Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

GALNS gene variants and clinical severity in pediatric mucopolysaccharidosis type IV: A retrospective cohort study from Duhok, Iraq

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Article Info

Article history:

Received: March 10, 2026
Accepted: May 14, 2026
Published: May 31, 2026

Use your device to scan and read the article online

Abstract

Mucopolysaccharidosis type IV (MPS IV; Morquio syndrome) is a rare lysosomal storage disorder caused by pathogenic variants in the GALNS gene, resulting in deficiency of N-acetylgalactosamine-6-sulfatase and progressive accumulation of glycosaminoglycans. The disease exhibits substantial clinical heterogeneity, and the relationship between specific GALNS variants and disease severity remains incompletely understood. This retrospective cross-sectional observational study evaluated the association between GALNS variants and clinical severity in 10 children with genetically confirmed MPS IV treated at a tertiary pediatric center in Duhok, Iraq, with data collected up to September 2025. Clinical, radiological, echocardiographic, and genetic data were retrospectively extracted from medical records. A study-derived, non-validated Clinical Severity Index (CSI; range, 0–6) was constructed from six clinically relevant skeletal, neurological, and functional manifestations, with higher scores indicating greater recorded disease burden. Three GALNS variants were identified: c.860C>T (50%), c.421T>A (30%), and c.1196delA (20%). The overall mean CSI was 2.9 ± 2.0. Patients with the frameshift variant c.1196delA had the highest mean CSI (4.0 ± 1.4), followed by c.860C>T (2.8 ± 2.6) and c.421T>A (2.3 ± 0.6); however, the difference among mutation groups was not statistically significant (Kruskal–Wallis p = 0.564). Overall, 20% of patients had mild, 50% had moderate, and 30% had severe disease according to the study-derived CSI. Multisystem involvement was common, including skeletal abnormalities in 70%, abnormal echocardiographic findings in 70%, cervical spinal cord compression in 30%, and carpal tunnel syndrome and/or communicating hydrocephalus in 40% of patients. The findings demonstrate substantial clinical variability among children with MPS IV and suggest a possible trend toward greater disease burden among patients with the frameshift variant c.1196delA, although this association was not statistically significant. Given the small sample size and the non-validated nature of the CSI, these findings should be considered exploratory and require confirmation in larger, multicenter cohorts using standardized clinical and biochemical measures.

Keywords: Mucopolysaccharidosis type IV, Morquio syndrome, *GALNS*, genotype–phenotype correlation, clinical severity, pediatric

1. Introduction

Mucopolysaccharidosis type IV (MPS IV; Morquio syndrome) is a rare autosomal recessive lysosomal storage disorder caused by deficiency of N-acetylgalactosamine-6-sulfatase, resulting from mutations in the *GALNS* gene [1, 2]. This enzymatic defect leads to accumulation of glycosaminoglycans, particularly keratan sulfate, causing progressive multisystem involvement [3].

MPS IV has a marked geographical variation in reported frequency. Birth prevalence ranges approximately from 1 in 71,000 live births in the United Arab Emirates to 1 in 500,000 in Japan, reflecting substantial population and methodological variability [4]. Data from the Middle East remain comparatively limited, although high rates of GALNS variants and consanguinity may influence the regional molecular spectrum [5]. An Iraqi pediatric cohort has also reported considerable allelic heterogeneity and genotype–phenotype variability [5].

Clinically, MPS IV is characterized by skeletal dysplasia, short stature, joint laxity, and spinal abnormalities, with preservation of intelligence in most cases [3, 6]. Neurological complications, particularly cervical spinal cord compression, and cardiac involvement, including valvular disease, contribute significantly to morbidity [7, 8].

Despite advances in diagnostic approaches, including enzymatic and molecular testing, MPS IV demonstrates marked phenotypic heterogeneity, even among patients with similar genetic variants [7]. Previous studies suggest that mutation type, particularly null or truncating mutations, may be associated with more severe clinical phenotypes; however, genotype–phenotype correlations remain inconsistent [9, 10].

Furthermore, the absence of a standardized clinical severity scoring system limits the ability to compare disease

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Doi: http://dx.doi.org/10.14715/cmb/2026.72.5.8

burden across patients and genetic subtypes. Composite indices incorporating multisystem involvement have been proposed as practical tools in rare disease research [11].

Therefore, this study aimed to evaluate the association between *GALNS* gene variants and clinical severity in pediatric patients with MPS IV using a study-derived composite severity index.

2. Materials and Methods

2.1. Study Design and Setting

This was a retrospective cross-sectional observational study conducted at Heevi Pediatric Teaching Hospital, Duhok, Iraq, including pediatric patients with mucopolysaccharidosis type IV (MPS IV). Data were collected up to September 2025. The study adhered to institutional and ethical standards.

2.2. Participants

All children with genetically confirmed MPS IV were included. Diagnosis was established based on compatible clinical features and confirmation of *GALNS* variants. Molecular genetic testing was performed at ARCHIMED Life Laboratories, Vienna, Austria, and the identified *GALNS* variants were extracted from the patients' genetic reports. Patients with incomplete clinical or genetic data were excluded. Given the rarity of the condition, all eligible cases during the study period were included.

2.3. Data Collection

Data were retrospectively extracted from medical records using a standardized form, including:

- **Demographics and history**: age, sex, residence, consanguinity, and family history of MPS IV.
- **Clinical features**: skeletal abnormalities (dysostosis multiplex, joint stiffness, genu valgum, kyphoscoliosis, pectus carinatum, and hip dysplasia), neurological involvement (cervical spinal cord compression, communicating hydrocephalus, and carpal tunnel syndrome), macrocephaly, and functional status (wheelchair dependence).
- **Cardiac findings**: echocardiographic abnormalities.
- **Genetic data**: GALNS mutation type.

2.4. Exposure Variable

The primary exposure was the specific GALNS gene variant identified in each patient. Based on the molecular testing results, variants were categorized into three distinct groups according to their nucleotide and protein changes:

- c.860C>T (p.Ser287Leu; missense variant)
- c.421T>A (p.Trp141Arg; missense variant)
- c.1196delA (p.Lys399ArgfsTer42; frameshift/truncating variant)

This categorization allowed for an exploratory comparison of clinical severity between patients carrying missense variants and those with a frameshift (presumably null) variant, given that truncating mutations have been associated with more severe phenotypes in previous literature.

2.5. Outcome Measure: Clinical Severity

In the absence of a validated clinical severity scale suitable for retrospective data, a study-derived, non-validated composite Clinical Severity Index (CSI) was developed as an exploratory measure of disease burden. The CSI comprised six clinically significant domains that were consistently documented in the medical records: wheelchair dependence; dysostosis multiplex/joint stiffness/genu valgum; kyphoscoliosis; hip dysplasia; cervical spinal cord compression; and carpal tunnel syndrome and/or communicating hydrocephalus. These domains were chosen to capture the skeletal, neurological, and functional dimensions of MPS IV.

Each domain received one point using equal weighting, as no evidence-based differential weights are available and the small sample size precluded reliable statistical derivation. The total CSI score, ranging from 0 to 6, represents the cumulative number of documented manifestations, with higher scores indicating greater recorded clinical burden.

Short stature was excluded because it was universally present in all patients, and cardiac involvement was not incorporated into the predefined CSI. The CSI was developed specifically for this exploratory study and has not undergone formal validation. Internal consistency (Cronbach's alpha) was not computed, as the small sample (n = 10) rendered such analysis unreliable. The specific components and severity classification are detailed in Section 2.6.

2.6. Clinical Severity Index (CSI; 0–6)

The CSI was calculated as the unweighted sum of six dichotomous clinical items, each scored as 1 point if present:

1. Wheelchair dependence
2. Dysostosis multiplex / joint stiffness / genu valgum
3. Kyphoscoliosis
4. Hip dysplasia
5. Cervical spinal cord compression
6. Carpal tunnel syndrome and/or communicating hydrocephalus

The total score ranges from 0 to 6, with higher scores indicating a greater recorded disease burden. Based on the total CSI score, patients were further classified into three severity groups: mild (0–1), moderate (2–3), and severe (4–6).

2.7. Statistical Analysis

Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized using median and range, together with mean and standard deviation where appropriate to describe central tendency and dispersion. Categorical variables were presented as frequencies and percentages.

Owing to the small sample size and unequal group sizes across the three GALNS mutation groups, the non-parametric Kruskal–Wallis test was employed to compare CSI scores between groups. Exact p-values were reported whenever available. A two-sided p-value of <0.05 was considered statistically significant.

Given the limited cohort size, all inferential results were treated as exploratory and interpreted with caution. No adjustments for multiple comparisons were made, as the analysis was primarily descriptive and hypothesis-generating.

2.8. Ethical Considerations

This study was approved by the Ethics and Scien-

tific Committee of the College of Medicine, University of Zakho, Duhok, Kurdistan Region, Iraq (Approval No.FEB2026/UOZEA070, issued on 10 February 2026). The study involved retrospective review and analysis of previously existing clinical and genetic data. The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient confidentiality was maintained, and all data were anonymized prior to analysis.

3. Results

3.1. Baseline Characteristics

A total of 10 pediatric patients with confirmed mucopolysaccharidosis type IV (MPS IV) were included. The mean age was 7.94 ± 2.97 years, with a female predominance (60%). A high prevalence of consanguinity (90%) and positive family history (70%) was observed. All patients exhibited short stature (100%), consistent with the characteristic growth impairment of the disease.

3.2. Distribution of *GALNS* Gene Variants

Three *GALNS* gene variants were identified: c.860C>T (50%, n=5), c.421T>A (30%, n=3), and c.1196delA (20%, n=2). A statistically significant association was observed between mutation type and geographic distribution (p = 0.006); however, this finding should be interpreted cautiously given the small sample size. No significant differences were observed for age, sex, or consanguinity.

3.3. Clinical Severity Assessment

A study-derived Clinical Severity Index (CSI) (range 0–6) was calculated based on major clinical domains. The overall mean CSI was 2.9 ± 2.0, with a median of 2.5 (range: 0–6).

3.4. Association Between *GALNS* Variants and Clinical Severity

The distribution of CSI across mutation groups demonstrated variability in clinical severity. Patients with the frameshift variant c.1196delA had the highest mean CSI (4.0 ± 1.4), followed by c.860C>T (2.8 ± 2.6) and c.421T>A (2.3 ± 0.6) (Table 1)

However, the difference in CSI across mutation groups was not statistically significant (Kruskal–Wallis p = 0.564). These findings are illustrated in Figure 1. Patient-level CSI data are presented in Table 2.

3.5. Severity Classification

Based on CSI categorization, 20% (n=2) of patients were classified as mild, 50% (n=5) as moderate, and 30% (n=3) as severe (Table 3).

Patients with the c.1196delA variant demonstrated moderate-to-severe disease exclusively, whereas c.421T>A was associated only with moderate severity. The c.860C>T variant showed the broadest phenotypic variability, ranging from mild to severe disease.

3.6. Distribution of Clinical Manifestations

Multisystem involvement was common. Skeletal ab-

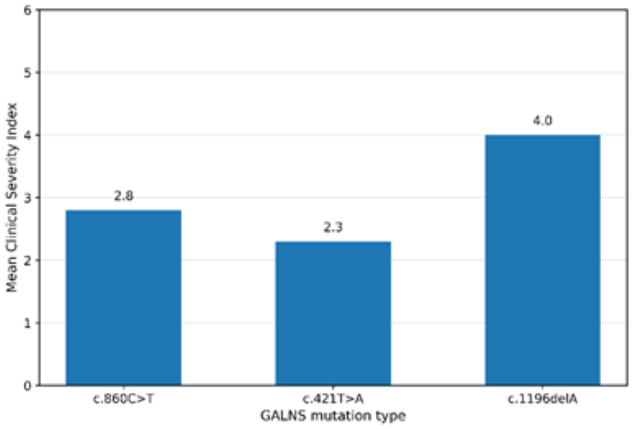


Fig. 1. Mean Clinical Severity Index (CSI) according to *GALNS* mutation type. Error bars represent standard deviation. Differences between mutation groups were not statistically significant (Kruskal–Wallis test, p = 0.564).

Table 1. Clinical Severity Index According to *GALNS* Mutation Type.

GALNS mutation	n	Mean CSI ± SD	Median	Range
c.1196delA (p.Lys399ArgfsTer42)	2	4.0 ± 1.4	4	3–5
c.421T>A (p.Trp141Arg)	3	2.3 ± 0.6	2	2–3
c.860C>T (p.Ser287Leu)	5	2.8 ± 2.6	2	0–6
Total	10	2.9 ± 2.0	2.5	0–6

Abbreviation: CSI, Clinical Severity Index. *p* value for between-group comparison (Kruskal–Wallis test): 0.564.

Table 2. Patient-Level Clinical Severity Index According to *GALNS* Mutation Type.

Patient ID	*GALNS* Mutation	CSI	Severity
P1	c.860C>T (p.Ser287Leu)	0	Mild
P2	c.860C>T (p.Ser287Leu)	5	Severe
P3	c.421T>A (p.Trp141Arg)	2	Moderate
P4	c.860C>T (p.Ser287Leu)	2	Moderate
P5	c.860C>T (p.Ser287Leu)	6	Severe
P6	c.1196delA (p.Lys399ArgfsTer42)	5	Severe
P7	c.1196delA (p.Lys399ArgfsTer42)	3	Moderate
P8	c.421T>A (p.Trp141Arg)	2	Moderate
P9	c.860C>T (p.Ser287Leu)	1	Mild
P10	c.421T>A (p.Trp141Arg)	3	Moderate

Table 3. Severity Category According to *GALNS* Mutation Type.

GALNS mutation	Mild	Moderate	Severe	Total
c.1196delA (p.Lys399ArgfsTer42)	0	1	1	2
c.421T>A (p.Trp141Arg)	0	3	0	3
c.860C>T (p.Ser287Leu)	2	1	2	5
Total	2	5	3	10

Severity categories were defined as mild (CSI 0–1), moderate (CSI 2–3), and severe (CSI 4–6).

Table 4. Distribution of Clinical Manifestations According to *GALNS* Mutation Type.

Clinical manifestation	c.860C>T (n=5)	c.421T>A (n=3)	c.1196delA (n=2)	Total n (%)
Positive family history	4	1	2	7 (70%)
Consanguinity	4	3	2	9 (90%)
Macrocephaly	4	2	2	8 (80%)
Wheelchair dependence	3	0	0	3 (30%)
Dysostosis/genu valgum	4	1	2	7 (70%)
Kyphoscoliosis	2	3	2	7 (70%)
Hip dysplasia	1	2	2	5 (50%)
Cervical cord compression	2	0	1	3 (30%)
CTS/hydrocephalus	2	1	1	4 (40%)
Pectus carinatum	2	3	2	7 (70%)
Abnormal echocardiography	3	2	2	7 (70%)

CTS: Carpal Tunnel Syndrome.

normalities were highly prevalent, including dysostosis multiplex/genu valgum (70%), kyphoscoliosis (70%), and pectus carinatum (70%). Hip dysplasia was observed in 50% of patients. Neurological complications included cervical spinal cord compression in 30% of patients and carpal tunnel syndrome and/or communicating hydrocephalus in 40%. Abnormal echocardiographic findings were identified in 70% of cases (Table 4).

4. Discussion

4.1. Summary of Key Findings

This study explored the relationship between GALNS variants and clinical severity in children with MPS IVA from Duhok, Iraq. Considerable clinical variability was observed among the three identified variants. Patients carrying c.1196delA had the highest severity scores, whereas c.860C>T showed the widest range of clinical severity. However, the difference between mutation groups was not statistically significant ($p = 0.564$). Given the small number of patients, these findings should be considered exploratory and do not establish a genotype–phenotype association.

Phenotypic heterogeneity is well recognized in MPS IV and has been demonstrated in much larger molecular studies [9, 12, 13].

4.2. Comparison with International Genotype–Phenotype Studies

The phenotypic heterogeneity observed in our cohort is well recognized in the MPS IV literature and has been documented in larger molecular studies. Yi et al. evaluated 108 unrelated patients and identified 101 GALNS variants. Most patients carrying at least one null variant had severe disease, whereas missense variants were associated with a broader spectrum of severity [9]. Similarly, the large international analysis of GALNS variants showed that although many individual variants were associated predominantly with classical or nonclassical disease, the same genotype could occasionally be associated with different phenotypes [13]. These observations suggest that genotype is an important determinant of disease expression but is unlikely to explain the full clinical variability of MPS IV.

The c.860C>T (p.Ser287Leu) variant was the most frequent variant in our cohort and was associated with severity ranging from mild to severe. This finding is particularly interesting when considered alongside international molecular data. In the large analysis of 1,190 subjects reported by Zanetti et al., c.860C>T was documented in several homozygous patients and was predominantly associated with the classical phenotype [14]. The variability seen in our patients therefore reinforces the need for caution when predicting an individual patient's clinical course from genotype alone, particularly in small cohorts.

4.3. Regional Molecular Spectrum and Comparison with Other Iraqi Cohorts

The findings can also be compared with regional experience. Tüysüz et al. described substantial phenotypic variability among Turkish patients with MPS IVA, including severe and attenuated forms associated with different GALNS variants [15]. More recently, Wahhab and Thejeal reported 33 Iraqi children from 26 unrelated families and identified 15 different GALNS variants, including five novel variants [5]. Their most frequent variant was c.949G>A (p.Gly317Arg), which was associated with severe disease and absent enzyme activity. Although allele-specific genotype–phenotype trends were observed, statistically significant correlations could not be established because of the limited cohort size [5]. The different variant distribution in our Duhok cohort may indicate regional genetic het-

erogeneity within Iraq, although larger multicenter studies would be required to determine whether true geographic clustering or founder effects are present.

4.4. Multisystem Clinical Manifestations

The clinical findings in our patients were broadly consistent with the established multisystem nature of MPS IV [1, 3, 16, 17]. Short stature and skeletal abnormalities were prominent, while kyphoscoliosis, hip dysplasia, cervical cord compression, and cardiac abnormalities contributed to the overall disease burden. Cervical spinal involvement is particularly important because progressive instability and cord compression can result in substantial neurological morbidity [6, 8, 18]. Cardiac involvement also requires continued surveillance, particularly for progressive valvular disease [1]. The high frequency of skeletal and cardiac abnormalities reported in the recent Iraqi cohort further supports the importance of multidisciplinary follow-up in affected children [5].

For this study, clinical burden was summarized using a simple study-derived Clinical Severity Index based on six major manifestations. The index was intended only to provide a consistent descriptive measure for comparison within this small cohort and should not be regarded as a validated MPS IVA severity scale. Although multidimensional approaches have previously been used to assess disease severity in mucopolysaccharidoses [19], our index has not undergone external validation, assessment of reliability, or formal determination of weighting for its individual components. Equal weighting was used for simplicity, and manifestations such as short stature and cardiac involvement were not incorporated into the score. These limitations may influence the observed relationship between genotype and severity. The CSI should therefore be regarded as an exploratory study measure rather than a clinical assessment tool, and validation in a larger independent population would be required before clinical application.

The small sample size remains the principal limitation of this study and substantially reduces statistical power. Additional limitations include the single-center design, retrospective review of clinical records, absence of longitudinal assessment, lack of systematic biochemical markers for genotype–phenotype analysis, and limited generalizability beyond this regional population. Nevertheless, the study provides additional molecular and clinical information from the Kurdistan Region of Iraq, where published MPS IVA data remain limited. Together with the recent Iraqi cohort [5], our findings suggest that the GALNS mutation spectrum may vary between Iraqi populations and support the development of larger multicenter studies and national registries. Such studies should combine standardized clinical assessment with enzyme activity, molecular characterization, biomarkers, and longitudinal follow-up to better define genotype–phenotype relationships in MPS IVA.

4.5. Utility of the Clinical Severity Index

In the absence of a standardized severity scoring system for MPS IV, we developed a composite Clinical Severity Index (CSI) incorporating key domains of disease burden. Similar multidimensional clinical assessment approaches have been used in studies of MPS disorders to capture disease heterogeneity and progression [19].

Although not externally validated, the CSI provided a practical framework for comparing severity across genetic subgroups in this cohort. However, it should be considered an exploratory tool pending validation in larger studies.

4.6. Strengths

This study has several strengths. First, all included patients had genetically confirmed MPS IVA, minimizing diagnostic misclassification. Second, the use of a multidimensional CSI, integrating skeletal, neurological, and functional domains, provided a consistent descriptive framework for comparing disease burden. Third, the provision of patient-level data with standardized scoring enables transparent assessment of the observed heterogeneity. Finally, this is one of the few reports from the Kurdistan Region of Iraq, contributing valuable molecular and clinical data from an underrepresented population.

4.7. Limitations

The principal limitation of this study is the small sample size (n = 10), which substantially reduces statistical power and limits generalizability; all findings should therefore be considered exploratory. The retrospective, single-center design and extraction of data from medical records carry inherent risks of incomplete documentation and information bias. The absence of longitudinal follow-up precludes assessment of disease progression or temporal genotype–phenotype relationships. Additionally, objective functional measures (e.g., 6-minute walk test, pulmonary function tests) and biochemical markers (e.g., enzyme activity, keratan sulfate levels) were not available for correlation with genotype or severity scores. Finally, the study-derived CSI is non-validated, and the equal weighting of its components may not accurately reflect the differential clinical impact of each manifestation.

4.8. Clinical Implications

Despite its exploratory nature, our study offers several clinically relevant observations. Patients harboring frameshift/truncating *GALNS* variants (e.g., c.1196delA) may exhibit greater disease burden and could benefit from closer surveillance, particularly for spinal cord compression and cardiac involvement. The high frequency of skeletal and cardiac abnormalities supports early, structured screening protocols, including periodic spinal imaging and echocardiography. Overall, these findings reinforce the need for a multidisciplinary care model, involving pediatrics, orthopedics, neurology, and cardiology, tailored to the individual patient's disease burden.

4.9. Future Directions

Larger, multicenter studies are urgently needed to validate genotype–severity relationships and improve generalizability. The development and external validation of a standardized MPS IV severity scoring system, incorporating objective functional tests, biochemical biomarkers (e.g., keratan sulfate), and longitudinal data, would represent a significant advance. National or regional registries, combining standardized clinical assessment with molecular characterization and long-term follow-up, would greatly enhance our understanding of disease progression and enable more precise genotype–phenotype correlations.

5. Conclusion

GALNS gene variants demonstrated variability in clinical severity among pediatric patients with MPS IV, with a trend toward higher severity in those with frameshift mutations. Although this association did not reach statistical significance, the findings suggest a potential genotype–severity relationship and underscore the importance of genotype-informed clinical assessment. These findings highlight the need for further evaluation and validation of standardized severity measures in larger multicenter cohorts and highlight the need for further validation in larger multicenter cohorts.

Declarations

Ethics Approval

This study was approved by the Ethics and Scientific Committee of the College of Medicine, University of Zakho, Duhok, Kurdistan Region, Iraq (Reference No.: FEB2026/UOZEA070; issued on 10 February 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent to Participate

The requirement for informed consent was waived by the Research Ethics Committee due to the retrospective nature of the study and the use of anonymized medical records.

Consent for Publication

Not applicable.

Funding

No funding was received.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Bashar I. Mohammed: Conceptualization, study design, data collection, data analysis, interpretation of results, manuscript drafting, critical revision of the manuscript, and approval of the final version.

Use of Artificial Intelligence Tools

Some sentences in this manuscript were revised with the assistance of artificial intelligence, using language models to improve clarity and readability. All intellectual content, interpretations, and conclusions are solely the responsibility of the authors.

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