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RESEARCH

Clinical and molecular findings in 44 Turkish patients with infantile-onset Pompe disease

İnfantil başlangıçlı Pompe hastalığı olan 44 Türk hastada klinik ve moleküler bulgular

Deniz Kor[1], Caner Hacıoğlu[1], Fatma Derya Bulut[1], İrem Kaplan[1], Nazmiye Tüzel Gündüz[1], Ezgi Burgaç[1,2], Burcu Köşeci[1,2], Esra Kara[1,3], Sevcan Tuğ Bozdoğan[1], Halise Neslihan Önenli Mungan[1]

[1]Cukurova University, Adana, Türkiye
[2]Adana City Hospital, Adana, Türkiye
[3]Cengiz Gökçek Gynecology and Pediatrics Hospital, Gaziantep, Türkiye

Abstract

Purpose: This study aims to investigate genotype–phenotype correlations in a cohort of 44 patients diagnosed with Infantile-onset Pompe disease (IOPD)
Materials and Methods: This retrospective study analyzed the clinical and genetic characteristics of 44 Turkish infants diagnosed with IOPD between 2009 and 2025. Data on clinical presentation, *GAA* mutations, treatment, and outcomes were collected and evaluated.
Results: The majority of patients (95.5%) presented with the classic IOPD phenotype. The mean age at symptom onset was 59.1 days, with cardiomegaly being the most common initial symptom. ERT was initiated at a mean age of 114.9 days. Despite treatment, the mortality rate remained high at 56.8%, with respiratory failure being the leading cause of death. All surviving patients exhibited improvement in cardiomyopathy; however, complications such as muscle weakness, kyphoscoliosis, and oropharyngeal dysfunction persisted. A total of 18 distinct *GAA* mutations were identified, including four novel variants. The most frequent mutation was p. L299P (42.9%). No definitive genotype–phenotype correlation was observed.
Conclusion: These findings highlight the genetic heterogeneity and clinical complexity of IOPD in a highly consanguineous population. The high prevalence of the p.L299P mutation suggests that it may represent a founder mutation in the Turkish population..

Keywords:. Enzyme replacement therapy; genotype–phenotype correlation; Infantile-onset pompe disease

Öz

Amaç: Bu çalışma, infantil başlangıçlı Pompe hastalığı (IOPD) tanısı konmuş 44 hastadan oluşan bir kohortta genotip-fenotip korelasyonlarını araştırmayı amaçlamaktadır.
Gereç ve Yöntem: Bu retrospektif çalışmada, 2009 ile 2025 yılları arasında IOPD tanısı alan 44 Türk bebekte klinik ve genetik özellikler değerlendirilmiştir. Klinik bulgular, *GAA* mutasyonları, tedavi süreçleri ve sonuçlara ilişkin veriler analiz edilmiştir.
Bulgular: Hastaların büyük çoğunluğu (%95,5) klasik IOPD fenotipi göstermiştir. Semptomların ortalama başlangıç yaşı 59,1 gündür ve en sık ilk belirti kardiyomegali olmuştur. ERT ortalama 114,9 günlükken başlatılmıştır. Tedaviye rağmen mortalite oranı %56,8 olarak bulunmuş, en sık ölüm nedeni solunum yetmezliği olmuştur. Hayatta kalan tüm hastalarda kardiyomiyopatide düzelme gözlenmiş, ancak kas güçsüzlüğü, kifoskolyoz ve orofaringeal disfonksiyon gibi komplikasyonlar devam etmiştir. Toplam 18 farklı *GAA* mutasyonu saptanmış, bunlardan dördü literatürde daha önce bildirilmemiştir. En sık rastlanan mutasyon, %42,9 oranıyla p. L299P olmuştur. Genotip-fenotip arasında belirgin bir korelasyon saptanmamıştır.
Sonuç: Bulgularımız, yüksek oranda akraba evliliği görülen bir popülasyonda IOPD'nin genetik çeşitliliğini ve klinik karmaşıklığını vurgulamaktadır. p.L299P mutasyonunun yüksek sıklığı, bunun Türk toplumuna özgü bir kurucu (founder) mutasyon olabileceğini düşündürmektedir.
Anahtar kelimeler: İnfantil başlangıçlı pompe hastalığı, enzim replasman tedavisi, genotip-fenotip koreasyonu

Address for Correspondence: Deniz Kor, Cukurova University, Faculty of Medicine, Division of Pediatric Metabolism and Nutrition, Department of Pediatrics, Adana, Türkiye E-mail: dozonur@yahoo.com
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INTRODUCTION

Pompe disease (glycogen storage disease type II, OMIM #232300) is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in the *GAA* gene, which encodes the enzyme acid alpha-glucosidase (GAA). Deficiency or complete absence of this enzyme leads to the accumulation of glycogen within lysosomes, primarily affecting cardiac, skeletal, and smooth muscle tissues[1]. The estimated incidence of Pompe disease is approximately 1 in 40,000 live births. The clinical presentation of Pompe disease varies widely, ranging from predominant cardiac involvement to skeletal muscle manifestations, with considerable variability in age at onset and disease severity. It is generally classified into two major forms: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD)[2]

IOPD is the most severe form, typically presenting within the first few months of life. Clinical features include generalized hypotonia, hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, and progressive respiratory insufficiency. Without treatment, most patients die within the first year of life. A nonclassic form of IOPD may also present during infancy but follows a slower disease course and is associated with milder cardiomyopathy [3]. In contrast, LOPD presents in childhood or adulthood and is characterized by slowly progressive muscle weakness—primarily affecting the lower limbs—along with cardiomyopathy and respiratory dysfunction[4]. The introduction of enzyme replacement therapy (ERT) using recombinant human GAA has markedly improved survival rates and quality of life in affected infants[5].

The *GAA* gene (OMIM #606800) is located on chromosome 17 and spans approximately 20 kb, comprising 20 exons and 19 introns. The first exon is noncoding, with the start codon located at position 33 of exon 2. To date, more than 560 variants have been identified in the *GAA* gene, with most classified as pathogenic, although some remain of uncertain significance. Certain pathogenic variants show a higher prevalence in specific populations[4]. Genotype–phenotype correlation studies suggest that the type and combination of *GAA* mutations influence disease severity and age of onset. However, clinical variability observed even among individuals with the same genotype suggests that other modifying factors—such as epigenetic mechanisms, environmental influences, and genetic background—also contribute to disease expression[6].

This study aims to investigate genotype–phenotype correlations in a cohort of 44 patients diagnosed with IOPD. The primary objective is to evaluate the relationship between GAA gene variants and clinical outcomes, including age at symptom onset, severity of cardiac involvement, respiratory function, motor abilities, and response to treatment. To the best of our knowledge, this represents one of the largest single-center cohorts of IOPD patients reported from our region. The findings from this study may contribute to improved risk stratification, more personalized treatment strategies, and optimized long-term care for infants affected by this serious lysosomal storage disorder.

MATERIALS AND METHODS

Procedure

This retrospective cohort study was conducted at the Department of Pediatric Metabolism and Nutrition, Faculty of Medicine, Çukurova University, between November 2009 and April 2025. Patient data were collected from existing medical records. Written informed consent was obtained from all participants during clinical visits, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Detailed physical examinations were performed at diagnosis and during follow-up visits at the outpatient clinic. Clinical, echocardiographic, and laboratory findings, genetic analysis results, and patient outcomes were retrospectively reviewed. All patients were initially diagnosed based on characteristic clinical features, which were confirmed by enzyme activity assays and subsequently validated through *GAA* gene mutation analysis.

Patients were included if they had a diagnosis of IOPD and confirmed *GAA* gene mutation analysis results. Patients without available genetic testing data were excluded. Given the rarity of Pompe disease, no formal power analysis was conducted. Instead, all clinically and laboratory-confirmed Pompe disease patients with available genetic analysis results who were followed at our center during the study period were included. The study was approved by the Ethics

Committee of the Faculty of Medicine, Çukurova University (Approval No. 155/16.05.2025).

Mutation analysis

Mutation analysis was performed for all participants, and results were obtained retrospectively from medical records. Genomic DNA was isolated from 2 mL of peripheral blood collected in EDTA tubes via venipuncture of the antecubital vein. DNA extraction was conducted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. DNA quality was assessed using a Qubit Fluorometer (Thermo Fisher Scientific, Waltham, Massachusetts).

Next-generation sequencing was performed on all coding exons, exon–intron junctions, 5' promoter regions, and 3' untranslated regions of the *GAA* gene. Library preparation followed the manufacturer's protocols, and sequencing was conducted on an Illumina MiSeq platform (Foster City, California), achieving a minimum coverage depth of 150x.

Identified variants were interpreted using publicly available databases, including the Human Gene Mutation Database (HGMD), ClinVar, NCBI dbSNP, and Pompe-specific variant registries. Variant classification followed the guidelines of the American College of Medical Genetics and Genomics. Variants not listed in HGMD, dbSNP, ClinVar, or VarSome were considered novel. These novel variants were further analyzed using *in silico* prediction tools, including PolyPhen, MutationTaster, CADD, SIFT, BLOSUM, PhyloP, GeneSplicer, and B-SIFT.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 20.0 (IBM Corp., Armonk, New York). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was used to assess the normality of distribution for continuous variables. For group comparisons, Student's *t* test was applied to normally distributed variables, and the Mann–Whitney *U* test was used for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, depending on cell counts. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

A total of 44 Turkish infants diagnosed with IOPD were included in the study. Based on age at onset, age at diagnosis, and clinical features, 42 patients (95.5%) were classified as having classic IOPD and two (4.5%) as having non-classic IOPD. The cohort included 21 males and 23 females. Parental consanguinity was present in 84% of cases.

The mean age at symptom onset was 59.1 ± 56.4 days (range: 0–225 days). The most common initial symptom was cardiomegaly (29.5%), followed by respiratory distress (22.7%), a positive family history (20.5%), muscular hypotonia (15.9%), a murmur detected during routine check-up (9.1%), and malnutrition (2.3%). All patients developed macroglossia and myopathic facies during the follow-up period. Detailed patient characteristics and clinical data are summarized in Table 1.

The mean age at initiation of ERT was 114.9 ± 70.6 days (range: 15–306 days). All patients received Myozyme at a dose of 40 mg/kg every 2 weeks. Among the surviving patients, cardiomyopathy improved with ERT. At the time of analysis, 19 patients were alive, while 25 had died. Among those treated for at least 1 yr, the primary cause of death was respiratory failure; six patients died due to heart failure. The mean age at death was 41.3 ± 34.2 months (range: 4–135 months). The mean duration of ERT was 116.5 ± 44.1 months in surviving patients and 38.0 ± 35.0 months in those who had died. Four of the 19 surviving patients were dependent on mechanical ventilation. Morbidities among survivors included kyphoscoliosis, restrictive lung disease, oropharyngeal dysfunction, speech delay, and hearing impairment.

Cross-reactive immunologic material (CRIM) status was definitively determined in 37 of 44 patients (84%). Of these, 25 patients (57%) were CRIM-positive, and 12 (27%) were CRIM-negative; CRIM status remained indeterminate in seven patients (16%). At the last follow-up, survival was significantly higher in the CRIM-positive group (14 of 25; 56%) than in the CRIM-negative group (2 of 12; 17%). Mechanical ventilation was required in three CRIM-positive patients (12%) and one CRIM-negative patient (8%). Cardiac conduction defects were observed in five CRIM-positive patients (20%) and three CRIM-negative patients (25%). Hearing loss was reported in seven CRIM-positive patients (28%) and two CRIM-negative patients (17%). These

findings support the prognostic relevance of CRIM status, as CRIM-negative patients exhibited lower survival rates and more limited clinical responses to ERT (Tables 2 and 3).

All patients had reduced GAA enzymatic activity. Eighteen distinct *GAA* gene mutations were identified across 44 patients from 42 families, including four novel variants. In seven patients, there was no reported parental consanguinity; of these, three were compound heterozygotes. The most common mutation was p.L299P, found in 36 alleles (42.9%), followed by p.E888* (7 alleles; 8.3%) and p.N87Qfs*9 (6 alleles; 7.1%). All identified mutations are listed in Table 2, and allele frequencies are provided in Table 3.

The novel variants identified were p.Y136D, p.D399Pfs*105, p.I477Mfs*43, and p.N316I, none of which have been previously reported in disease variant databases. No significant genotype–phenotype correlation could be established. The rarity and genetic heterogeneity of IOPD, combined with the relatively small sample size and diverse mutation spectrum of our cohort, limited the ability to perform robust statistical correlation analyses. Consequently, our observations remain descriptive. Larger-scale studies are needed to clarify potential genotype–phenotype associations.

Table 1. Clinical characterization of the IOPD patients

Patient no	Gender	Age at presentation (day)	Presenting features	Age at start of ERT(day)	Duration of ERT (mo)	Mechanically ventilated*	Alive/exitus**	Cardiac conduction deficit (+/-)	Hearing loss
1	M	98	Respiratory insufficiency	149	89	90	Alive/93		
2	F	66	Routine control	78	43		Alive/46		
3	F	62	Respiratory insufficiency	131	26		Exitus/30		
4	M	1	Family history	17	25		Exitus/26		
5	F	10	Hypotonia	115	135		Alive/139	-	+
6	M	105	Malnutrition	180	37		Exitus/43		
7	M	62	Respiratory insufficiency	117	20		Exitus/24		
8	F	150	Respiratory insufficiency	185	41		Exitus/47	-	-
9	M	65	Respiratory insufficiency	85	158	149	Alive/160	+	-
10	M	1	Family history	24	134		Exitus/135	-	+
11	M	110	Hypertrophic cardiomyopathy	148	7		Exitus/12		
12	M	1	Hypotonia	195	127		Alive/134	+	-
13	F	1	Hypertrophic cardiomyopathy	43	143	139	Alive/144	+	+
14	M	25	Hypertrophic cardiomyopathy	47	153		Alive/155	+	+
15	F	100	Respiratory insufficiency	142	102		Alive/107	-	-
16	F	0	Respiratory insufficiency	66	49		Exitus/51	-	+
17	F	2	Family history	33	80		Exitus/81	-	-
18	F	1	Family history	41	73		Exitus/75		-
19	F	90	Hypotonia	306	113	9	Alive/123	-	

20	F	40	Hypertrophic cardiomyopathy	132	0		Exitus/4		
21	M	120	Hypertrophic cardiomyopathy	155	8		Exitus/13		
22	M	120	Hypertrophic cardiomyopathy	184	16		Exitus/22		
23	M	45	Family history	53	83		Exitus/84		
24	M	1	Family history	26	127		Alive/128	-	+
25	F	105	Routine control	196	91		Alive/97	-	+
26	M	60	Hypertrophic cardiomyopathy	169	77	79	Alive/83	-	-
27	M	63	Hypotonia	99	9		Exitus/12	+	
28	F	45	Respiratory insufficiency	81	179		Alive/182	-	-
29&	M	225	Routine control	285	134		Alive/144		-
30	F	1	Hypertrophic cardiomyopathy	45	86		Exitus/87	+	+
31	F	80	Hypotonia	126	53		Exitus/58	-	
32	M	135	Family history	173	2		Exitus/8		
33	M	90	Hypertrophic cardiomyopathy	96	25		Exitus/28		
34	F	1	Family history	28	186		Alive/187	-	+
35	M	1	Hypotonia	27	18		Exitus/19	+	
36	F	1	Family history	15	13		Exitus/13	+	
37	M	1	Routine control	83	22		Exitus/24		
38	F	120	Respiratory insufficiency	133	171		Alive/175		-
39	M	20	Hypertrophic cardiomyopathy	77	90		Alive/92	-	-
40	F	100	Hypertrophic cardiomyopathy	137	0		Exitus/4	-	
41	F	60	Hypertrophic cardiomyopathy	160	31		Exitus/36		
42	F	1	Hypertrophic cardiomyopathy	83	93		Exitus/96	+	-
43	F	30	Respiratory insufficiency	158	50		Alive/55		
44&	F	186	Hypotonia	234	46		Alive/53		

&non-classic IOPD; * age at the need for mechanical ventilation in months; ** If alive, current age in months. If exitus, age of death in months; F:female, M:male, mo:month

Table 2. *GAA* gene variants

No	Protein change	Protein change	Zygosity	CRIM status*	ACMG	Severity score*
1	p.L299P	p.E888*	CH	Pos/Neg	Pathogenic	Potentially less severe / Very severe
2	p.L299P	p.R40*	CH	Pos/Neg	Pathogenic	Potentially less severe/ Very severe
3	p.E888*	p.E888*	H	Neg	Pathogenic	Very severe
4	**p.N316I**	**p.N316I**	H	Pos	This study	Potentially less severe
5	IVS10+1G>T	IVS10+1G>T	H	Pos	Pathogenic/Likely pathogenic	Potentially less severe
6	p.A261T	p.A261T	H	NK	Uncertain significance	Potentially less severe
7	p.D399Pfs*105	p.D399Pfs*105	H	Neg	This study	NK
8	p.D616E	p.D616E	H	NK	Likely pathogenic	NK
9	p.E888*	p.E888*	H	Neg	Pathogenic	Very severe
10	p.E888*	p.E888*	H	Neg	Pathogenic	Very severe
11	**p.I477Mfs*43**	**p.I477Mfs*43**	H	NK	This study	NK
12	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
13	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
14	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
15	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
16	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
17	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
18	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
19	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
20	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
21	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
22	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
23	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
24	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
25	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
26	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
27	p.L299R	p.L299R	H	Pos	Likely pathogenic	Potentially less severe
28	p.L299R	p.L299R	H	Pos	Likely pathogenic	Potentially less severe
29	p.M519T	p.M519T	H	Pos	Pathogenic	Potentially less severe
30	**p.N316I**	**p.N316I**	H	Pos	This study	Potentially less severe
31	p.N87Qfs*9	p.N87Qfs*9	H	Neg	Pathogenic	Very severe
32	p.N87Qfs*9	p.N87Qfs*9	H	Neg	Pathogenic	Very severe
33	p.N87Qfs*9	p.N87Qfs*9	H	Neg	Pathogenic	Very severe
34	p.Q914Pfs*30	p.Q914Pfs*30	H	Neg	Pathogenic	Very severe
35	p.R608X	p.R608X	H	Neg	Pathogenic	Very severe
36	p.R608X	p.R608X	H	Neg	Pathogenic	Very severe
37	p.R660C	p.R660C	H	Pos	Pathogenic	Potentially less severe
38	p.R660C	p.R660C	H	Pos	Pathogenic	Potentially less severe
39	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
40	p.W746*	p.W746*	H	Neg	Pathogenic	Very severe
41	p.W746*	p.W746*	H	Neg	Pathogenic	Very severe
42	p.Y136D	p.R870*	CH	NK/Neg	This study / Pathogenic	-/Very severe
43	p.L299P	p.L299P	H	Pos	Pathogenic	Potentially less severe
44	p.Y136D	p.Y136D	H	NK	This study	NK

Novel variants are shown in bold; *CRIM status and severity score predicted based on Erasmus Pompe database (http://www.pompevariantdatabase.nl/ updated in Dec 2020); Neg: negative, NK: not known, Pos: positive, ACMG: American college of medical genetics, H: homozygous, CH: compound heterozygous, CRIM: Cross-Reactive Immunologic Material

Table.3 Allele frequency

Allele	Frequency	Percent (%)
p.L299P	36	42.9
p.E888*	7	8.3
p.N87Qfs*9	6	7.1
p.R660C	4	4.8
p.L299R	4	4.8
p.W746*	4	4.8
p.Y136D	3	3.6
p.D399Pfs*105	2	2.4
p.I477Mfs*43	2	2.4
p.N316I	2	2.4
IVS10+1G>T	2	2.4
p.A261T	2	2.4
p.D616E	2	2.4
p.M519T	2	2.4
p.Q914Pfs*30	2	2.4
p.R608X	2	2.4
p.R870*	1	1.2
p.R40*	1	1.2

Novel variants are shown in bold

DISCUSSION

This study represents one of the most comprehensive cohorts of Turkish patients with IOPD and provides valuable insights into the clinical, biochemical, and molecular characteristics of the disease in a highly consanguineous population.

Infantile-onset Pompe disease is diagnosed in individuals who present before 12 months of age with cardiomegaly. Although the disease may be apparent *in utero*, it more commonly presents around 4 months of age with hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, respiratory distress, and hypertrophic cardiomegaly. Without appropriate therapy, such as ERT, most affected infants die from cardiorespiratory failure by the age of 2 years[7]. The predominance of the classic phenotype (95.5%) in our cohort aligns with findings from previous studies in populations with high rates of consanguinity, such as Saudi Arabia[8].

In our patient group, the mean ages at symptom onset and diagnosis were within the expected ranges. The most frequently observed initial symptoms were cardiomegaly and dyspnea, consistent with the typical cardiac and skeletal muscle involvement seen in IOPD[3].

No statistically significant differences were observed in the age at symptom onset or the initiation of ERT between survivors and deceased patients. This suggests that while early diagnosis and treatment are important, they may not be sufficient to determine long-term outcomes, especially in patients with severe systemic involvement at birth. Previous studies have reported that some patients continue to experience poor outcomes despite early initiation of ERT, particularly when significant cardiovascular or neuromuscular dysfunction is already present at diagnosis[9,10]. These findings suggest that multiple factors may contribute to prognosis.

Although all surviving patients in our cohort showed improvement in cardiomyopathy, skeletal muscle weakness persisted, resulting in delayed motor milestone achievement and progressive functional decline. These outcomes are consistent with previous reports involving long-term ERT in IOPD patients[10–12].

The overall mortality rate in our cohort was 56.8%, with respiratory failure being the leading cause of death during long-term follow-up. This finding is consistent with studies that have demonstrated the limited ability of ERT to reverse respiratory dysfunction, especially when irreversible pulmonary damage has occurred before treatment[9,12].

A study from Saudi Arabia reported a median ERT initiation age of 4.5 months and a high mortality rate of 83.3%, with a median age at death of 12 months[8]. In contrast, our cohort exhibited a lower mortality rate (56.8%) and longer survival, which may be attributable to the higher ERT dose administered.

While cardiac function improved in all surviving patients, complications such as kyphoscoliosis, restrictive lung disease, speech delay, and hearing loss were common. These findings are in line with previous studies showing that although ERT significantly improves survival, its impact on skeletal muscle and respiratory function remains limited, particularly over the long term [12].

Eighteen distinct *GAA* gene mutations were identified in our patients, including four novel variants, highlighting the allelic heterogeneity of Pompe disease. The identification of novel variants contributes to our understanding of the genetic landscape and underlines the importance of expanding population-specific mutation databases. A large-scale study involving 458 IOPD patients reported 196 different *GAA* gene variants, with c.896T>C (p.L299P) being the most frequent among homozygous early-onset cases[13]. Similarly, p.L299P was the most common mutation in our cohort, identified in 42.9% of alleles. This supports its potential role as a founder mutation in the Turkish population.

Comparable patterns have been observed in other populations. For instance, a large Mexican cohort that included both infantile and late-onset cases identified c.-32-13T>G as the most frequent variant and reported two novel mutations, thereby expanding the regional *GAA* variant spectrum[14]. Despite extensive genetic characterization, we found no clear genotype–phenotype correlation. This is consistent with findings from the Mexican study and other international cohorts, suggesting that additional genetic, epigenetic, or environmental modifiers influence disease expression[4,14].

The high rate of consanguinity (84%) in our cohort likely contributed to the high frequency of homozygous mutations, which may partly explain the predominance of the classic IOPD phenotype. Among the four novel *GAA* variants identified—p.N316I, p.D399Pfs*105, p.I477Mfs*43, and p.Y136D—pathogenicity has not yet been definitively established. However, observed CRIM positivity and clinical severity suggest a potential association with milder disease phenotypes. Further functional and *in silico* studies are necessary to evaluate their impact on disease progression and treatment response.

The main limitation of this study is the small sample size, which is inherent to the rarity of IOPD and limits the statistical power for genotype–phenotype analysis. The retrospective, single-center design may introduce selection bias. Additionally, CRIM status was unavailable for some patients, and differences in follow-up duration, age at ERT initiation, and access to supportive care may have influenced outcomes.

Our findings further expand the mutational spectrum of Pompe disease in the Turkish population and emphasize the need for early diagnosis and high-dose ERT. Despite these efforts, high mortality and persistent morbidities remain significant challenges. Future therapeutic strategies should explore immune modulation, gene therapy, and next-generation ERT formulations. Prospective, multicenter studies with long-term standardized follow-up are essential to refine genotype–phenotype correlations and enable more individualized treatment protocols aimed at improving both survival and quality of life.

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