

Clinical and genetic spectrum of congenital myasthenic syndromes in Palestine: a retrospective cohort of 35 genetically confirmed patients

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Abstract

Background

Congenital myasthenic syndromes (CMS) are rare inherited disorders of neuromuscular transmission with marked genetic and clinical heterogeneity. Because disease severity, respiratory involvement, and treatment response vary by genotype, molecular diagnosis has direct clinical relevance. The genetic spectrum and clinical burden of CMS in Palestine have not previously been systematically characterized.

Methods

We conducted a retrospective clinical cohort of CMS-associated genetic records identified in Palestine between 2013 and 2026. Prenatal records without postnatal follow-up and records with insufficient clinical documentation were excluded from the clinical analysis. Demographic, genetic, clinical, diagnostic, severity, treatment, and outcome data were extracted from laboratory and clinical records and summarized descriptively using available-case denominators without imputation.

Results

Among 48 genetic records, 35 patients were clinically evaluable. COLQ was the predominant gene in both the overall records (34/48, 70.8%) and the clinical cohort (27/35, 77.1%). The remaining patients had CHRNE, SYT2, CHAT, CHRND, or CHRNB1 variants. Median age at diagnosis was 17 months (interquartile range, 9–39.5); parental consanguinity was documented in 26 patients (74.3%), and 20 (57.1%) had a positive clinical family history. Ptosis occurred in 32/35 patients (91.4%), developmental delay in 25/33 (75.8%), proximal weakness in 24/32 (75.0%), respiratory symptoms in 24/35 (68.6%), and hypotonia in 23/35 (65.7%). Critical-care admission was documented in 21 patients (60.0%), respiratory support in 12/34 (35.3%), and one death occurred. Beta-agonist use was documented in 22/31 patients, predominantly in COLQ-related disease; 19/21 patients with an assessable beta-agonist response had positive reported improvement. Overall clinical improvement was documented in 21/24 patients with confirmed treatment exposure and an assessable outcome.

Conclusions

To our knowledge, this is the first systematic clinical and genetic characterization of CMS in Palestine. The cohort showed marked COLQ predominance, substantial phenotypic heterogeneity, and a considerable respiratory and critical-care burden. The alignment between genotype, treatment selection, and reported clinical improvement supports timely molecular diagnosis, although the retrospective design precludes conclusions about comparative treatment efficacy.

Introduction

Congenital myasthenic syndromes (CMS) comprise a genetically and clinically heterogeneous group of inherited disorders caused by impaired neuromuscular transmission [1, 2]. Although rare, they are clinically important because many subtypes are potentially treatable, whereas delayed recognition may expose patients to recurrent respiratory deterioration, prolonged weakness, feeding difficulties, and prolonged or potentially avoidable supportive interventions [1–3]. Clinical presentation is highly variable and may include fatigable muscle weakness, ptosis, bulbar dysfunction, hypotonia, limb-girdle weakness, episodic apnea, or respiratory crises. Age at onset, distribution of weakness, disease severity, and response to treatment differ substantially according to the underlying molecular defect [1–3]. This variability may obscure the diagnosis, particularly when the phenotype resembles congenital myopathy, muscular dystrophy, motor neuron disease, mitochondrial disease, or seronegative autoimmune myasthenia [1–3].

More than 30 genes have been implicated in CMS, and the associated disorders may be classified according to the site or mechanism of neuromuscular-junction dysfunction as presynaptic, synaptic or basal-lamina-associated, postsynaptic, glycosylation-related, defects in endplate development and maintenance, or miscellaneous mechanisms [1, 2]. Postsynaptic disorders include primary acetylcholine receptor deficiency, acetylcholine receptor kinetic abnormalities, and defects in receptor clustering. CHRNE variants, for example, may result in acetylcholine receptor deficiency, altered channel kinetics, or a combination of both, whereas RAPSN variants interfere with receptor clustering [1, 4, 5]. A principal synaptic subtype is endplate acetylcholinesterase deficiency caused by COLQ variants, which impair the anchoring of acetylcholinesterase within the synaptic basal lamina [6, 7]. Presynaptic forms may result from impaired acetylcholine synthesis, synaptic-vesicle release, or axonal transport [1, 2, 8]; SYT2 variants, for instance, disrupt calcium-dependent synaptic-vesicle exocytosis [9, 10]. Additional CMS subtypes arise from defects in protein glycosylation and post-translational processing at the neuromuscular junction [1, 2]. This molecular heterogeneity has direct clinical relevance because genetic subtype influences both the expected phenotype and the selection of therapy [1–3].

The distribution of CMS-associated genes differs considerably across populations. CHRNE, RAPSN, and COLQ are among the genes most frequently reported in international CMS cohorts, but their relative contribution varies according to ancestry, consanguinity, founder variants, referral patterns, and access to genetic testing [1, 11, 12]. Population-based estimates remain scarce and inconsistent, with reported prevalence of approximately 1.8 per million in Spain and southern Brazil [12, 13], compared with 9.2 per million children in the United Kingdom [14] and 22.2 per million children in Slovenia [15]. These estimates may not capture the full disease burden because CMS can remain unrecognized in patients with atypical presentations or limited access to neuromuscular and genetic services [1–3].

To our knowledge, no previous study has provided a systematic clinical and genetic characterization of CMS in Palestine. Consequently, the local distribution of causative genes, the spectrum of clinical manifestations, the burden of respiratory and supportive-care requirements, and patterns of genotype-

directed treatment remain poorly defined. This gap is particularly relevant in a setting where familial clustering of recessive disorders may coexist with fragmented access to specialized neuromuscular assessment, molecular testing, and longitudinal follow-up.

The present study therefore assembled a substantial cohort of genetically confirmed patients to characterize both the dominant genetic pattern and the clinical heterogeneity of less common CMS subtypes in Palestine. We aimed to describe the genetic spectrum, clinical phenotype, disease severity, diagnostic investigations, supportive interventions, treatment exposure, reported clinical response, and vital outcomes in this cohort.

Methodology

Study design and setting

We conducted a retrospective clinical cohort of patients with genetically confirmed congenital myasthenic syndrome (CMS) identified in Palestine between 2013 and 2026. The study was carried out through a collaboration between the Faculty of Medicine, Al-Quds University, and the Department of Pediatrics at Al-Makassed Charitable Hospital, Jerusalem. Al-Makassed Charitable Hospital served as the main referral and genetic testing center for most cases, while additional genetically confirmed cases were identified through Al-Istishari Hospital and outpatient clinical services.

The study was designed to describe the clinical phenotype, diagnostic workup, disease severity, and reported treatment response of patients with pathogenic variants in CMS-related genes. Given the predominance of COLQ-related disease in the cohort, patients with COLQ-related CMS were analyzed as the principal clinical subgroup.

Case ascertainment and study population

Patients were identified retrospectively from genetic laboratory reports, hospital records, neurology assessments, admission and discharge records, and available follow-up documentation. Genetic testing had been requested during routine clinical care in patients with clinical features suggestive of CMS and/or a positive family history of a similar neuromuscular disorder.

During the study period, 48 individuals or fetal genetic records with pathogenic variants in CMS-related genes were identified. Thirteen records were excluded from the clinical analysis. Six represented prenatal diagnoses established by chorionic villous sampling in the setting of a positive family history and were followed by pregnancy termination. Seven additional records were excluded because the available clinical documentation was insufficient for reliable extraction of the principal study variables and/or follow-up information was unavailable.

The final clinical cohort included 35 patients with genetically confirmed CMS and sufficient clinical data for analysis. Of these, 27 had COLQ-related CMS, two had CHRNE-related CMS, two had SYT2-related CMS, two had CHAT-related CMS, one had CHRND-related CMS, and one had CHRNB1-related CMS. The full group of 48 genetically positive records was used only to summarize the overall distribution of identified CMS-related genes. Detailed clinical, diagnostic, treatment, and outcome analyses were restricted to the 35 clinically evaluable patients.

Inclusion and exclusion criteria

Patients were included in the clinical analysis if they had a laboratory report documenting a pathogenic variant in a CMS-related gene and available clinical records sufficient to extract the core demographic, phenotypic, diagnostic, and treatment variables.

Records were excluded from the clinical analysis if they represented prenatal diagnoses without postnatal clinical data, or if the available documentation was insufficient to determine the principal study variables. Cases excluded because of inadequate clinical documentation were not included in phenotype, diagnostic-workup, treatment-response, or outcome analyses.

Availability of complete variant notation was not required for inclusion, provided that the original laboratory report documented a pathogenic CMS-related variant and the affected gene could be identified.

Genetic testing

Genetic testing was performed as part of routine diagnostic care. Most tests were conducted at the molecular and genetic laboratory of Al-Makassed Charitable Hospital. Genetic methods included Sanger or targeted direct sequencing, whole-exome sequencing or exome analysis, and single-exome sequencing. In selected cases, genomic amplification of specific gene exons followed by direct sequencing was performed. The testing method and genetic findings were extracted from the available laboratory reports.

For this study, genetic results were used to confirm CMS and classify patients according to the affected gene. Variant-level molecular analysis was not the primary objective of the study. Pathogenic variants were therefore reported as documented in the original laboratory records, and the main analyses were conducted at the gene-group level. Variant nomenclature was not inferred or modified when the exact coding DNA or protein notation was not explicitly stated in the source report.

Data collection

Data were extracted retrospectively from genetic laboratory reports, hospital records, neurology assessments, admission and discharge records, electrophysiological reports, and available follow-up

documentation. A structured data extraction sheet was used to collect demographic, genetic, clinical, diagnostic, treatment, and outcome variables.

Baseline variables included sex, city or governorate, age at diagnosis, family history of CMS or a clinically similar neuromuscular disorder, parental consanguinity, and available familial segregation information.

Age at diagnosis was defined as the age at the first documented diagnosis of CMS in the available medical record. When the first documented diagnosis was established through genetic confirmation, age at genetic confirmation was used. If the age at diagnosis could not be established reliably from the available records, it was recorded as missing. Age at diagnosis was converted into months for analysis. Patients with available diagnostic-age data were also categorized as diagnosed during the neonatal period, infancy, childhood, or adolescence.

Clinical variables included developmental delay, including documented gross motor delay; ptosis and other ocular manifestations; respiratory symptoms; hypotonia; proximal muscle weakness; dysphagia or choking; failure to thrive; constipation; scoliosis; feeding-tube or gastrostomy requirement; need for respiratory support; tracheostomy; ICU admission or shock; cardiac or respiratory arrest; wheelchair use or other mobility assistance; vital status; and age at death when applicable. Other clinically relevant manifestations that were not included among the prespecified variables were retained as descriptive findings.

Diagnostic-workup variables included creatine kinase level, brain MRI, electrophysiological testing, and neuromuscular autoantibody testing when documented. Electrophysiological investigations included conventional EMG, nerve conduction studies, repetitive nerve stimulation, and single-fiber EMG when available. Creatine kinase was recorded quantitatively when a numerical value was available and descriptively as normal or abnormal when only a qualitative interpretation was documented. Autoantibody testing was summarized descriptively and was not required for inclusion, as all included patients had genetically confirmed CMS.

Treatment variables included use of acetylcholinesterase inhibitors or other neuromuscular junction modulators, beta-agonist use, reported response to these treatments, treatment duration, respiratory support during follow-up, ICU admission during follow-up, and subjective or chart-documented clinical improvement.

Definitions

CMS was defined as a compatible clinical phenotype together with a documented pathogenic variant in a CMS-related gene.

Positive clinical family history was defined as a relative with diagnosed CMS or a documented clinically similar congenital neuromuscular disorder. Carrier status alone, or the presence of a homozygous

relative whose clinical status was uncertain, was not considered a positive clinical family history. Such findings were recorded separately as familial segregation information.

Parental consanguinity was defined as documented consanguinity between the patient's parents, including first-cousin relationships or other specified parental relatedness.

Respiratory symptoms included recurrent respiratory infections, respiratory distress, cyanotic episodes, respiratory failure, or other respiratory manifestations attributed clinically to the neuromuscular disorder. Respiratory support included supplemental oxygen, noninvasive ventilatory support, invasive mechanical ventilation, or other documented ventilatory assistance. Tracheostomy status was recorded separately and was not considered evidence of ongoing ventilatory dependence unless respiratory support was explicitly documented.

Failure to thrive was recorded when it was explicitly documented in the medical record or clearly identified by the treating clinical team. Low weight measurements alone were not used to retrospectively assign failure to thrive in the absence of a documented clinical interpretation.

ICU admission, shock, cardiac or respiratory arrest, invasive respiratory support, tracheostomy, gastrostomy, wheelchair use, and death were considered markers of disease severity.

A medication was classified as used only when administration or ongoing treatment was documented. A treatment recommendation or intended treatment plan without confirmation that therapy had been started was not classified as treatment exposure.

Reported treatment response was defined as subjective or chart-documented clinical improvement after treatment, including improvement in daily function, fatigability, ptosis, drooling, muscle strength, gait, swallowing, respiratory stability, or frequency of severe clinical episodes when documented. Responses were categorized as marked or significant improvement, partial improvement, no documented improvement, or not assessable according to the available record.

When two treatments were administered concurrently and their individual effects could not be distinguished, overall clinical improvement was recorded, but treatment-specific response was classified as not separately assessable. Because response assessment was retrospective and was not based on a standardized neuromuscular scale, treatment response was interpreted as reported clinical improvement rather than formal treatment efficacy.

Treatment duration was calculated from the first documented treatment date to the last documented date of continued use when both dates were available. When treatment initiation, continuation, or follow-up dates could not be established reliably, treatment duration was recorded as missing.

Outcomes

The main outcomes were clinical phenotype, disease severity indicators, and reported treatment response among patients with genetically confirmed CMS.

Clinical phenotype outcomes included developmental delay, ptosis, respiratory symptoms, hypotonia, proximal muscle weakness, dysphagia or choking, failure to thrive, constipation, and scoliosis.

Disease severity outcomes included feeding-tube or gastrostomy requirement, need for respiratory support, tracheostomy, ICU admission or shock, cardiac or respiratory arrest, wheelchair use or other mobility assistance, vital status, and age at death when applicable.

Treatment-related outcomes included use of beta-agonists, reported response to beta-agonists, use of acetylcholinesterase inhibitors or other neuromuscular junction modulators, reported response to these agents, overall documented clinical improvement, and treatment duration when available.

Statistical analysis

The analysis was descriptive. Categorical variables were summarized as frequencies and percentages. Continuous variables, including age at diagnosis and treatment duration, were summarized as mean with standard deviation or median with interquartile range according to their distribution and data completeness.

Patients were grouped according to the affected gene. Because all non-COLQ gene groups were small, gene-specific comparisons were descriptive only. No inferential statistical testing was performed, as the study was not powered for formal comparisons between genetic subgroups.

Missing data were not imputed. Each variable was analyzed using available data only, and the denominator was reported when it differed from the total cohort. Variables with substantial missingness or inconsistent documentation were excluded from the principal analysis or summarized descriptively when clinically relevant. Laboratory improvement in creatine kinase was not analyzed as a treatment outcome because follow-up CK measurements were not consistently available.

Ethical considerations

The study was approved by the ethics committee of Al-Quds University before data collection began, approval number 318/REC/2023. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. The requirement for informed consent was waived by the Ethics Committee of Al-Quds University because of the retrospective nature of the study and the use of de-identified clinical data.

All data were handled confidentially. Direct identifiers, including patient names, national identification numbers, contact numbers, hospital IDs, and laboratory IDs, were removed from the analytic dataset and replaced with study-specific codes before analysis.

Results

Cohort ascertainment and genetic distribution

A total of 48 genetic records from individuals or fetuses with pathogenic variants in congenital myasthenic syndrome (CMS)-associated genes were identified between 2013 and 2026. Thirteen records were excluded from the clinical analysis: six represented prenatal diagnoses established by chorionic villus sampling and followed by pregnancy termination, and seven had insufficient clinical documentation and/or unavailable follow-up information. The final clinically evaluable cohort therefore comprised 35 patients (Fig. 1). Across all 48 genetic records, COLQ was the most frequently affected gene (34/48, 70.8%). Among the 35 clinically evaluable patients, 27 (77.1%) had COLQ-related CMS; CHRNE, SYT2, and CHAT accounted for two patients each (5.7% each), while CHRND and CHRNB1 accounted for one patient each (2.9% each). The complete genetic distribution and patient-level genetic characteristics are provided in Fig. 1 and Supplementary Table S1.

Demographic and diagnostic characteristics

The cohort included 18 females (51.4%) and 17 males (48.6%). The median age at diagnosis was 17 months (interquartile range [IQR], 9–39.5 months; range, 0–168 months), and 23 patients (65.7%) were diagnosed during childhood. A positive clinical family history was documented in 20 patients (57.1%), and parental consanguinity in 26 (74.3%). Geographic distribution and genetic testing methods are summarized in Table 1.

Table 1
Demographic, diagnostic, and genetic characteristics of the clinically evaluable CMS cohort

Characteristic	Overall (n = 35)	COLQ (n = 27)	Non-COLQ (n = 8)
Demographic characteristics			
Female sex	18 (51.4%)	13 (48.1%)	5 (62.5%)
Age at diagnosis, median (IQR), months	17 (9–39.5)	14 (8–36)	26.5 (15–54.8)
Age at diagnosis, range, months	0–168	0–168	2–128
Age category at diagnosis			
Neonatal	3 (8.6%)	3 (11.1%)	0 (0.0%)
Infancy	8 (22.9%)	6 (22.2%)	2 (25.0%)
Childhood	23 (65.7%)	17 (63.0%)	6 (75.0%)
Adolescence	1 (2.9%)	1 (3.7%)	0 (0.0%)
Family characteristics			
Positive clinical family history	20 (57.1%)	16 (59.3%)	4 (50.0%)
Parental consanguinity	26 (74.3%)	19 (70.4%)	7 (87.5%)
Geographic distribution			
Jerusalem	13 (37.1%)	11 (40.7%)	2 (25.0%)
Jenin	6 (17.1%)	5 (18.5%)	1 (12.5%)
Nablus	6 (17.1%)	5 (18.5%)	1 (12.5%)
Gaza	5 (14.3%)	3 (11.1%)	2 (25.0%)
Ramallah	4 (11.4%)	2 (7.4%)	2 (25.0%)
Tulkarm	1 (2.9%)	1 (3.7%)	0 (0.0%)
Genetic testing method			
Sanger sequencing	22 (62.9%)	20 (74.1%)	2 (25.0%)
Exome-based sequencing	12 (34.3%)	7 (25.9%)	5 (62.5%)
Targeted direct sequencing	1 (2.9%)	0 (0.0%)	1 (12.5%)
Affected gene distribution			
COLQ	27 (77.1%)	27 (100.0%)	0 (0.0%)
CHRNE	2 (5.7%)	0 (0.0%)	2 (25.0%)

Characteristic	Overall (n = 35)	COLQ (n = 27)	Non-COLQ (n = 8)
Demographic characteristics			
SYT2	2 (5.7%)	0 (0.0%)	2 (25.0%)
CHAT	2 (5.7%)	0 (0.0%)	2 (25.0%)
CHRND	1 (2.9%)	0 (0.0%)	1 (12.5%)
CHRNA1	1 (2.9%)	0 (0.0%)	1 (12.5%)
Notes			
• Data are presented as n (%) unless otherwise indicated.			
• Percentages are calculated using available-case denominators. No baseline variable included in this table had missing data.			
• Non-COLQ includes CHRNE (n = 2), SYT2 (n = 2), CHAT (n = 2), CHRND (n = 1), and CHRNA1 (n = 1).			
• Age categories: neonatal, 0–28 days; infancy, 29 days to < 12 months; childhood, 12 months to < 13 years; adolescence, 13–18 years.			
• Exome-based sequencing includes whole-exome sequencing, exome analysis, and single-exome sequencing.			
• CMS, congenital myasthenic syndrome; IQR, interquartile range.			

Overall clinical phenotype

Ptosis was the most frequent clinical manifestation, affecting 32 of 35 patients (91.4%). Developmental delay was present in 25 of 33 patients with available data (75.8%), proximal muscle weakness in 24 of 32 (75.0%), respiratory symptoms in 24 of 35 (68.6%), and hypotonia in 23 of 35 (65.7%). Dysphagia or choking was documented in 13 of 32 patients (40.6%), failure to thrive in 10 of 35 (28.6%), constipation in four (11.4%), and scoliosis in two (5.7%) (Table 2).

Table 2
Clinical phenotype of the clinically evaluable CMS cohort by affected gene

Clinical feature	Overall (n = 35)	COLQ (n = 27)	CHRNE (n = 2)	SYT2 (n = 2)	CHAT (n = 2)	CHRND (n = 1)	CHRNA1 (n = 1)
Developmental delay	25/33 (75.8%)	22/26 (84.6%)	0/2 (0.0%)	2/2 (100.0%)	1/2 (50.0%)	0/1 (0.0%)	NR
Ptosis	32 (91.4%)	27/27 (100.0%)	2/2 (100.0%)	0/2 (0.0%)	1/2 (50.0%)	1/1 (100.0%)	1/1 (100.0%)
Respiratory symptoms	24 (68.6%)	19/27 (70.4%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/1 (0.0%)	1/1 (100.0%)
Hypotonia	23 (65.7%)	21/27 (77.8%)	0/2 (0.0%)	2/2 (100.0%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Proximal muscle weakness	24/32 (75.0%)	18/25 (72.0%)	2/2 (100.0%)	2/2 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)
Dysphagia or choking	13/32 (40.6%)	8/24 (33.3%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/1 (0.0%)	1/1 (100.0%)
Failure to thrive	10 (28.6%)	6/27 (22.2%)	2/2 (100.0%)	0/2 (0.0%)	1/2 (50.0%)	0/1 (0.0%)	1/1 (100.0%)
Constipation	4 (11.4%)	3/27 (11.1%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
Scoliosis	2 (5.7%)	2/27 (7.4%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)

Notes

• Data are presented as n/N (%) when one or more observations were missing and as n (%) when data were complete.

• NR indicates that the feature could not be reliably assessed from the available record.

• Percentages within individual gene groups are descriptive only; no inferential comparisons were performed because of the small and unequal group sizes.

• Developmental delay was unavailable for 2 patients; proximal muscle weakness and dysphagia/choking were each unavailable for 3 patients.

• CMS, congenital myasthenic syndrome.

Phenotype by affected gene

All 27 patients with COLQ-related CMS had ptosis. Among those with available data, developmental delay occurred in 22 of 26 patients (84.6%), hypotonia in 21 of 27 (77.8%), proximal muscle weakness in 18 of 25 (72.0%), respiratory symptoms in 19 of 27 (70.4%), and dysphagia or choking in eight of 24 (33.3%). The non-COLQ subgroup showed substantial clinical heterogeneity. Both CHRNE-related patients had ptosis, proximal weakness, and failure to thrive, whereas both SYT2-related patients had

developmental delay, respiratory symptoms, hypotonia, proximal weakness, and dysphagia or choking but no ptosis. The two CHAT-related cases differed substantially: one had developmental delay, severe respiratory and bulbar involvement, aspiration-related complications, and a cardiorespiratory arrest; the other had ptosis, lower-limb weakness, muscle wasting, impaired mobility, tracheostomy, and gastrostomy. The CHRND-related patient presented with ptosis, a myopathic facial appearance, and drooling without respiratory symptoms, hypotonia, proximal weakness, or documented dysphagia or choking. The CHRNB1-related patient had neonatal respiratory and feeding difficulties followed by ptosis, proximal weakness, dysphagia, failure to thrive, and constipation. Patient-level characteristics of the non-COLQ subgroup are provided in Supplementary Table S2.

Disease severity and supportive interventions

Twenty-one patients (60.0%) had at least one documented ICU, PICU, or NICU admission. Respiratory-support history was available for 34 patients, of whom 12 (35.3%) had required support at some point. Noninvasive ventilation and invasive mechanical ventilation were each documented in two patients (5.7%), and two patients (5.7%) experienced a cardiac or respiratory arrest. Gastrostomy had been used in three patients (8.6%). One CHAT-related patient required a tracheostomy and wheelchair or other mobility assistance. One death occurred (1/35, 2.9%) in a patient with SYT2-related CMS who died at 5 months of age (Table 3).

Table 3

Disease severity and supportive interventions in the clinically evaluable CMS cohort by affected gene

Severity indicator	Overall (n = 35)	COLQ (n = 27)	CHRNE (n = 2)	SYT2 (n = 2)	CHAT (n = 2)	CHRND (n = 1)	CHRNA1 (n = 1)
Respiratory support	12/34 (35.3%)	8/26 (30.8%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)
Noninvasive ventilation	2 (5.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Invasive mechanical ventilation	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)
ICU/PICU/NICU admission	21 (60.0%)	17 (63.0%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)
Cardiac or respiratory arrest	2 (5.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)
Gastrostomy	3 (8.6%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)
Tracheostomy	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)
Wheelchair or mobility assistance	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)
Death	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Notes

• Data are presented as n/N (%) when one or more observations were missing and as n (%) when data were complete.

• Respiratory support included supplemental oxygen, noninvasive ventilation, or invasive mechanical ventilation documented at any time.

• Respiratory-support history was unavailable for 1 COLQ patient; all other severity indicators were available for all 35 patients.

• ICU/PICU/NICU admission denotes any documented admission to an intensive or neonatal critical-care unit.

• Gastrostomy was coded as present if it had been used at any time, including when subsequently removed.

• Percentages within gene groups are descriptive only; no inferential comparisons were performed.

• CMS, congenital myasthenic syndrome; ICU, intensive care unit; PICU, pediatric intensive care unit; NICU, neonatal intensive care unit.

Diagnostic investigations

Numerical creatine kinase values were available for 11 patients (31.4%), with a median recorded value of 65 (IQR, 51.5–76.9). Brain magnetic resonance imaging status was available for 19 patients, of whom 12 (63.2%) had undergone imaging. Electrophysiological testing status was available for 19 patients, of whom seven (36.8%) had undergone testing. Detailed repetitive nerve stimulation results were available for two patients and single-fiber electromyography results for one. Neuromuscular autoantibody testing status was available for 20 patients, and testing had been performed in two (10.0%). Because investigation selection and documentation were heterogeneous, these findings were summarized descriptively.

Treatment exposure and reported response

Information on acetylcholinesterase inhibitor (AChEI) exposure was available for 28 patients, of whom seven (25.0%) had documented use. Among six AChEI-treated patients with an assessable drug-specific response, five (83.3%) had a positive reported response and one (16.7%) had no documented improvement. In one additional patient receiving concurrent therapy, the AChEI-specific response could not be assessed separately. AChEI therapy was recommended for the CHRNB1-related patient, but administration was not confirmed; this patient was not classified as treated. Beta-agonist exposure was available for 31 patients, of whom 22 (71.0%) had documented use. Among 21 beta-agonist-treated patients with an assessable drug-specific response, 19 (90.5%) had a positive reported response and two (9.5%) had no documented improvement; all 21 assessable beta-agonist responses occurred in the COLQ subgroup. Three patients received concurrent AChEI and beta-agonist therapy. Among patients with confirmed treatment exposure and an assessable overall outcome, 21 of 24 (87.5%) had positive overall clinical improvement. The median treatment duration among patients with confirmed exposure and a valid documented duration was 30 months (IQR, 12–70.5 months; n = 20) (Table 4). These findings represent retrospectively reported clinical responses and were not interpreted as estimates of comparative treatment efficacy.

Table 4

Treatment exposure and reported clinical response in the clinically evaluable CMS cohort by affected gene

Treatment characteristic	Overall (n = 35)	COLQ (n = 27)	CHRNE (n = 2)	SYT2 (n = 2)	CHAT (n = 2)	CHRND (n = 1)	CHRNA1 (n = 1)
Treatment exposure							
AChEI used	7/28 (25.0%)	2/21 (9.5%)	1 (50.0%)	1/1 (100.0%)	2 (100.0%)	1 (100.0%)	0 (0.0%)
AChEI recommended but administration unconfirmed	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Beta-agonist used	22/31 (71.0%)	21/24 (87.5%)	0 (0.0%)	0/1 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)
Concurrent AChEI and beta-agonist therapy	3 (8.6%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)
Reported AChEI response							
Positive reported response among assessable treated patients	5/6 (83.3%)	1/2 (50.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	—
No documented improvement among assessable treated patients	1/6 (16.7%)	1/2 (50.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	—
Response not separately assessable among treated patients	1/7 (14.3%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/2 (50.0%)	0/1 (0.0%)	—
Reported beta-agonist response							
Positive reported response among assessable treated patients	19/21 (90.5%)	19/21 (90.5%)	—	—	—	—	—

Treatment characteristic	Overall (n = 35)	COLQ (n = 27)	CHRNE (n = 2)	SYT2 (n = 2)	CHAT (n = 2)	CHRND (n = 1)	CHRNA1 (n = 1)
Treatment exposure							
No documented improvement among assessable treated patients	2/21 (9.5%)	2/21 (9.5%)	—	—	—	—	—
Response not separately assessable among treated patients	1/22 (4.5%)	0/21 (0.0%)	—	—	1/1 (100.0%)	—	—
Overall reported outcome							
Positive overall clinical improvement among patients with confirmed treatment exposure and assessable outcomes	21/24 (87.5%)	18/20 (90.0%)	—	0/1 (0.0%)	2/2 (100.0%)	1/1 (100.0%)	—
Treatment duration among patients with confirmed treatment exposure, median (IQR), months	30 (12–70.5); n = 20	30 (13.5–69); n = 18	—	2 (2–2); n = 1	—	131 (131–131); n = 1	—

Treatment characteristic	Overall (n = 35)	COLQ (n = 27)	CHRNE (n = 2)	SYT2 (n = 2)	CHAT (n = 2)	CHRND (n = 1)	CHRNA1 (n = 1)
Treatment exposure							
Notes							
	• Data are presented as n/N (%) when treatment exposure or response information was incomplete and as n (%) when complete.						
	• AChEI exposure was available for 28/35 patients; beta-agonist exposure was available for 31/35 patients.						
	• A positive reported response included marked/significant or partial clinical improvement.						
	• Drug-specific response denominators include only treated patients whose response could be assessed for that drug.						
	• Response was classified as not separately assessable when AChEI and beta-agonist therapy were initiated or continued concurrently and the individual drug effect could not be isolated.						
	• Overall clinical improvement was summarized only among patients with confirmed AChEI and/or beta-agonist exposure and an assessable overall outcome. The CHRNA1 patient was not counted as treated because AChEI therapy was recommended but administration was not confirmed.						
	• Treatment duration was summarized only among patients with confirmed treatment exposure when a positive duration in months could be derived from documented treatment dates or duration; values recorded as 0, recent, or unavailable were excluded.						
	• Treatment findings describe reported clinical response and should not be interpreted as estimates of comparative efficacy.						
	• AChEI, acetylcholinesterase inhibitor; CMS, congenital myasthenic syndrome; IQR, interquartile range.						

Discussion

To our knowledge, this is the first systematic clinical and genetic characterization of congenital myasthenic syndromes in Palestine. The study identified a marked predominance of COLQ-related disease, which accounted for 34 of 48 genetic records and 27 of 35 clinically evaluable patients. At the same time, the cohort showed substantial heterogeneity in age at diagnosis, clinical presentation, disease severity, supportive-care requirements, and treatment exposure. Respiratory manifestations and critical-care admissions were common, while the less frequent genetic subtypes included clinically distinct ocular, bulbar, respiratory, and motor phenotypes. These findings provide an initial framework for understanding CMS in Palestine and emphasize the importance of combining clinical assessment with molecular diagnosis in a disorder in which genotype may directly influence treatment selection.

The predominance of COLQ in this cohort is one of its most notable findings. Internationally, CHRNE, RAPSN, and COLQ are among the most frequently reported CMS-associated genes, although their relative contribution varies substantially across populations [4, 11, 12]. In contrast to cohorts in which

postsynaptic acetylcholine receptor deficiency or RAPSN-related disease predominate, more than three-quarters of the clinically evaluable patients in the present study had COLQ-related CMS. Regional observations may support the possibility that COLQ-related disease is enriched in some Middle Eastern and North African populations. In an Israeli CMS cohort, four recessive COLQ variants were identified across 11 kinships, 10 of which were of Muslim-Arab descent [16]. COLQ-related CMS has also been described in a Syrian family [17] and in three Algerian families [18]. These reports do not establish a regional prevalence pattern, but they suggest that recurrent or population-enriched COLQ variants may warrant further investigation.

The high level of parental consanguinity in the present cohort may have contributed to the concentration of autosomal-recessive disease. However, the observed gene distribution should not be interpreted as a population-based estimate. The cohort was assembled through clinical referral and available genetic records, and testing practices changed during the study period. Early genetic evaluation was more heavily directed toward COLQ, whereas broader exome-based testing became available later. Familial clustering, referral patterns, differential access to testing, and survival to diagnosis may therefore have influenced the apparent gene proportions. Confirmation of a founder effect would require systematic variant comparison, segregation studies, and haplotype analysis, which were beyond the scope of this study.

The clinical profile of COLQ-related CMS in our cohort was broad. Ptosis was present in all 27 patients, while developmental delay, hypotonia, proximal weakness, and respiratory symptoms were also frequent. Previous COLQ series have similarly described combinations of ptosis, ophthalmoparesis, facial weakness, proximal weakness, hypotonia, dysphagia, and respiratory involvement [6, 16, 19, 20]. Ptosis was among the most common manifestations in the Israeli and Turkish series [16, 20], whereas proximal weakness was particularly prominent in the cohort reported by Wargon et al. [19]. These differences likely reflect the wide phenotypic spectrum of COLQ-related disease, as well as differences in age, disease duration, referral setting, and clinical definitions across studies.

Developmental delay was documented in a high proportion of patients, especially in the COLQ subgroup. This finding requires cautious interpretation. In a retrospective record review, developmental delay may not always have been distinguished from delayed gross motor acquisition related to chronic weakness, hypotonia, respiratory illness, prolonged hospitalization, or reduced mobility. The present study therefore cannot determine whether developmental delay represented a primary neurodevelopmental manifestation or was secondary to neuromuscular impairment. Prospective studies using domain-specific developmental assessment would be needed to clarify this observation.

The non-COLQ subgroup illustrates the clinical heterogeneity that characterizes CMS. Both patients with SYT2-related disease had early hypotonia, proximal weakness, respiratory involvement, and bulbar symptoms, but neither had ptosis. SYT2 encodes synaptotagmin-2, a presynaptic protein involved in calcium-dependent neurotransmitter release, and pathogenic variants can impair synaptic vesicle

exocytosis [8–10]. The absence of ptosis in both patients is clinically relevant because it shows that reliance on ocular manifestations alone may fail to identify some CMS subtypes.

The two CHAT-related cases differed substantially despite sharing the same familial codon-level variant. One patient had recurrent respiratory and aspiration-related complications, required prolonged intensive-care support, and experienced cardiorespiratory arrest. The second had a more chronic motor phenotype characterized by ptosis, lower-limb weakness, muscle wasting, impaired mobility, gastrostomy, and tracheostomy. CHAT-related CMS is particularly associated with episodic apnea and acute worsening of myasthenic symptoms during infections, fever, or physiological stress, although the severity and interictal phenotype may vary considerably [21]. The contrasting presentations of these two related patients are therefore consistent with the recognized clinical variability of CHAT-associated disease. However, the small number of cases and the absence of functional or longitudinal comparative data preclude firm conclusions regarding intrafamilial genotype–phenotype relationships.

The acetylcholine receptor subunit disorders in this cohort were also clinically diverse. Both CHRNE-related patients had ptosis and proximal weakness, while failure to thrive was documented in both. The CHRND-related patient had a predominantly ocular and facial phenotype, with ptosis, a myopathic facial appearance, and drooling, but no documented respiratory or proximal weakness. In contrast, the CHRNB1-related patient had neonatal respiratory and feeding difficulties, later followed by ptosis, proximal weakness, dysphagia, failure to thrive, and constipation. These individual cases reinforce the broad phenotypic range of postsynaptic CMS [1, 4]. Because each of these subgroups contained only one or two patients, the findings should be regarded as clinical descriptions rather than estimates of gene-specific frequency or severity.

Respiratory morbidity represented a major component of disease burden. More than one-third of patients with available information had required respiratory support, 60% had at least one documented admission to an intensive or neonatal critical-care unit, and two patients experienced cardiac or respiratory arrest. Gastrostomy, invasive ventilation, tracheostomy, and mobility assistance were also required in a small but clinically important subset. These observations show that CMS in this cohort was not limited to ocular fatigability or chronic limb weakness. In some patients, respiratory or feeding complications were among the most consequential manifestations.

This has a direct clinical implication. CMS should be considered in children with recurrent unexplained respiratory deterioration, episodic weakness, feeding difficulty, hypotonia, or a congenital myopathy-like presentation, particularly when there is parental consanguinity or a similarly affected relative. The absence of ptosis should not exclude the diagnosis, as illustrated by both SYT2-related patients. Early recognition is especially important because respiratory decompensation may precede definitive neuromuscular diagnosis and because therapeutic response varies by molecular subtype [1, 4, 22].

The diagnostic investigations recorded in this cohort were heterogeneous. Brain magnetic resonance imaging, electrophysiological studies, repetitive nerve stimulation, single-fiber electromyography, creatine kinase testing, and neuromuscular autoantibody testing were performed or documented in only

subsets of patients. CMS is generally suspected in the presence of early-onset fatigable weakness, ocular, facial, bulbar, respiratory, or limb involvement, a compatible family history, absent neuromuscular autoantibodies, and electrophysiological evidence of impaired neuromuscular transmission [1, 4, 22]. Nevertheless, no single clinical or paraclinical feature is sufficient across all genetic subtypes.

The variability in diagnostic evaluation in the present study may reflect changes in referral pathways and test availability over the long study period. Patients with a strong family history or a previously identified familial variant may have proceeded relatively directly to genetic testing, whereas sporadic or atypical cases may have undergone broader neurological investigations. However, the study did not systematically capture the order, timing, or clinical rationale for every investigation; it therefore cannot quantify diagnostic delay or determine whether particular tests were unnecessary. A standardized pathway that integrates neuromuscular assessment, electrophysiology when available, and early molecular testing in appropriately selected patients may reduce diagnostic uncertainty.

The treatment findings were broadly consistent with genotype-directed management. Beta-agonists were used predominantly in COLQ-related CMS, whereas acetylcholinesterase inhibitors were used in several non-COLQ subtypes. This pattern is biologically plausible because COLQ variants produce endplate acetylcholinesterase deficiency by impairing the anchoring of acetylcholinesterase to the synaptic basal lamina [6, 7]. In COLQ-related CMS, acetylcholinesterase inhibitors are frequently ineffective and may aggravate symptoms, whereas beta-adrenergic agonists, particularly salbutamol and ephedrine, are generally regarded as the preferred pharmacological approach [23]. A recent synthesis of the published COLQ literature reported favorable responses to beta-adrenergic agonists in most treated patients, although the available evidence was derived predominantly from case reports and small observational series rather than controlled trials [23].

Among patients with an assessable drug-specific response, five of six AChEI-treated patients and 19 of 21 beta-agonist-treated patients had a positive reported response. Among patients with confirmed treatment exposure and an assessable overall outcome, 21 of 24 showed positive overall clinical improvement. These observations should not be interpreted as estimates of treatment efficacy. Treatment was not assigned randomly, response was derived from retrospective clinical documentation, standardized functional scales were not used, and follow-up duration varied. Concurrent treatment also prevented attribution of response to an individual drug in one CHAT-related patient. Nonetheless, the close alignment between genetic subtype and treatment selection, together with the high proportion of documented improvement among assessable patients, supports the clinical value of obtaining a molecular diagnosis.

The Palestinian context gives these findings additional relevance. Inherited neuromuscular disorders may be concentrated within families because of consanguinity, while access to pediatric neurology, electrophysiology, molecular testing, respiratory services, and longitudinal follow-up may differ across regions. Geographic separation and administrative restrictions can also fragment care between institutions and complicate repeated clinical assessment. These factors were not directly measured as

study outcomes, and they should not be assumed to have caused diagnostic delay in individual patients. However, they provide an important context for understanding why clinical documentation, testing pathways, and follow-up were not uniform.

The findings support several practical steps. First, clinicians should maintain a low threshold for considering CMS in children with congenital or early-onset weakness, recurrent respiratory crises, feeding difficulty, or a positive family history. Second, treatment should not be selected on the basis of a generic CMS diagnosis alone, because therapeutic response can differ substantially by molecular subtype. Third, affected families may benefit from coordinated genetic counseling, segregation testing, and cascade assessment of relatives. Finally, a Palestinian multicenter registry for inherited neuromuscular disorders could improve case ascertainment, enable standardized phenotyping, document treatment and functional outcomes prospectively, and determine whether recurrent COLQ variants represent founder or population-enriched alleles.

This study has several strengths. It provides the first systematic clinical-genetic description of CMS in Palestine and includes a substantial number of genetically confirmed patients for a rare disorder. The analysis integrates genetic findings with phenotype, respiratory morbidity, supportive interventions, treatment exposure, reported response, and vital status. The inclusion of patient-level information for rare non-COLQ genotypes also preserves clinically important heterogeneity that would be obscured by aggregate reporting. In addition, treatment exposure was distinguished from treatment recommendation, and drug-specific response was not assigned when concurrent therapy prevented reliable attribution.

limitation

Several limitations should also be acknowledged. First, the retrospective design resulted in incomplete and nonuniform documentation. Available-case denominators were therefore used, and missing values were not imputed. Second, the referral-based cohort was not population based and cannot be used to estimate CMS prevalence in Palestine. Cases managed outside the participating clinical and genetic services may not have been captured. Third, changes in genetic testing over time may have favored the identification of COLQ-related disease during earlier years and broader gene detection later. Fourth, standardized severity, developmental, respiratory, and treatment-response scales were not consistently available. Reported improvement therefore reflects clinician- or family-documented change rather than prospectively measured efficacy. Fifth, the non-COLQ groups were small, preventing inferential comparisons or robust genotype–phenotype analysis. Sixth, some variant details were incomplete, and no haplotype analysis was performed to investigate possible founder effects. Finally, the study did not directly measure diagnostic delay, healthcare access, or the effects of geographic fragmentation; these contextual interpretations should therefore remain cautious.

Conclusion

This study provides the first systematic clinical and genetic characterization of CMS in Palestine and identifies a marked predominance of COLQ-related disease within the referred cohort. Despite this genetic concentration, the clinical spectrum was heterogeneous, with substantial respiratory, bulbar, motor, and supportive-care burden across different subtypes. The occurrence of severe respiratory presentations, including in patients without ptosis, highlights the need to consider CMS in children with unexplained early-onset weakness, feeding difficulty, or recurrent respiratory deterioration. Genotype-aligned treatment patterns and the documented improvement observed in many assessable treated patients further support timely molecular diagnosis, while not establishing comparative treatment efficacy. Prospective multicenter studies and a coordinated national registry are needed to define the population-level burden, investigate recurrent variants, and standardize long-term assessment and care.

Abbreviations

AChE: Acetylcholinesterase

AChEI: Acetylcholinesterase inhibitor

AChR: Acetylcholine receptor

CHAT: Choline O-acetyltransferase

CHRNA1: Cholinergic receptor nicotinic alpha 1 subunit

CHRND: Cholinergic receptor nicotinic delta subunit

CHRNE: Cholinergic receptor nicotinic epsilon subunit

CK: Creatine kinase

CMS: Congenital myasthenic syndromes

COLQ: Collagen-like tail subunit of asymmetric acetylcholinesterase

CPR: Cardiopulmonary resuscitation

EMG: Electromyography

ICU: Intensive care unit

IQR: Interquartile range

MRI: Magnetic resonance imaging

NICU: Neonatal intensive care unit

NIV: Noninvasive ventilation

NMJ: Neuromuscular junction

PICU: Pediatric intensive care unit

RAPSN: Receptor-associated protein of the synapse

RNS: Repetitive nerve stimulation

SFEMG: Single-fiber electromyography

SYT2: Synaptotagmin 2

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Al-Quds University before data collection began (approval number: 318/REC/2023). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. The requirement for informed consent was waived by the Ethics Committee of Al-Quds University because of the retrospective nature of the study and the use of de-identified clinical data.

All data were handled confidentially. Direct identifiers, including patient names, national identification numbers, contact numbers, hospital identification numbers, and laboratory identification numbers, were removed from the analytical dataset and replaced with study-specific codes before analysis.

Consent for publication

Not applicable. The manuscript and supplementary materials contain no directly identifiable personal information, and all individual-level clinical and genetic data were de-identified before analysis and reporting.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain sensitive clinical and genetic information from patients with a rare disorder, which could pose a risk of re-identification. De-identified data may be made available by the corresponding author upon reasonable request, subject to approval by the relevant institutional and ethical authorities and in accordance with applicable data-protection requirements.

Competing interests

The authors declare that they have no competing interests.

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The authors received no funding for this study.

Authors' contributions

MA contributed to the conceptualization and supervision of the study, clinical oversight, validation and interpretation of the findings, project administration, and critical revision of the manuscript for important intellectual content.

OA, MSS, and ANAR contributed to the conceptualization and coordination of the study, case identification, data collection, medical-record review, data curation, and project administration.

BAL and NR contributed to clinical oversight, verification and interpretation of the clinical data, critical review of the methodology and results, and substantive revision of the manuscript for important intellectual content.

YKAA contributed to the study methodology, development of the data-extraction framework, data validation and curation, formal analysis, interpretation of the findings, literature review, preparation of the tables and figures, and writing of the original manuscript draft.

All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

MA, OA, MSS, and ANAR contributed equally to this work and share first authorship.

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Figures

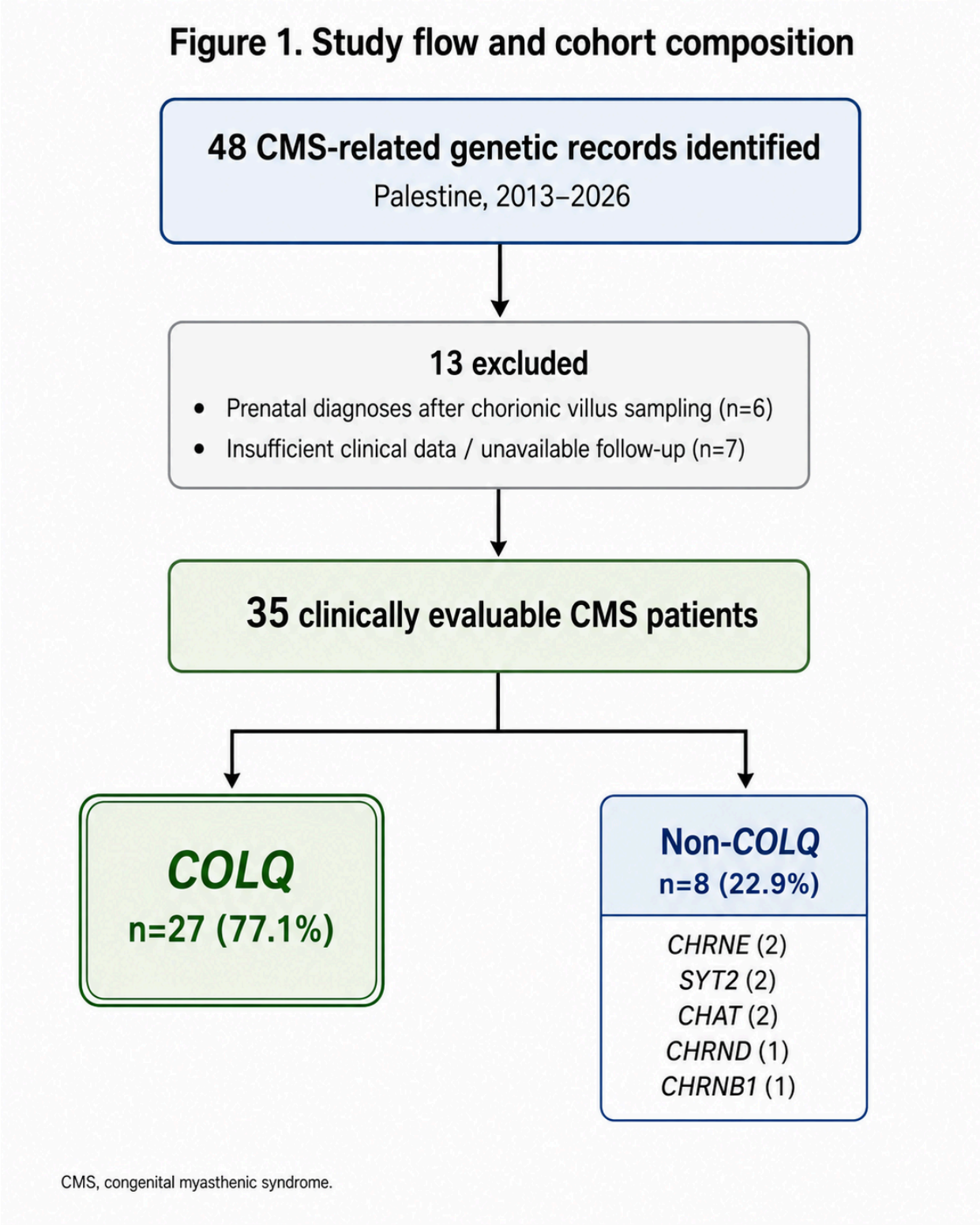


Figure 1

Study flow and cohort composition.

Supplementary Files

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