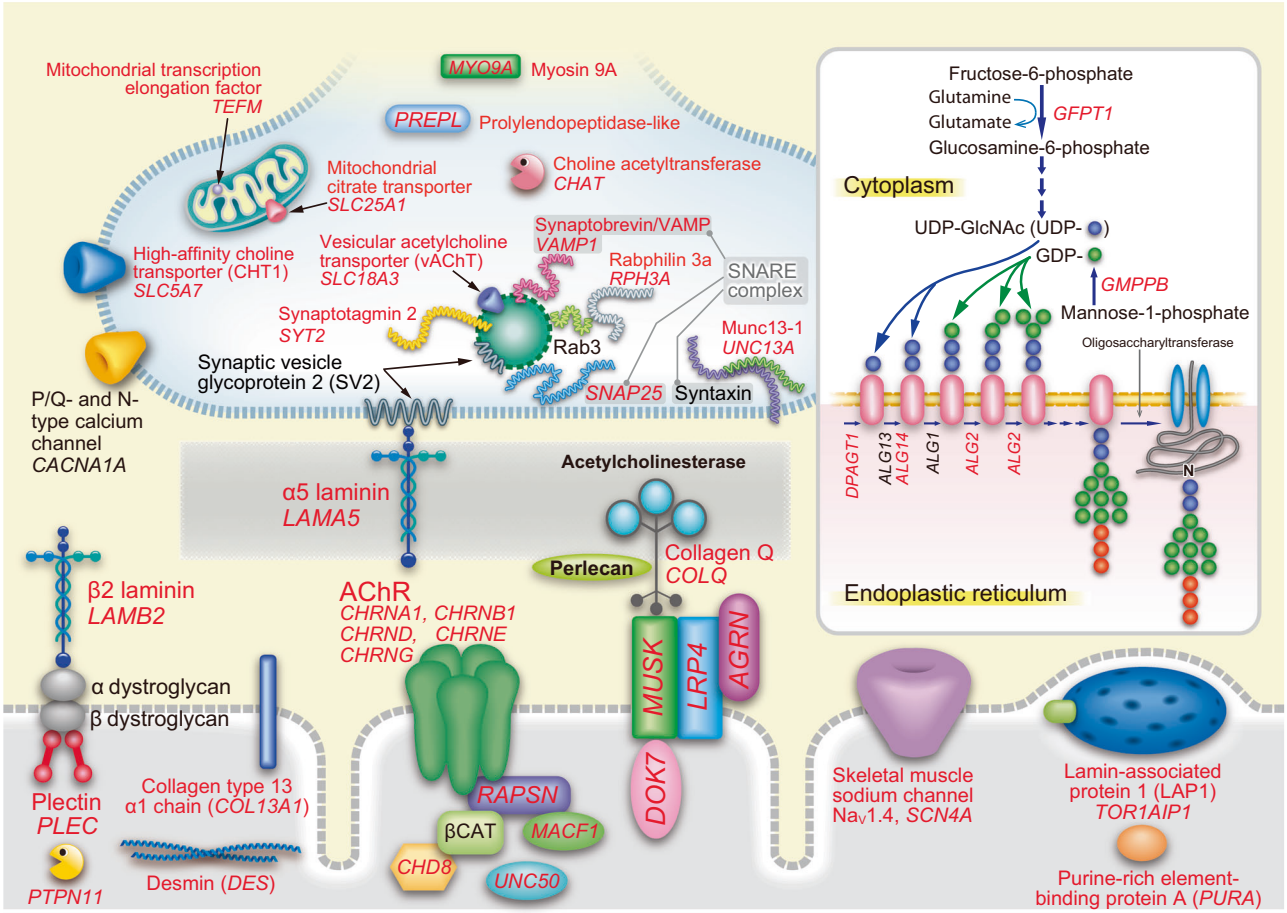

Fig. 1 Schematic of 40 genes (red letters) causing congenital myasthenic syndromes. Five representative groups of gene products that cooperatively work at the NMJ and are compromised in CMS are explained below. First, adult AChR is comprised of α, β, δ and ε subunits encoded by *CHRNA1*, *CHRNB1*, *CHRND* and *CHRNE*, respectively. Gene products of *RAPSN*, *CHD8* and *MACF1* make subsynaptic structural network on which AChRs are clustered. UNC50 (*UNC50*) is essential for trafficking AChR. Defects in these genes cause endplate AChR deficiency (subtype 1). Second, agrin (*AGRN*) released from the motor nerve terminal binds to LRP4 (*LRP4*) at the motor endplate, and triggers MuSK (*MUSK*) phosphorylation, which is enhanced by cytoplasmic adaptor protein DOK7 (*DOK7*). Defects in these genes compromise AChR clustering (subtype 6). Third, choline generated by hydrolysis of acetylcholine by acetylcholinesterase in the synaptic space is taken up by high-affinity choline transporter (CHT1. *SLC5A7*) at the motor nerve terminal. Acetylcholine is resynthesized from choline by choline acetyl transferase (*CHAT*) and is incorporated into the synaptic vesicle by vesicular acetylcholine transporter (vAChT, *SLC18A3*). Defects in these genes compromise recycling of acetylcholine (subtype 8). Fourth, the action potential that reached the motor nerve terminal opens P/Q- and N-type calcium channels. Ca^{2+} ions entered in the nerve terminal bind to synaptotagmin 2 (*SYT2*) and activate the SNARE complex comprised of synaptobrevin/VAMP (*VAMP1*), SNAP25 (*SNAP25*), and syntaxin. Rabphilin 3a (*RPH3A*), α5 laminin (*LAMA5*), and Munc13-1 (*UNC13A*) are SNARE-associated proteins that play pivotal roles in the release of the synaptic vesicles. Defects in these genes cause LEMS-like CMS (subtype 9). Fifth, GFPT1 (*GFPT1*) is the rate limiting enzyme to generate UDP-GlcNAc that is required for N- and O-linked glycosylation of glycoproteins, as well as for making glycosaminoglycans and glycolipids. DPAGT1 (*DPAGT1*), ALG14 (*ALG14*) and ALG2 (*ALG2*) are enzymes in the N-glycosylation pathway. GMPPB (*GMPPB*) generates GDP-mannose, a major mannosyl donor for mannose-containing polymers. Defects in these genes cause glycosylation-deficient CMS (subtype 10)

lack of the effects of ChEIs in CMS associated with defective AChR clustering (*AGRN*, *LRP4*, *MUSK* and *DOK7*) remains unknown.

The sympathetic nerve directly innervate the NMJ, and sympathomimetics ameliorates electrophysiological and morphological deficits of the NMJ induced by sympathectomy in a mouse model of CMS [28]. Similarly, adrenaline, but not noradrenaline, increases the action potential-elicited Ca^{2+} entry into the motor nerve terminal and increases both spontaneous and evoked acetylcholine release [29]. The positive effect of natural agonist adrenaline is reproduced only by β_2-adranergic agonist, fenoterol, but not by α_1-, α_2-, or β_1-adranergic agonist [29]. In contrast to ChEIs, β-adrenergic agents are effective in most forms of CMS including SCCMS and *COLQ*-CMS, in which excessive openings of AChRs compromise the NMJ signal transmission [26]. Although some patients do not respond to β-adrenergic agents, no patients worsened with β-adrenergic agents. Especially, β-adrenergic agents are effective for CMS associated with defective AChR clustering (*AGRN*, *LRP4*, *MUSK* and *DOK7*). Amifampridine, a blocker of the voltage-gated potassium channel at the nerve terminal, is another commonly used drug for CMS. Amifampridine is also effective in many forms of CMS, but worsening of symptoms is observed in some patients with *AGRN*-CMS and *DOK7*-CMS [26]. Quinidine [30, 31] and fluoxetine [32] block AChR openings and ameliorate SCCMS. A marked effect of fluoxetine was reported in a case of *COLQ*-CMS [33]. Acetazolamide was effective in two patients of *SCN4A*-CMS [34, 35], but was not in another *SCN4A*-CMS [36].

MACF1-CMS IN THE SUBTYPE OF 'ENDPLATE ACETYLCHOLINE RECEPTOR DEFICIENCY'

Screening for rapsyn-dependent AChR-binding molecules detected MACF1 (microtubule-actin cross-linking factor 1) that

Table 1. Thirteen subtypes of CMS

	CMS subtype	Genes
1	Endplate AChR deficiency	*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *RAPSN*, *CHD8*, *MACF1*
2	CMS with arthrogryposis multiplex congenita (AMC)	*CHRNA1*, *CHRND*, *CHRNG*, *MUSK*, *RAPSN*, *DOK7*, *SLC18A3*, *UNC50*
3	Slow- and fast-channel CMS (SCCMS and FCCMS)	*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*
4	Synaptic CMS	*COLQ*, *LAMB2*, *COL13A1*
5	Sodium channel CMS	*SCN4A*
6	Defective AChR clustering	*AGRN*, *LRP4*, *MUSK*, *DOK7*
7	CMS caused by defective structural molecule at the NMJ	*PLEC*, *DES*
8	CMS caused by defective recycling of acetylcholine	*CHAT*, *SLC18A3*, *SLC5A7*, *PREPL*
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*SYT2*, *SNAP25*, *VAMP1*, *UNC13A*, *RPH3A*, *LAMA5*
10	Glycosylation-deficient CMS	*GFPT1*, *DPAGT1*, *ALG2*, *ALG14*, *GMPPB*
11	CMS caused by defective nerve terminal formation	*MYO9A*, *SLC25A1*, *TEFM*
12	CMS caused by defective nuclear membrane protein	*TOR1AIP1*
13	CMS associated with developmental disorders	*PURA*, *PTPN11*

Genes that are specifically introduced in this review are underlined

carries binding sites for microtubules and action [37]. MACF1 links rapsyn to microtubule-associated proteins including end-binding protein 1 (EB1) and microtubule-associated protein 1b (MAP1b), as well as to actin-associated protein, vinculin [37]. MACF1 is essential for the structural integrity, functional maturation, and long-term maintenance of the NMJ.

In two CMS patients in Serbia and India, recessive missense variants were identified in *MACF1* [37]. Both patients showed decremental response to repetitive nerve stimulation. The Indian patient showed late-onset fatigable limb-girdle muscle weakness without ophthalmoparesis, and responded well to cholinesterase inhibitors and salbutamol [37]. In 197 pedigrees with CMS in India in another report, a patient with late-onset limb-girdle CMS was homozygous for a missense variant in *MACF1* [27].

De novo heterozygous variants in *MACF1* were previously reported in nine patients with lissencephaly 9 with complex brainstem malformation (LIS9) (OMIM #618325) [38]. In LIS9, heterozygous pathogenic missense or inframe variants were observed the GAR domain, and a dominant negative effect was speculated [38]. In contrast, in three patients with *MACF1*-CMS, homozygous or compound homozygous pathogenic variants were observed either in the plakin domain or the spectrin repeats [27, 37]. Thus, affected domains may determine the phenotype and heredity.

Although lack of ophthalmoparesis is unusual in the subtype of 'endplate AChR deficiency', *MACF1*-CMS is classified into 'endplate AChR deficiency', in which pathogenic variants are also present in *CHRNA1, CHRNB1, CHRND, CHRNE*, *RAPSN* and *CHD8* encoding chromodomain helicase DNA-binding protein 8 (Tables 1 and 2).

TEFM-CMS IN THE SUBTYPE OF 'CMS CAUSED BY DEFECTIVE NERVE TERMINAL FORMATION'

TEFM (transcription elongation factor, mitochondrial) is essential for mitochondrial DNA transcription by mitochondrial RNA polymerase [39]. Knockout of *Tefm* in zebrafish showed defective NMJ structures and defective mitochondrial transcription [40]. Especially, synaptic vesicles at the nerve terminal were markedly decreased in *Tefm*-knockout zebrafish.

In seven patients in five families with mitochondrial myopathy, eight recessive pathogenic variants were identified in *TEFM* [40]. Three patients showed fatigable muscle weakness, and one patient showed decremental response to repetitive nerve stimulation. Two patients were treated with salbutamol with favorable responses. The other patients variably showed lactic acidosis, epilepsy, developmental delay, and motor ataxia, which are characteristic of mitochondrial diseases. In biopsied skeletal muscle and primary skin fibroblasts, marked reduction of the transcription of the H and L strands of mitochondrial DNA was observed [40]. The protein levels of mitochondrial electron transport complex proteins were markedly decreased, but mitochondrial outer membrane protein TOMM20 as well as the number of mitochondria were preserved. Another report showed that two siblings were homozygous for a missense variant in *TEFM* [27]. They showed fatigable limb and ocular muscle weakness along with epilepsy and ataxia, and abnormal decrement on repetitive nerve stimulation. They also showed elevated lactate and decreased mitochondrial electron transport chain complexes I and IV in muscle biopsy. Pathogenic variants in *TEFM* have not been reported in any other diseases.

TEFM-CMS is classified into 'CMS caused by defective nerve terminal formation', in which pathogenic variants are also observed in *MYO9A* encoding myosin 9A and *SLC25A1* encoding mitochondrial tricarboxylate transporter [41] (Tables 1 and 2). The gene product of *SLC25A1* shuttles citrate and malate between mitochondria and cytoplasm. The nerve terminal is rich in mitochondria due to high energy demand required for the recycling of acetylcholine and the repeated releases of synaptic vesicles. Based on the presence of *TEFM*-CMS and *SLC25A1*-CMS, mitochondrial CMS was proposed [42]. Mitochondrial CMS is an attractive idea because of the essential roles of mitochondrial energy production at the NMJ. However, most patients with mitochondrial disease do not exhibit defects in the NMJ signal transmission, and genetic and mechanistic factors that affect the NMJ signal transmission remain unelucidated. In addition, *MYO9A*-CMS that shows defective nerve terminal formation fits well with *SLC25A1*-CMS. We thus classified *MYO9A*-CMS, *SLC25A1*-CMS and *TEFM*-CMS into the subtype of 'defective nerve terminal formation'.

PTPN11-CMS IN THE SUBTYPE OF 'CMS ASSOCIATED WITH DEVELOPMENTAL DISORDERS'

PTPN11 (protein-tyrosine phosphatase, nonreceptor type 11) encodes SHP-2 (src homology region 2-domain phosphatase-2). SHP-2 is a ubiquitously expressed signaling molecule especially in the RAS/MAPK pathway, and plays essential roles in cell proliferation, differentiation, migration, and apoptosis [43].

In four patients with Noonan/Leopard syndrome with muscle weakness, heterozygous *PTPN11* variants were observed [10]. Three showed fatigability and bulbar signs. One showed delayed motor milestones. Two out of three who were examined for

Table 2. OMIM, inheritance, and therapies of each gene in each CMS subtype

	CMS Subtype	Gene[a]	OMIM[b]	Inheritance[c]	Drugs						
					Cholinesterase inhibitors	Ephedrine	Salbutamol (albuterol)	Amifampridine	Quinidine	Fluoxetine	Acetazolamide
1	Endplate AChR deficiency	*CHRNA1*		AR	effective	effective	effective	effective			
1	Endplate AChR deficiency	*CHRNB1*	CMS2C	AR	effective	effective	effective	effective			
1	Endplate AChR deficiency	*CHRND*	CMS3C	AR	effective	effective	effective	effective			
1	Endplate AChR deficiency	*CHRNE*	CMS4C	AR	effective	effective	effective	effective			
1	Endplate AChR deficiency	*RAPSN*	CMS11	AR	effective	effective	effective	effective			
1	Endplate AChR deficiency	*CHD8*		AR	ineffective		ineffective	markedly effective			
1	Endplate AChR deficiency	*MACF1*		AR	effective		effective				
2	CMS with arthrogryposis multiplex congenita	*AGRN*		AR							
2	CMS with arthrogryposis multiplex congenita	*CHRNA1*		AR							
2	CMS with arthrogryposis multiplex congenita	*CHRNB1*		AR							
2	CMS with arthrogryposis multiplex congenita	*CHRND*		AR							
2	CMS with arthrogryposis multiplex congenita (Escobar syndrome)	*CHRNG*		AR							
2	CMS with arthrogryposis multiplex congenita	*DOK7*		AR							
2	CMS with arthrogryposis multiplex congenita	*MUSK*		AR							
2	CMS with arthrogryposis multiplex congenita	*MYO9A*		AR							
2	CMS with arthrogryposis multiplex congenita	*RAPSN*		AR							
2	CMS with arthrogryposis multiplex congenita	*SLC18A3*		AR							
2	CMS with arthrogryposis multiplex congenita	*SLC5A7*		AR							

Table 2. continued

	CMS Subtype	Gene[a]	OMIM[b]	Inheritance[c]	Drugs						
					Cholinesterase inhibitors	Ephedrine	Salbutamol (albuterol)	Amifampridine	Quinidine	Fluoxetine	Acetazolamide
2	CMS with arthrogryposis multiplex congenita	*SNAP25*		AR							
2	CMS with arthrogryposis multiplex congenita	*UNC50*		AR							
3	SCCMS	*CHRNA1*	CMS1A	AD	Worsening or ineffective [79], but effective in a patient [80]	Mostly ineffective, but effective in a patient [79]		Mostly ineffective [79], but effective in a patient [80]	effective	effective	
3	SCCMS	*CHRNB1*	CMS2A	AD	Worsening or ineffective				effective	effective	
3	SCCMS	*CHRND*	CMS3A	AD	Worsening or ineffective				effective	effective	
3	SCCMS	*CHRNE*	CMS4A	AD/AR	Worsening or ineffective				effective	effective	
3	FCCMS	*CHRNA1*	CMS1B	AR	effective	effective	effective	effective			
3	FCCMS	*CHRNB1*		AR	effective	effective	effective	effective			
3	FCCMS	*CHRND*	CMS3B	AR	effective	effective	effective	effective			
3	FCCMS	*CHRNE*	CMS4B	AR	effective	effective	effective	effective			
4	Synaptic CMS (endplate acetylcholinesterase deficiency)	*COLQ*	CMS5	AR	contraindication, but effective in 4 patients [81]	effective	effective			effective in a report [33]	
4	Synaptic CMS	*LAMB2*		AR	contraindication	effective					
4	Synaptic CMS	*COL13A1*	CMS19	AR	ineffective		effective	effective			
5	Sodium channel CMS	*SCN4A*	CMS16	AR	Effective, ineffective, or marked adverse effects		Slightly effective				effective or ineffective
6	Defective AChR clustering	*AGRN*	CMS8	AR	Ineffective or mildly effective	effective	effective	ineffective or slightly effective			
6	Defective AChR clustering	*MUSK*	CMS9	AR	Ineffective or worsened		effective	effective			
6	Defective AChR clustering	*LRP4*	CMS17	AR	worsened						
6	Defective AChR clustering	*DOK7*	CMS10	AR	Ineffective or worsening	effective	effective	effective in a report [82]		effective in a patient [83]	
7	CMS caused by defective structural molecules	*PLEC*		AR	effective or ineffective		effective in four patients [84]	effective or ineffective			
7	CMS caused by defective structural molecules	*DES*		AR	effective		effective				

Table 2. continued

	CMS Subtype	Gene[a]	OMIM[b]	Inheritance[c]	Drugs						
					Cholinesterase inhibitors	Ephedrine	Salbutamol (albuterol)	Amifampridine	Quinidine	Fluoxetine	Acetazolamide
8	CMS caused by defective recycling of acetylcholine	*CHAT*	CMS6	AR	effective			effective			
8	CMS caused by defective recycling of acetylcholine	*SLC18A3*	CMS21	AR	effective	effective		effective			
8	CMS caused by defective recycling of acetylcholine	*SLC5A7*	CMS20	AR	effective	effective		ineffective			
8	CMS caused by defective recycling of acetylcholine	*PREPL*	CMS22	AR	effective						
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*SYT2*	CMS7A/7B	AD/AR	effective		effective	effective			
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*SNAP25*		AD	ineffective		effective				
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*UNC13A*		AR	minimally effective			minimally effective			
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*VAMP1*	CMS25	AR	effective						
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*RPH3A*		AR			effective				
9	Lambert-Eaton myasthenic syndrome (LEMS)-like CMS	*LAMA5*		AR	effective			effective			
10	Glycosylation-deficient CMS	*GFPT1*	CMS12	AR	effective		effective				
10	Glycosylation-deficient CMS	*DPAGT1*	CMS13	AR	effective		effective	effective			
10	Glycosylation-deficient CMS	*ALG2*	CMS14	AR	effective or ineffective		effective	effective			
10	Glycosylation-deficient CMS	*ALG14*	CMS15	AR	effective						
10	Glycosylation-deficient CMS	*GMPPB*		AR	effective		effective				
11	CMS caused by defective nerve terminal formation	*MYO9A*	CMS24	AR	effective			effective			
11	CMS caused by defective nerve terminal formation	*SLC25A1*	CMS23	AR	ineffective			ineffective			
11	CMS caused by defective nerve terminal formation	*TEFM*		AR			effective				

Table 2. continued

	CMS Subtype	Gene[a]	OMIM[b]	Inheritance[c]	Drugs						
					Cholinesterase inhibitors	Ephedrine	Salbutamol (albuterol)	Amifampridine	Quinidine	Fluoxetine	Acetazolamide
12	CMS caused by defective nuclear membrane protein	*TOR1AIP1*		AR	effective		no additional effect				
13	CMS associated with developmental disorders	*PURA*		AD	ineffective in a patient [9], but effective in another patient [85]		effective in a patient [9]				
13	CMS associated with developmental disorders	*PTPN11*		AD	effective in a patient, but not in two other patients [10]		effective				

[a]Genes that are specifically introduced in this review are underlined
[b]OMIM entries with CMS numbers are indicated
[c]*AD* autosomal dominant, *AR* autosomal recessive

repetitive nerve stimulation showed decremental responses. Pyridostigmine was effective in a patient but not in two other patients. Salbutamol was effective in a single patient. Patients with Noonan and Leopard syndrome show variable degrees of muscle weakness, but the ratio of the patients exhibiting CMS symptoms remains unclear.

Pathogenic variants in *PTPN11* have been reported in Noonan syndrome [43] and Leopard syndrome [44]. Noonan syndrome is an autosomal dominant disorder characterized by short stature, hypertelorism, mild mental retardation, skeletal malformation, and congenital heart defects [45]. Sixteen causative genes have been reported in Noonan syndrome (OMIM PS163950), and heterozygous *PTPN11* variants are responsible for ~50% of the patients. Clinical features of Leopard syndrome are overlapping with those of Noonan syndrome. Leopard is an acronym for Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness [46]. Leopard syndrome is also called 'Noonan syndrome with multiple lentigines'. Three causative genes (*PTPN11*, *RAF1*, and *BRAF*) have been reported in Leopard syndrome (OMIM PS151100), and *PTPN11* variants constitute most of them. Factors that drive the expression of CMS phenotypes remain unknown.

PTPN11-CMS is classified into 'CMS associated with developmental disorders', in which pathogenic variants also are observed in *PURA* encoding purine-rich element-binding protein A (Tables 1 and 2).

DES-CMS IN THE SUBTYPE OF 'CMS CAUSED BY DEFECTIVE STRUCTURAL MOLECULE AT THE NMJ'

Desmin encoded by *DES* is a muscle-specific intermediate filament protein [47]. Desmin forms a cytoplasmic scaffold in skeletal, cardiac, and smooth muscles.

In three unrelated patients with fatigable muscle weakness, ptosis, and ophthalmoparesis without cardiomyopathy, a homozygous intronic variant in *DES* (NM_001927.4: c.1023 + 5 G > A) was observed [27, 48]. The patients showed decremental responses to repetitive nerve stimulation. Pyridostigmine was effective in two patients, and salbutamol was effective in one patient. The intronic variant caused leaky retention of complete intron 5 of *DES*, and the protein levels of desmin in skeletal muscle were reduced to 60–75% of normal. There was another report of *DES*-CMS in 2016, in which two cousins with homozygous truncating *DES* variants showed fatigable limb and facial muscle weakness, ptosis, and severe ophthalmoparesis [49]. Decremental responses to repetitive nerve stimulation were observed in both patients. Salbutamol was effective in both patients.

Pathogenic variants in *DES* have been reported in desmin-related myopathy (DRM) that is characterized by myofibrillar degeneration with desmin-positive aggregates [50]. DRM is also referred to as myofibrillar myopathy [51]. Heterozygous missense variants in *DES* in DRD show dominant negative effects and generate abnormal desmin aggregates [50]. Homozygous *DES* variants are rare and are reported in 19 DRM patients [52]. Fifteen patients carried truncating *DES* variants and four were homozygous for missense variants. In all the patients, loss-of-function mechanisms were speculated. Lack of dominant negative effect and mild degrees of desmin reduction in patients with *DES*-CMS may account for the CMS phenotype.

DES-CMS is classified into 'CMS caused by defective structural molecule at the NMJ', in which pathogenic variants are also observed in *PLEC* encoding plectin (Tables 1 and 2).

UNC50-CMS IN THE SUBTYPE OF 'CMS WITH ARTHROGRYPOSIS MULTIPLEX CONGENITA (AMC)'

UNC50 (Unc-50 inner nuclear membrane RNA-binding protein) is a transmembrane protein in the Golgi apparatus. *UNC50* was

identified by screening for a mammalian homolog of *unc-50* in *C. elegans*, and found to be an essential molecule for trafficking AChR [53, 54].

In a stillborn baby with arthrogryposis multiplex congenita (AMC), a homozygous frameshift variant was detected in *UNC50* [55]. *C. elegans* carrying an orthologous mutant showed a marked decrease in the surface expression of muscle AChR [55]. Similarly, in five babies in two families, three resulted in stillbirth or neonatal death, one pregnancy was terminated, and one baby died in early infancy [56]. Two genetically identified babies were homozygous for an intronic deletion in the polypyrimidine tract that activated a cryptic 3′ splice site in *UNC50* causing a frameshift. Although electrophysiological or morphological studies of the NMJ were not available due to early neonatal death, the babies were reported to be a subtype of CMS [56].

AMC is a key symptom of multiple pterygium syndrome (MPS), which is characterized by pterygia across multiple joints. MPS is divided into the lethal variant (LMPS, OMIM #253290) and the nonlethal variant (Escobar syndrome, OMIM #265000). Similarly, AMC is a key feature of fetal akinesia deformation sequence (FADS, OMIM #618388, #618389, #618393), which is characterized by multiple deformities including pulmonary hypoplasia, craniofacial anomalies, and hypoplastic dermal ridges. AMC/LMPS/Escovar/FADS are caused by reduced fetal movements. Although more than 320 causative genes have been identified in AMC/LMPS/Escobar/FADS, AMC/LMPS/Escobar/FADS are frequently caused by pathogenic variants affecting the NMJ signal transmission. Escobar syndrome is exclusively caused by pathogenic variants in *CHRNG* [57–60]. *CHRNG* encodes the fetal γ subunit of AChR, and is expressed only in embryos. Defects in AChR γ subunit affect fetal movements, but not neonatal or later movements. Thus, Escovar syndrome is mostly benign and nonprogressive.

AMC/LMPS/FADS are also caused by pathogenic variants in *AGRN* [56, 61], *CHRNA1* [62, 63], *CHRNB1* [64–66], *CHRND* [62, 67], *DOK7* [68, 69], *MUSK* [70–73], *MYO9A* [74], *RAPSN* [62, 75, 76], *SLC18A3* [77], *SLC5A7* [78] and *SNAP25* [11] (Tables 1 and 2). These genes also cause other subtypes of CMS, but pathogenic variants in AMC/LMPS/FADS are more deleterious than those in the other subtypes of CMS.

CONCLUSIONS

CMS are caused by pathogenic germline variants in 40 genes, which are classified into 13 subtypes according to clinical, mechanical, and therapeutic features. Concomitant recognition of myasthenic features in other mostly severer diseases facilitated the identification of novel genes in recent years. Prevalences of CMS in total population and under 18 years of age are 2.2 and 9.7 per million, respectively. Five forms of CMS (SCCMS, *PURA*-CMS, *PTPN11*-CMS, *SNAP25*-CMS and *SYT2*-CMS) are caused by autosomal dominant variant, and the others are by autosomal recessive variants.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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