ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Molecular Spectrum of *DMD*-related Dystrophinopathies and Non-*DMD* Neuromuscular Disorders in Children Evaluated for Elevated Serum Creatine Kinase: A Single-centre Experience

Serum Kreatin Kinaz Yüksekliği Nedeniyle Değerlendirilen Çocuklarda *DMD* İlişkili Distrofinopatiler ve *DMD* Dışı Nöromusküler Hastalıkların Moleküler Spektrumu: Tek Merkez Deneyimi

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Abstract

Introduction: Dystrophinopathy-focused studies characterise variants in the dystrophin gene *(DMD)* generally without addressing alternative causes, whereas series of elevated creatine kinase are often restricted to asymptomatic or minimally symptomatic individuals. *DMD*-related and non-*DMD* diagnoses are therefore rarely described together within one referred cohort. This study aimed to describe the distribution of explanatory molecular diagnoses in children evaluated for elevated creatine kinase.

Materials and Methods: Children aged 0–18 years evaluated between 2020 and 2025 with a documented peak creatine kinase above the institutional upper reference limit of 200 U/L and at least one molecular genetic test were reviewed in this single-centre retrospective study. Results were assigned to three mutually exclusive categories: explanatory molecular diagnosis consistent with the expected mode of inheritance, heterozygous *DMD* variant in a girl, and molecularly unsolved. Proportions used patients with an explanatory diagnosis as the denominator (Wilson score 95% confidence intervals) and were not interpreted as a diagnostic yield.

Results: Of 58 children, 38 had an explanatory molecular diagnosis, nine girls had a heterozygous *DMD* variant and 11 were molecularly unsolved. Among the 38 diagnoses, 26 (68.4%; 95% confidence interval [CI] 52.5-80.9) were *DMD*-related dystrophinopathies and 12 (31.6%; 95% CI 19.1-47.5) were non-*DMD* neuromuscular disorders. Of 26 dystrophinopathy cases, 20 carried an exon-level deletion, 13 overlapping exons 45-52; no exon-level duplication was identified. The 12 non-*DMD* diagnoses involved 10 genes (*GAA, CAPN3, SGCA, TCAP, POMT1, PYGM, COL6A1, EMD, CLCN1, SCN4A*), seven disease groups and three modes of inheritance. Peak creatine kinase values overlapped substantially among categories.

Conclusion: *DMD*-related dystrophinopathies accounted for most explanatory diagnoses, yet about one third arose from non-*DMD* disorders spanning multiple genes, inheritance patterns and mechanisms, including clinically actionable metabolic and channel disorders. After persistence and clinical findings are assessed, the evaluation of unexplained creatine kinase elevation in children should extend beyond *DMD* when initial dystrophinopathy testing is unrevealing or the phenotype is atypical. The retrospective design and non-uniform testing are the principal limitations.

Keywords
Creatine kinase, Duchenne muscular dystrophy, neuromuscular diseases, genetic testing, hyperCKemia

Anahtar kelimeler
Kreatin kinaz, Duchenne musküler distrofisi, nöromusküler hastalıklar, genetik test, hiperCKemi

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Öz

Giriş: Distrofinopatiye odaklanan çalışmalar distrofin geni *(DMD)* varyantlarını ayrıntılı tanımlarken alternatif nedenleri ele almamakta, kreatin kinaz yüksekliği serileri ise sıklıkla asemptomatik veya minimal semptomatik olgularla sınırlı kalmaktadır. Bu nedenle *DMD* ilişkili ve *DMD* dışı tanıların aynı kohortta birlikte tanımlanması seyrektir. Bu çalışmada, serum kreatin kinaz yüksekliği nedeniyle değerlendirilen çocuklarda açıklayıcı moleküler tanıların dağılımının tanımlanması amaçlandı.

Gereç ve Yöntem: Bu tek merkezli, retrospektif çalışmada, 2020-2025 arasında değerlendirilen, kurumsal üst referans sınırı olan 200 U/L'nin üzerinde en yüksek kreatin kinaz değeri belgelenmiş ve en az bir moleküler genetik test yapılmış 0-18 yaş çocuklar incelendi. Sonuçlar birbirini dışlayan üç kategoriye ayrıldı: kalıtım modeliyle uyumlu açıklayıcı moleküler tanı, kızlarda heterozigot *DMD* varyantı ve moleküler olarak açıklanamamış olgular. Oranlar açıklayıcı tanı alan hastalar payda alınarak hesaplandı; %95 güven aralıkları (GA) Wilson skor yöntemiyle verildi. Test seçimi klinik endikasyona göre yapıldığından oranlar biçimsel tanı verimi olarak yorumlanmadı.

Bulgular: Toplam 58 çocuğun 38'inde açıklayıcı moleküler tanı saptandı; dokuz kızda heterozigot *DMD* varyantı bulundu, 11 olgu açıklanamadı. Bu 38 tanının 26'sı (%68,4; %95 GA 52,5-80,9) *DMD* ilişkili distrofinopati, 12'si (%31,6; %95 GA 19,1-47,5) *DMD* dışı nöromusküler hastalıktı. Distrofinopatili 26 olgunun 20'sinde ekzon düzeyinde delesyon vardı; 13'ü ekzon 45–52 aralığıyla örtüşüyordu; ekzon düzeyinde duplikasyon saptanmadı. *DMD* dışı 12 tanı 10 farklı geni (*GAA, CAPN3, SGCA, TCAP, POMT1, PYGM, COL6A1, EMD, CLCN1, SCN4A*), yedi hastalık grubunu ve üç kalıtım modelini kapsıyordu. En yüksek kreatin kinaz değerleri moleküler kategoriler arasında belirgin biçimde örtüşmekteydi.

Sonuç: *DMD* ilişkili distrofinopatiler açıklayıcı tanıların çoğunluğunu oluşturmakla birlikte, tanıların yaklaşık üçte biri farklı gen, kalıtım modeli ve mekanizmalara sahip *DMD* dışı hastalıklardan kaynaklandı; bunlar arasında klinik olarak yönetilebilir metabolik hastalıklar ve kanalopatiler de yer aldı. Bu bulgular, açıklanamayan kreatin kinaz yüksekliğinin değerlendirilmesinde, kalıcılık ve klinik bulgular değerlendirildikten sonra, başlangıç distrofinopati incelemesi sonuç vermediğinde veya fenotip atipik olduğunda ayırıcı tanının *DMD* ile sınırlı tutulmaması gerektiğini göstermektedir. Retrospektif tasarım ve test kapsamının hastalar arasında farklılığı başlıca kısıtlılıklardır.

Introduction

Elevated serum creatine kinase (CK) is a common reason for referring children for evaluation of a suspected inherited neuromuscular disorder. Elevation may be an early or isolated marker of such a disorder, sometimes preceding overt weakness. Interpretation in children is nevertheless complicated by reference limits that vary with age and sex (1), by transient elevation after exercise, trauma or intercurrent illness, and by the fact that, in largely adult series of asymptomatic or minimally symptomatic individuals with persistently elevated CK, most remain without a definitive diagnosis (2,3). The institutional upper reference limit of 200 U/L applied here has also been used in population-based CK screening of adult women (4). A recent paediatric series recommended confirming the elevation by repeated measurement and letting history, physical examination, family history and targeted laboratory tests guide further investigation (5).

In paediatric series of CK elevation, dystrophinopathies are the most frequent inherited neuromuscular diagnosis (5-7), and exon-level deletions are the most frequent type of variant in the dystrophin gene *(DMD)*, clustering mainly in a central hotspot spanning exons 45-52 (8,9). The differential diagnosis is nonetheless wider and includes limb-girdle muscular dystrophies (LGMD), collagen VI-related and congenital muscular disorders, metabolic myopathies and skeletal muscle channelopathies (6,10-12). Several of these disorders have been identified in paediatric and mixed-age series of CK elevation and suspected inherited myopathies (13-17), and the spectrum detected by multigene sequencing panels depends on panel content and cohort selection (13-15).

How these diagnoses are distributed within a single clinically referred cohort remains incompletely characterised. Dystrophinopathy-focused studies generally do not characterise alternative diagnoses, whereas series of CK elevation are often restricted to asymptomatic or minimally symptomatic patients (3,14), in whom overt dystrophinopathy phenotypes are underrepresented. Reporting is further complicated by girls with a heterozygous *DMD* variant, whose clinical status cannot be inferred from the molecular finding alone.

We therefore reviewed children referred to a paediatric genetics clinic for evaluation of elevated serum CK who had undergone molecular genetic testing. The study aimed to describe the explanatory molecular diagnoses in this cohort, to characterise the *DMD* variant spectrum in *DMD*-related dystrophinopathy, to describe the distribution of non-*DMD* neuromuscular disorders across genes, inheritance patterns and disease groups, and to report girls with a heterozygous *DMD* variant and molecularly unsolved patients as separate categories, together with their clinical features at the first genetic evaluation.

Materials and Methods

Study Design and Setting

This was a single-centre retrospective observational study with a descriptive molecular spectrum analysis. Records of children referred to the paediatric genetics clinic of Samsun City Hospital for evaluation of elevated serum CK between 1 January 2020 and 31 December 2025 were reviewed. As genetic testing was directed by clinical indication and was not applied uniformly, the study was designed to characterise the molecular spectrum among patients who received an explanatory molecular diagnosis rather than to estimate diagnostic yield or to compare testing strategies. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (18).

Ethics

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Samsun University (protocol code GOKAEK 2026/8/12; date of approval 6 May 2026) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective design and the use of anonymised data. Direct identifiers were removed before analysis, and individual cases are presented using anonymised codes.

Participants

Eligible patients were aged 0-18 years, had been referred for evaluation of elevated serum CK, had a documented peak CK above the institutional laboratory upper reference limit of 200 U/L applied throughout the study period, and had undergone at least one molecular genetic test. Patients were excluded if no CK value was documented; if the peak CK did not exceed the upper reference limit; if testing had been performed solely as familial cascade screening in the absence of personal CK elevation; if the documented referral indication was unrelated to CK elevation; or if only a preliminary laboratory report was available. All patients meeting these criteria during the study period were included, yielding a study population of 58 patients; no formal sample-size calculation was performed.

Data Collection and Variables

Data were extracted from electronic and paper medical records and from the corresponding clinical laboratory reports. Demographic variables comprised age at first evaluation and sex. Biochemical variables comprised serum CK, aspartate aminotransferase (AST) and alanine aminotransferase (ALT); for each patient the highest documented value was used. These peak recorded values describe the maximum documented biochemical abnormality and do not represent standardised baseline measurements. Molecular variables comprised the gene, the variant description in Human Genome Variation Society (HGVS) nomenclature, zygosity, the reported pathogenicity classification, the mode of inheritance and the associated disorder. HGVS descriptions are reported as recorded in the source laboratory reports; reference transcript identifiers were not consistently stated and were not added retrospectively. Extracted data were checked against the original reports, and identified discrepancies were resolved after re-examination of the source documents. No imputation was performed, and descriptive analyses were based on the available observations for each variable: age, sex and peak recorded CK were available for all 58 patients, whereas AST and ALT were not documented in four patients.

Clinical features were extracted from outpatient, inpatient and laboratory records with a structured form. They comprised the context in which CK elevation was first detected; neuromuscular complaints and examination findings at the first genetic evaluation (including weakness, Gowers sign, calf muscle pseudohypertrophy, gait disturbance, myalgia, exercise intolerance, myotonia, hypotonia and motor delay), patients being classified as symptomatic when any of these other than isolated calf muscle pseudohypertrophy was recorded, and other clinical findings recorded at the same evaluation; parental consanguinity and family history of neuromuscular disease; and all CK measurements available in the hospital information system. Using a definition modified from a previous paediatric series (16), CK elevation was considered persistent when CK exceeded the upper reference limit on at least two occasions more than 8 weeks apart without subsequent normalisation, transient when it normalised during follow-up, and not assessable otherwise. Findings not mentioned in the records were recorded as not documented. Clinical findings were described with Human Phenotype Ontology terms, as in a previous hyperCKemia series (13), and findings recorded as equivocal were considered present.

Genetic Testing

Genetic testing had been performed as part of routine diagnostic care, and its choice, sequence and extent were determined by the treating clinician according to the clinical

presentation, family history and local availability. The methods used were multiplex ligation-dependent probe amplification (MLPA) for *DMD* deletion and duplication analysis, targeted gene or Sanger sequence analysis, multigene next-generation sequencing (NGS) panels for neuromuscular and muscular dystrophy genes, whole-exome sequencing, and chromosomal microarray analysis. In two patients an Xp21.1 deletion involving *DMD* was first identified by chromosomal microarray and subsequently confirmed at the exon level by MLPA. Because this clinician-directed strategy resulted in heterogeneous investigation across the cohort, the tests performed are reported descriptively and their diagnostic performance was not compared.

Variant Interpretation and Definition of a Molecular Diagnosis

Variants had been classified in the reporting laboratories according to the standards and guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (19). Pathogenicity classifications were taken from the final clinical laboratory reports; because ACMG/AMP evidence codes were not consistently reported, an independent re-scoring was not undertaken, and the reported classifications were instead cross-checked against the ClinVar database (accessed October 2026).

A molecular diagnosis was assigned when the reported variant or variants were considered explanatory for the associated disorder and were consistent with the expected mode of inheritance. Four conditions had to be met. First, the variant or variants had to be reported as pathogenic or likely pathogenic. Second, the observed zygosity had to be compatible with the expected mode of inheritance: two variants consistent with biallelic involvement for autosomal recessive genes, a hemizygous variant in male patients for X-linked recessive genes, and a single heterozygous variant for genes with established autosomal dominant disease mechanisms. Third, when family information was available, the finding could not be inconsistent with the expected mode of inheritance. Fourth, the associated disorder had to be compatible with the documented clinical indication and with a disorder known to be associated with CK elevation or neuromuscular involvement. The documented clinical indication was taken from the referral and clinical genetics records and comprised the reason for referral together with the clinical findings recorded at evaluation, such as motor developmental delay, muscle weakness, gait abnormality, myalgia, muscle stiffness or isolated CK elevation.

For genes with established autosomal dominant disease mechanisms, a single heterozygous pathogenic or likely pathogenic variant was accepted as explanatory when the known molecular mechanism and the documented clinical indication were concordant. This applied to the heterozygous *COL6A1* glycine substitution, as Bethlem myopathy can be caused by dominant as well as recessive variants in the collagen VI genes (11), to the heterozygous *CLCN1* variant associated with autosomal dominant myotonia congenita, and to the heterozygous *SCN4A* variant associated with autosomal dominant periodic paralysis. Variants of uncertain significance, and single heterozygous variants in genes associated exclusively with autosomal recessive disease, were not accepted as explanatory.

Classification of Molecular Results

Patients were assigned to one of three mutually exclusive categories. The first comprised patients with an explanatory molecular diagnosis as defined above, subdivided into *DMD*-related dystrophinopathy and non-*DMD* neuromuscular disorder. The second comprised girls with a heterozygous *DMD* variant. Standardised clinical and muscle strength assessment was not available for these patients, so their findings were not classified as disease diagnoses; they were reported separately and excluded from the denominator used for the aetiological spectrum. The third comprised molecularly unsolved patients, in whom no explanatory molecular finding was identified with the investigations performed; because the extent of testing differed between patients, these cases were not interpreted as true negatives.

Analysis of the DMD Variant Spectrum

In patients with *DMD*-related dystrophinopathy, variants were categorised as exon-level deletions, exon-level duplications or small sequence variants. The deleted exon range was recorded for each deletion, and a deletion was considered to overlap the central region when its range partially or completely included exons 45–52. In the exonic distribution analysis each exon within a deleted range was counted once per patient, so that a multi-exon deletion contributed to more than one exon. Small intragenic duplications described using HGVS sequence nomenclature were classified as small sequence variants rather than exon-level duplications. The predicted effect of each exonic deletion on the translational reading frame was determined from the coding lengths of the deleted exons (reference transcript NM_004006): deletions were classified as in-frame when the deleted coding length was divisible by three and

as out-of-frame otherwise, in accordance with the reading-frame rule (9).

Laboratory Data

Peak recorded CK, AST and ALT values are reported descriptively. Beyond the institutional upper reference limit used for eligibility, no additional CK-based cut-off, severity classification or analytical grouping was applied.

Statistical Analysis

Analyses were descriptive. Continuous variables are presented as median with interquartile range (IQR) and, where relevant, minimum and maximum values; categorical variables are presented as counts and percentages. Quartiles were calculated using Tukey's hinges. Two-sided 95% confidence intervals (CI) for proportions were calculated using the Wilson score method. Proportions describing the aetiological spectrum use the number of patients with an explanatory molecular diagnosis as the denominator, which is stated explicitly wherever proportions are reported. No inferential comparison was performed between patients with and without an explanatory molecular diagnosis, because the extent of genetic testing was not equivalent across the cohort. Accordingly, diagnostic yield was not calculated, testing methods were not compared, and no predictive model for molecular positivity was constructed. Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Cohort Characteristics

During the study period, 58 children fulfilled the eligibility criteria. An explanatory molecular diagnosis consistent with the expected mode of inheritance was established in 38 of 58 patients; this figure is reported as an observed frequency rather than as a formal diagnostic yield. Nine girls carried a heterozygous *DMD* variant, and 11 patients remained molecularly unsolved (Figure 1). MLPA-based *DMD* deletion/duplication analysis had been performed in all 58 patients, and all 11 molecularly unsolved patients had also undergone a multigene NGS panel; none had undergone whole-exome sequencing. In total, 42 patients were male and 16 were female, and the median age at evaluation was 4 years (range <1-18). Demographic and laboratory characteristics of the three molecular categories are summarised in Table 1.

Distribution of Molecular Diagnoses

Among the 38 patients with an explanatory molecular diagnosis, 26 (68.4%; 95% CI 52.5-80.9) had a *DMD*-related dystrophinopathy and 12 (31.6%; 95% CI 19.1-47.5) had a non-*DMD* neuromuscular disorder. Girls with a heterozygous *DMD* variant were analysed as a separate molecular category and were not included in this denominator. The distribution of diagnoses is shown in Table 2.

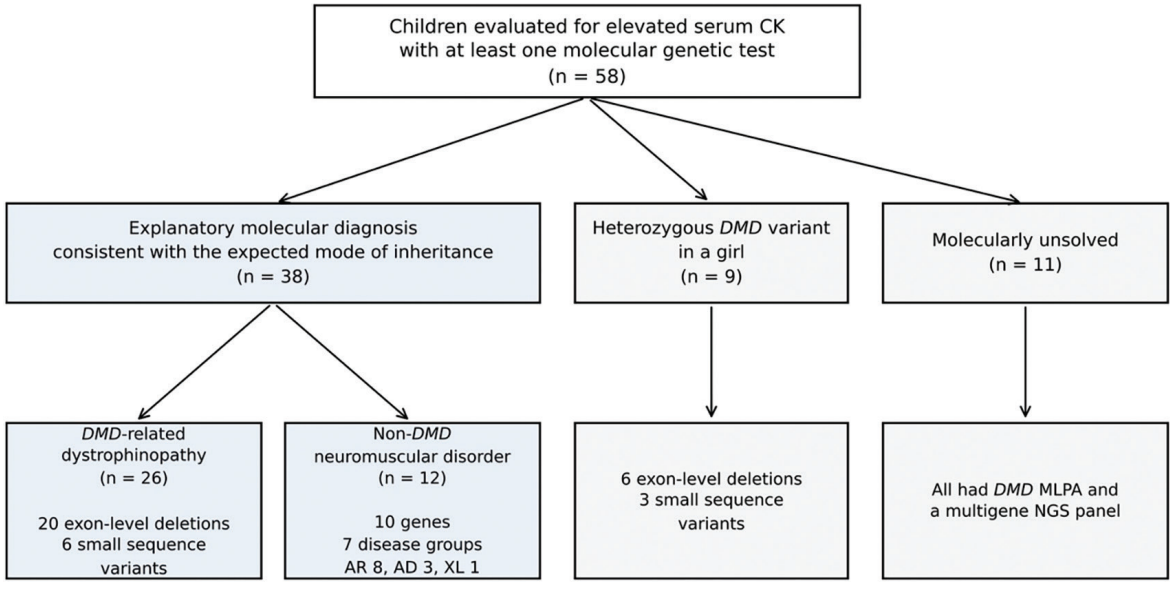


Figure 1. Classification of the cohort according to molecular results.

DMD Variant Spectrum in Dystrophinopathy

Of the 26 patients with *DMD*-related dystrophinopathy, 20 (76.9%; 95% CI 57.9-89.0) carried an exon-level deletion and 6 (23.1%) carried a small sequence variant; no exon-level duplication was identified. Of the 20 deletions, 13 (65.0%; 95% CI 43.3-81.9) partially or completely overlapped exons 45-52. Exon 48 was the single exon most frequently included within a deleted interval, followed by exons 46, 47, 49 and 50 (Figure 2). Of the 19 deletions that could be classified, 11 were predicted to be out-of-frame and 8 in-frame. Peak CK values were lower in patients with an in-frame deletion (median 3,466 U/L, range 611-12,046) than in those with an out-of-frame deletion (median 11,385 U/L, range 5,107-21,221). At the first genetic evaluation, five of the eight patients with an in-frame deletion and four of the nine patients with an out-of-frame deletion and a documented evaluation were asymptomatic; all four of the latter were aged 3 years or younger. Two patients, twin brothers, carried the same splice-site variant. In two patients the deletion was initially detected by chromosomal microarray and subsequently confirmed at the exon level by MLPA. Patient-level variant and clinical data are presented in Table 3.

Non-DMD Molecular Diagnoses

The 12 non-*DMD* diagnoses were identified in 10 different genes, and only *CAPN3* was represented more than once. They comprised seven distinct disease groups: LGMD (n=6), Bethlem myopathy (n=1), Emery-Dreifuss muscular dystrophy (n=1), Pompe disease (n=1), McArdle disease (n=1), myotonia congenita (n=1) and periodic paralysis (n=1), and three modes of inheritance, with eight autosomal recessive diagnoses (*GAA*, *CAPN3* in three patients, *SGCA*, *TCAP*, *POMT1*, *PYGM*), three autosomal dominant diagnoses (*COL6A1*, *CLCN1*, *SCN4A*) and one X-linked diagnosis (*EMD*). This distribution illustrates the potential genetic and mechanistic heterogeneity of non-*DMD* causes in this setting, although the small number of patients precludes firm conclusions regarding their relative frequencies. Nine of the 12 patients had a neuromuscular complaint or finding at the first genetic evaluation. Variant-level and clinical data are presented in Table 4.

Table 1. Demographic and laboratory characteristics of the cohort by molecular category

Variable	Explanatory molecular diagnosis (n=38)	Heterozygous *DMD* variant (n=9)	Molecularly unsolved (n=11)	Whole cohort (n=58)
Sex, male/female	34/4	0/9	8/3	42/16
Age, years	2 (1-6)	9 (5-14)	1 (0-11)	4 (1-10)
Peak CK, U/L	7,249 (1,468-11,385)	3,005 (2,071-4,404)	1,030 (546-3,800)	4,314 (1,339-9,892)
Peak AST, U/L	176 (62-270)	82 (53-98)	52 (50-94)	111 (51-254)
Peak ALT, U/L	167 (62-271)	65 (46-87)	55 (30-101)	105 (48-263)

Continuous variables are presented as median (interquartile range) of peak recorded values. Age is given in completed years, so that children under one year of age contribute a value of 0 to the numerical summaries. "Molecularly unsolved" denotes patients in whom no explanatory molecular finding was identified with the investigations performed. AST and ALT values were available for 54 patients; summaries were calculated using available observations. The institutional upper reference limit for CK was 200 U/L. CK: Creatine kinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Table 2. Distribution of explanatory molecular diagnoses (n=38)

Diagnostic group	n (%)	Peak CK, U/L
DMD-related dystrophinopathy	26 (68.4)	9,519 (6,667-13,647)
Non-*DMD* neuromuscular disorder	12 (31.6)	1,558 (896-2,815)
Limb-girdle muscular dystrophy	6 (15.8)	NC
Bethlem myopathy	1 (2.6)	NC
Emery-Dreifuss muscular dystrophy	1 (2.6)	NC
Pompe disease	1 (2.6)	NC
McArdle disease	1 (2.6)	NC
Myotonia congenita	1 (2.6)	NC
Periodic paralysis	1 (2.6)	NC

Peak CK values are presented as median (interquartile range) in U/L. NC: Not calculated; CK summaries are not presented for individual non-*DMD* subgroups because of the small subgroup sizes. CK: Creatine kinase.

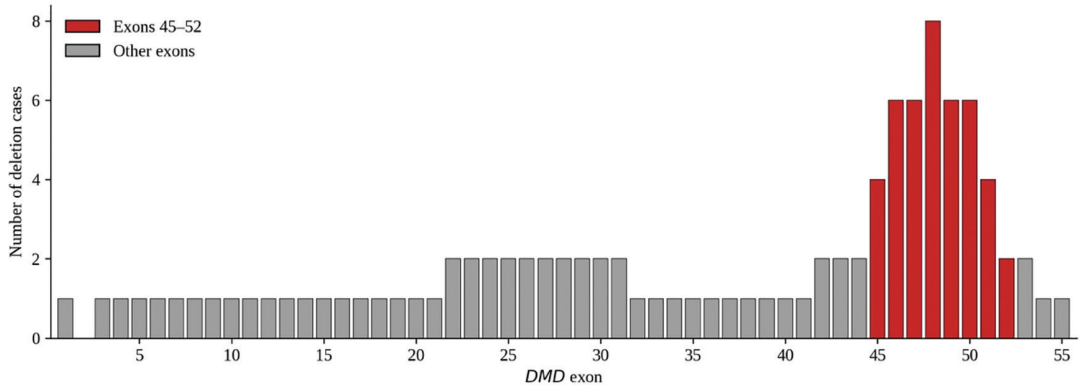


Figure 2. Distribution of *DMD* exonic deletions in dystrophinopathy cases (n=20). Exons within the 45-52 interval are shown in red, as indicated in the legend. The y-axis indicates the number of deletion cases involving the respective exon; a multi-exon deletion contributes to more than one exon column.

Heterozygous DMD Variants in Girls

Nine girls carried a heterozygous *DMD* variant, comprising six exon-level deletions and three small sequence variants. Standardised neuromuscular examination data, including muscle strength assessment, were not available for these patients; they were therefore analysed as a separate molecular category, and no inference regarding their clinical status was made. Four girls had a neuromuscular complaint or finding at the first genetic evaluation. Peak recorded CK values in this group ranged from 271 to 12,768 U/L (Table 5).

Peak Serum CK Values

The median peak CK in the whole cohort was 4,314 U/L (IQR 1,339-9,892; range 268-45,550). Median values were 7,249 U/L (1,468-11,385) in patients with an explanatory molecular diagnosis, 3,005 U/L (2,071-4,404) in girls with a heterozygous *DMD* variant and 1,030 U/L (546-3,800) in molecularly unsolved patients. Within the group with an explanatory molecular diagnosis, median peak CK was 9,519 U/L (6,667-13,647) in dystrophinopathy and 1,558 U/L (896-2,815) in non-*DMD* disorders, and within dystrophinopathy it was 8,889 U/L (5,286-13,883) in patients with an exonic deletion and 11,719 U/L (9,416-13,647) in those with a small sequence variant. Peak recorded CK values showed substantial descriptive overlap among molecular categories (Figure 3). No inferential statistical comparison between categories was performed.

Clinical Features and Course of CK Elevation

Clinical features are summarised in Table 6. The context in which CK elevation was first detected was documented in 46 patients: an incidental measurement in 17, investigation of elevated transaminases in 16, evaluation of muscle symptoms in 8 and other circumstances in 5. A neuromuscular complaint or finding was recorded at the first genetic evaluation in 35 of 56 patients. At least two CK measurements were available in 43 patients; CK elevation was persistent in 29 and transient in 2, and could not be assessed in 27 because fewer than two measurements, or only measurements less than 8 weeks apart, were available. Both patients with transient elevation were molecularly unsolved, whereas all non-*DMD* diagnoses with repeated measurements showed persistent elevation.

Discussion

In this single-centre cohort of children evaluated for elevated serum CK, *DMD*-related dystrophinopathy was the predominant molecular diagnosis, but it did not account for the whole of the explained aetiology. Approximately one third of molecular diagnoses were attributable to disorders unrelated to *DMD*, distributed across several genes, inheritance patterns and disease mechanisms rather than concentrated in a small number of alternative loci. Taken together, these observations indicate that the molecular basis of unexplained CK elevation in childhood is broader than dystrophinopathy alone, and that the differential diagnosis should be framed accordingly when a child is referred for genetic evaluation.

These findings do not imply that every child with elevated CK requires genetic testing. In this cohort, CK elevation was most often detected incidentally or during investigation of elevated transaminases, and persistence could not be

Table 3. Patient-level variant and clinical characteristics of *DMD*-related dystrophinopathy cases (n=26)

Case	Sex	Age, years	Peak CK, U/L	Exon range/HGVS	Variant type	Overlaps exons 45–52	Detection method	Reading frame	Clinical findings at first evaluation
D1	M	1	9,581	Exon 1 deletion	Exonic deletion	No	MLPA	NA	Asymptomatic (calf muscle pseudohypertrophy)
D2	M	2	7,122	Exon 3-7 deletion	Exonic deletion	No	MLPA	Out-of-frame	Gowers sign, calf muscle pseudohypertrophy, myalgia; other: arthralgia
D3	M	<1	9,457	Exon 8-44 deletion	Exonic deletion	No	MLPA	Out-of-frame	Asymptomatic; other: facial dysmorphism
D4	M	1	21,221	Exon 22-31 deletion	Exonic deletion	No	MLPA	Out-of-frame	Asymptomatic
D5	M	13	611	Exon 42-44 deletion	Exonic deletion	No	MLPA	In-frame	Asymptomatic; other: intellectual disability, seizure, scoliosis, facial dysmorphism
D6	M	4	6,667	Exon 45-48 deletion	Exonic deletion	Yes	MLPA	In-frame	Asymptomatic
D7	M	5	1,468	Exon 45-51 deletion	Exonic deletion	Yes	MLPA	In-frame	Gowers sign, gait disturbance, toe walking, myalgia
D8	M	12	8,321	Exon 45-47 deletion	Exonic deletion	Yes	MLPA	In-frame	Proximal lower limb muscle weakness, Gowers sign, calf muscle pseudohypertrophy; other: facial dysmorphism
D9	M	<1	1,396	Exon 45-47 deletion	Exonic deletion	Yes	MLPA	In-frame	Asymptomatic
D10	M	1	11,385	Exon 46-47 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Gowers sign, calf muscle pseudohypertrophy; other: arthralgia
D11	M	<1	17,860	Exon 46-50 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Not documented
D12	M	18	8,246	Exon 48-50 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Loss of ambulation; other: treated left ventricular systolic dysfunction
D13	M	3	20,909	Exon 48-50 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Asymptomatic
D14	M	2	5,464	Exon 48 deletion	Exonic deletion	Yes	MLPA	In-frame	Gowers sign
D15	M	3	19,069	Exon 48-52 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Not documented
D16	M	2	12,046	Exon 48-51 deletion	Exonic deletion	Yes	MLPA	In-frame	Asymptomatic
D17	M	6	15,720	Exon 51 deletion	Exonic deletion	Yes	MLPA	Out-of-frame	Gowers sign, calf muscle pseudohypertrophy
D18	M	2	1,379	Exon 52-53 deletion	Exonic deletion	Yes	MLPA	In-frame	Asymptomatic; other: facial dysmorphism
D19	M	<1	9,892	Exon 53-54 deletion	Exonic deletion	No	MLPA	Out-of-frame	Asymptomatic
D20	M	2	5,107	Exon 55 deletion	Exonic deletion	No	MLPA	Out-of-frame	Toe walking, calf muscle pseudohypertrophy
D21	M	1	13,300	c.10223+1G>A	Small sequence variant	NA	Sequence analysis	NA	Delayed ability to walk

Table 3. Continued

Case	Sex	Age, years	Peak CK, U/L	Exon range/HGVS	Variant type	Overlaps exons 45–52	Detection method	Reading frame	Clinical findings at first evaluation
D22	M	<1	13,647	c.7309+5G>C	Small sequence variant	NA	Sequence analysis	NA	Asymptomatic
D23	M	4	10,138	c.5899C>T (p.Arg1967Ter)	Small sequence variant	NA	Sequence analysis	NA	Gowers sign, toe walking, calf muscle pseudohypertrophy, exercise intolerance
D24	M	7	7,686	c.5287C>T (p.Arg1763Ter)	Small sequence variant	NA	Sequence analysis	NA	Difficulty climbing stairs, delayed ability to walk, exercise intolerance; other: delayed speech and language development
D25	M	1	9,416	c.2786_2788delinsG	Small sequence variant	NA	Sequence analysis	NA	Asymptomatic
D26	M	1	14,760	c.10223+1G>A	Small sequence variant	NA	Sequence analysis	NA	Delayed ability to walk

HGVS descriptions are presented as recorded in the available clinical laboratory reports; protein consequences are given in parentheses where reported. Small sequence variants comprise nonsense, frameshift, indel and splice-site changes. Ages below one year are shown as <1. M, male; MLPA, multiplex ligation-dependent probe amplification; NA, not applicable (overlap with exons 45-52 was assessed only for exon-level deletions). In cases D5 and D18 the deletion was initially detected by chromosomal microarray and confirmed by MLPA. Cases D21 and D26, who carried the same splice-site variant, are twin brothers. Reference transcripts, ACMG/AMP evidence codes and segregation analyses were not available in the source records. The reading frame was predicted for exon-level deletions from the coding lengths of the deleted exons; the exon 1 deletion was not classified, and NA in this column denotes small sequence variants. Clinical findings recorded at the first genetic evaluation are given as Human Phenotype Ontology terms in a fixed order (weakness, Gowers sign, motor and gait findings, muscle bulk, myalgia and exercise intolerance, myotonia, contractures), followed, after "other", by findings in other organ systems (developmental and growth, neurological, cardiac dysfunction, spinal and chest deformities, arthralgia and facial dysmorphism). Patients without any neuromuscular complaint or finding are designated asymptomatic, irrespective of findings in other organ systems; isolated calf muscle pseudohypertrophy, given in parentheses, did not classify a patient as symptomatic. Findings recorded as equivocal were considered present (Gowers sign in cases D10 and D14 and calf muscle pseudohypertrophy in case D20). Not documented, no record of the first evaluation available. CK: Creatine kinase; HGVS: Human Genome Variation Society.

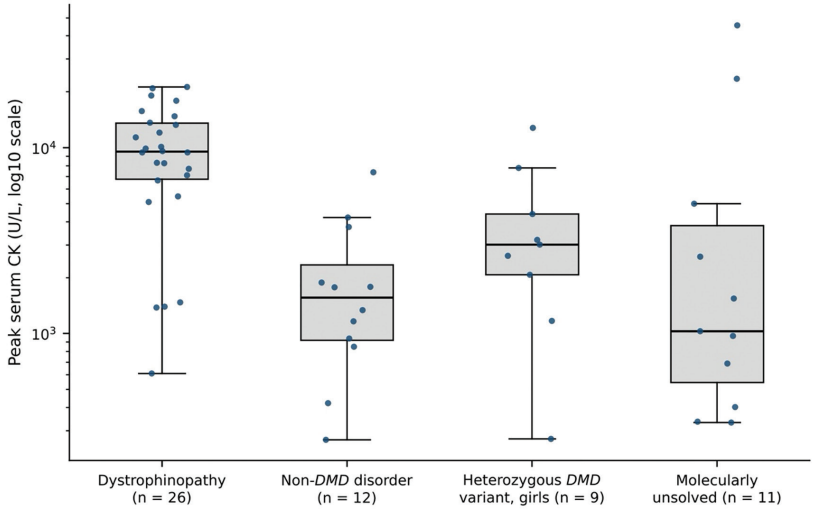


Figure 3. Distribution of peak serum creatine kinase across molecular categories (log10 scale). Boxes indicate the interquartile range, the line within the box the median, and whiskers the most extreme values within 1.5×IQR; points represent individual patients. No inferential comparison was performed between categories.

Table 4. Variant-level and clinical characteristics of non-*DMD* molecular diagnoses (n=12)

Case	Sex	Gene	Variant (HGVS)	Zygosity	Inh.	Disease	Peak CK, U/L	Detection method	Clinical findings at first evaluation
P1	M	*GAA*	c.1655T>C (p.Leu552Pro); c.2741delinsCAG (p.Gln914ProfsTer30)	Two variants; phase not determined	AR	Pompe disease	942	NGS panel	Asymptomatic
P2	F	*CAPN3*	c.1381C>T (p.Arg461Cys)	Homozygous	AR	LGMD R1 calpain3-related	1,777	NGS panel	Myalgia, exercise intolerance
P3	M	*COL6A1*	c.824G>A (p.Gly275Glu)	Heterozygous	AD	Bethlem myopathy	423	NGS panel	Proximal lower limb muscle weakness, frequent falls, tight Achilles tendon
P4	M	*POMT1*	c.598G>C (p.Ala200Pro)	Homozygous	AR	LGMD R11 *POMT1*-related	7,376	NGS panel	Delayed ability to walk; other: delayed speech and language development, growth delay, facial dysmorphism
P5	F	*SGCA*	c.739G>A (p.Val247Met)	Homozygous	AR	LGMD R3 α-sarcoglycan-related	4,224	NGS panel	Asymptomatic
P6	M	*CLCN1*	c.501C>G (p.Phe167Leu)	Heterozygous	AD	Myotonia congenita	268	NGS panel	Myotonia
P7	M	*EMD*	c.506_507del (p.Pro169ArgfsTer60)	Hemizygous	XL	Emery-Dreifuss muscular dystrophy	851	NGS panel	Difficulty climbing stairs, frequent falls, toe walking, exercise intolerance
P8	M	*TCAP*	c.90_91del (p.Ser31HisfsTer11)	Homozygous	AR	LGMD R7 telethonin-related	1,339	Exome sequencing	Limb-girdle muscle weakness, Gowers sign, limited elbow movement, limitation of knee mobility; other: kyphosis, pectus carinatum
P9	M	*SCN4A*	c.2111C>T (p.Thr704Met)	Heterozygous	AD	Periodic paralysis	1,163	Sequence analysis	Limb-girdle muscle weakness, episodic flaccid weakness, skeletal muscle atrophy
P10	F	*CAPN3*	c.1469G>A (p.Arg490Gln)	Homozygous	AR	LGMD R1 calpain3-related	1,786	NGS panel	Toe walking; other: facial dysmorphism
P11	M	*PYGM*	c.2262del	Homozygous	AR	McArdle disease	1,879	Sequence analysis	Asymptomatic
P12	F	*CAPN3*	c.245C>T (p.Pro82Leu); c.1621C>T (p.Arg541Trp)	Compound heterozygous	AR	LGMD R1 calpain3-related	3,751	NGS panel	Myalgia

HGVS descriptions are presented as recorded in the available clinical laboratory reports; gene symbols are italicised and protein consequences are given in parentheses where reported. M: Male, F: Female, AR: Autosomal recessive, AD: Autosomal dominant, XL: X-linked, Inh.: Inheritance, LGMD: Limb-girdle muscular dystrophy, NGS: Next-generation sequencing, CK: Creatine kinase, HGVS: Human Genome Variation Society. Reference transcripts, ACMG/AMP evidence codes and segregation analyses were not available in the source records. Clinical findings are reported as in Table 3. LGMD subtypes are named according to the current nomenclature (11). In case P1, two *GAA* variants were reported and the phase was not determined; echocardiography showed no cardiomyopathy.

Table 5. Molecular, laboratory and clinical characteristics of girls with a heterozygous *DMD* variant (n=9)

Case	Variant (HGVS)	Zygosity	Peak CK, U/L	Detection method	Clinical findings at first evaluation
T1	c.2104G>T (p.Glu702Ter)	Heterozygous	2,071	NGS panel	Exercise intolerance
T2	Exon 50 deletion	Heterozygous	2,614	MLPA	Asymptomatic; other: arthralgia
T3	Exon 48-50 deletion	Heterozygous	3,005	MLPA	Asymptomatic
T4	Exon 10-11 deletion	Heterozygous	1,170	MLPA	Proximal lower limb muscle weakness, Gowers sign
T5	c.5612dup (p.Ala1872GlyfsTer16)	Heterozygous	3,199	NGS panel	Limb-girdle muscle weakness
T6	c.519_522del (p.His174ValfsTer33)	Heterozygous	7,795	NGS panel	Asymptomatic
T7	Exon 42-44 deletion	Heterozygous	271	MLPA	Asymptomatic
T8	Exon 10-43 deletion	Heterozygous	4,404	MLPA	Gait disturbance, exercise intolerance; other: global developmental delay, spasticity, ophthalmoplegia, tremor, dysphagia, scoliosis
T9	Exon 45-47 deletion	Heterozygous	12,768	MLPA	Asymptomatic

HGVS descriptions are presented as recorded in the available clinical laboratory reports; protein consequences are given in parentheses where reported. MLPA: Multiplex ligation-dependent probe amplification; NGS: Next-generation sequencing, CK: Creatine kinase, HGVS: Human Genome Variation Society. Reference transcripts, ACMG/AMP evidence codes, segregation analyses and standardised neuromuscular examination data were not available in the source records. Clinical findings are reported as in Table 3.

Table 6. Clinical features at first evaluation and course of CK elevation by molecular category

Variable	Dystrophinopathy (n=26)	Non-*DMD* disorder (n=12)	Heterozygous *DMD* variant (n=9)	Molecularly unsolved (n=11)	Whole cohort (n=58)
Context of detection documented	18	11	7	10	46
Incidental measurement	7	3	4	3	17
Investigation of elevated transaminases	8	3	2	3	16
Evaluation of muscle symptoms	2	4	0	2	8
Other	1	1	1	2	5
Examination at first evaluation documented	24	12	9	11	56
Neuromuscular complaint or finding present	12	9	4	10	35
≥2 CK measurements available	16	10	8	9	43
CK course: persistent	11	10	5	3	29
CK course: transient	0	0	0	2	2
CK course: not assessable	15	2	4	6	27
Consanguinity documented	20	11	6	8	45
Consanguinity present (first cousins)	5 (1)	5 (4)	1 (0)	4 (3)	15 (8)
Family history documented	20	11	8	8	47
Family history of neuromuscular disease	8	5	3	2	18

Values are numbers of patients. Variables were extracted retrospectively from clinical records; "documented" denotes the number of patients in whom the variable was recorded. A neuromuscular complaint or finding denotes weakness, Gowers sign, gait disturbance, myalgia, exercise intolerance, myotonia, hypotonia or motor delay recorded at the first genetic evaluation; equivocal findings were considered present. CK course: persistent, CK above the upper reference limit on at least two occasions more than 8 weeks apart without subsequent normalisation; transient, normalisation during follow-up; not assessable, fewer than two measurements or measurements less than 8 weeks apart. The number of first-cousin unions is given in parentheses. CK: Creatine kinase.

assessed in almost half of the patients; conversely, more than half had a neuromuscular complaint or finding at the first genetic evaluation, all non-*DMD* diagnoses with repeated measurements showed persistent elevation, consanguinity was frequent among the non-*DMD* diagnoses, and the only two patients whose CK normalised remained molecularly unsolved. These observations are consistent with the stepwise, phenotype-driven approach proposed in paediatric series (5,16), in which the elevation is first confirmed on repeated measurement, with recent exercise, trauma or intercurrent illness excluded (5), and history, family history, physical examination and targeted laboratory tests then determine whether, and which, genetic test is indicated. In the two channelopathies in this cohort, myotonia and episodic weakness, rather than the CK level, pointed to the diagnosis.

The relevance of the non-*DMD* diagnoses lies less in their number than in their distribution. The 12 diagnoses involved 10 different genes, spanning seven disease groups and three modes of inheritance, and only *CAPN3* was represented more than once. This pattern illustrates the breadth of the differential diagnosis of paediatric CK elevation and is consistent with the marked genetic heterogeneity reported in NGS-based series of inherited myopathies and hyperCKemia (13-15). Because the number of patients is limited, these findings should not be taken to establish the relative frequencies of individual disorders; they suggest, rather, that a diagnostic approach directed only at the most common cause may leave a clinically meaningful minority unexplained. The predominance of autosomal recessive LGMD subtypes among our non-*DMD* diagnoses is consistent with a previous Turkish series in which all molecularly confirmed LGMD subtypes were autosomal recessive and consanguinity was frequent (20).

Four diagnoses fell outside the category of muscular dystrophy altogether: two metabolic myopathies (Pompe disease and McArdle disease) and two muscle channelopathies (myotonia congenita and periodic paralysis). Their identification is clinically relevant because disorders of this kind require different monitoring and, in the case of Pompe disease, disease-specific enzyme replacement therapy, for which a positive effect at group level, with considerable inter-individual variability in response, has been reported in children with non-classic disease during long-term follow-up (21). Recognising such conditions promptly is therefore of practical importance in a child whose only initial abnormality is a raised CK, and metabolic disorders have similarly been reported in paediatric series of CK elevation (16,17).

Although peak CK values were generally higher in dystrophinopathy than in other categories, the distributions overlapped substantially, and several non-*DMD* diagnoses were identified at comparatively modest CK concentrations. No inferential comparison was undertaken, so no discriminatory value can be attributed to CK in this cohort. From a practical standpoint, the magnitude of CK elevation should not by itself be used to prioritise or to exclude particular genetic diagnoses, and it is best interpreted alongside the clinical picture and family history, particularly as paediatric CK reference limits vary with age and sex (1).

Our dystrophinopathy findings are consistent with previous work. Exonic deletions predominated and most overlapped the central exon 45-52 hotspot, in line with the predominance and central clustering of deletions described in large dystrophinopathy cohorts (8,9). The absence of exon-level duplications contrasts with those cohorts, in which exon-level duplications accounted for 13% of registered patients and 10.7% of molecularly diagnosed patients, respectively (8,9), and may be related to the limited number of cases. Peak CK values were lower in patients with an in-frame deletion than in those with an out-of-frame deletion. Symptom status at the first evaluation, however, was not clearly different between the two small groups and largely reflected age, because most patients were evaluated in early childhood, whereas the Duchenne and Becker phenotypes are defined by the subsequent course of ambulation (8). These genotype–phenotype relationships are therefore descriptive and require longitudinal follow-up. The predominance of dystrophinopathy among our molecular diagnoses accords with paediatric series of CK elevation, in which dystrophinopathies were the most frequent inherited neuromuscular diagnosis (5-7), whereas the joint identification of dystrophinopathy and non-*DMD* diagnoses in our cohort may partly reflect the fact that it was not restricted by symptom status, in contrast to series confined to asymptomatic or minimally symptomatic individuals, in which overtly symptomatic dystrophinopathy is underrepresented or excluded by design (2,3,14).

Girls with a heterozygous *DMD* variant were analysed as a separate molecular category. Standardised neuromuscular assessment, including muscle strength testing, was not available for these patients. In a survey of 32 confirmed female carriers of *DMD* variants reported alongside a population-based CK screening programme, only half had

elevated CK, and CK values varied even among carriers of the same variant (4); the clinical status of a carrier cannot be inferred from the molecular finding or the CK level alone. Assigning these girls to either the diagnosed or the unexplained group would therefore have misrepresented their status and altered the denominator on which the aetiological proportions were calculated.

The main strengths of this study are the joint description of *DMD*-related and non-*DMD* diagnoses within a single referred cohort, its molecular classification and its transparency. All explanatory diagnoses were based on molecularly confirmed pathogenic or likely pathogenic variants. Results were assigned to three mutually exclusive categories with explicit denominators; heterozygous *DMD* variants in girls were analysed separately rather than merged with disease diagnoses; findings are reported at the level of individual patients and variants rather than as aggregate counts; and molecularly unsolved patients were interpreted conservatively rather than as true negatives.

Study Limitations

Several limitations should be considered. The study is retrospective and single-centre, and referral patterns to a tertiary genetics clinic are likely to have influenced the composition of the cohort. Genetic testing was performed according to clinical indication rather than a uniform protocol, so the extent of investigation differed between patients; although all molecularly unsolved patients had undergone both MLPA and a multigene NGS panel, none had undergone whole-exome or genome sequencing, and deep intronic variants, repeat expansions and genes not covered by the panels may therefore have been missed. Pathogenicity classifications were taken from the final clinical laboratory reports and cross-checked against ClinVar, but an independent ACMG/AMP re-scoring was not undertaken, and one variant accepted as explanatory (*CLCN1* p.Phe167Leu) has conflicting classifications in ClinVar. Clinical features were extracted retrospectively from routine records, standardised muscle strength assessment was not available, and persistence of CK elevation could not be assessed in almost half of the patients, which limits genotype–phenotype correlation. Because eligibility was based on a documented peak value rather than on demonstrated persistence, transient causes of CK elevation, such as recent exercise, trauma or viral myositis, cannot be excluded, particularly among molecularly unsolved patients. Consanguinity was not documented in 13 patients. The cohort size also limits the precision of the proportions reported.

Conclusion

DMD-related dystrophinopathies represented the majority of explanatory molecular diagnoses in this selected paediatric referral cohort. However, non-*DMD* diagnoses encompassed multiple genes, inheritance patterns and disease mechanisms, including clinically actionable metabolic and channel disorders. These findings illustrate that, once persistent elevation has been confirmed and the history, family history and examination have been evaluated, the evaluation of unexplained paediatric CK elevation should extend beyond *DMD* when initial dystrophinopathy testing is unrevealing or the phenotype is atypical. Prospective multicentre studies using uniform testing and standardised phenotyping are required to better define the diagnostic spectrum and genotype–phenotype relationships.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Samsun University (protocol code: GOKAEK 2026/8/12, date of approval: 6 May 2026).

Informed Consent: The requirement for informed consent was waived by the ethics committee because of the retrospective design and the use of anonymised data.

Footnotes

Authorship Contributions

Concept: E.S., Design: E.S., A.S., Data Collection or Processing: E.S., Ü.A., Analysis or Interpretation: E.S., A.U., Literature Search: E.S., Critical Review: E.S., G.A., A.S., N.A., Ü.A., A.U., Writing: E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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