

Early Cardiac Involvement in Late-Onset Pompe Disease: A Case Report from an Iranian Consanguineous Family

Atefeh Mir, PhD^{1,2*} ; Shadi Khedri, MD³; Zahra Abbasi, MSc¹, Ali Khajeh, MD^{4,5}

¹Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

²Department of Genetics, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

³Cellular and Molecular Research Center, Research Institute of Cellular and Molecular Sciences in Infectious Diseases, Zahedan University of Medical Sciences, Zahedan, Iran

⁴Children and Adolescence Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

⁵Department of Pediatrics, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

*Atefeh Mir & Shadi Khedri contributed equally to the work

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ABSTRACT

Pompe disease (glycogen storage disease type II) is a rare autosomal recessive lysosomal storage disorder caused by *GAA* gene mutations, leading to acid α -glucosidase deficiency and glycogen accumulation in multiple tissues. Late-Onset Pompe Disease (LOPD) typically manifests after infancy without significant cardiac involvement. The present study reports a 16-year-old Iranian girl of Baloch ethnicity, born to consanguineous parents, who presented at age 11 with progressive proximal muscle weakness, waddling gait, scoliosis, dysphagia, dyspnea, and mild conductive hearing loss. Developmental history revealed delayed walking, recurrent respiratory infections, and echocardiographic evidence of intraventricular septal hypertrophy. Dried Blood Spot (DBS) assay showed markedly reduced *GAA* activity at pH 3.8 (0.42 nmol/spot/21 h; reference: 1.5–10). Whole-exome sequencing identified a homozygous missense variant c.2015G > A (p.Arg672Gln) in exon 14 of *GAA*, classified as likely pathogenic by ACMG criteria. Sanger sequencing confirmed segregation. Enzyme replacement therapy with alglucosidase alpha (20 mg/kg biweekly) led to stabilization of disease progression and improvement in motor function over five years. While LOPD usually lacks early cardiac manifestations, our patient exhibited septal hypertrophy and probable cardiomegaly in infancy, suggesting a broader phenotypic range for the p.Arg672Gln mutation. The studied case underlines the importance of considering Pompe disease in patients with unexplained muscle weakness, even when cardiac involvement is present early. Early diagnosis through biochemical and molecular testing, particularly in high-consanguinity regions, allows timely initiation of ERT, potentially improving long-term outcomes in LOPD.

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Introduction

The most common of hearing loss is sensorineural hearing loss (SNHL), involving damage to the hair cells or auditory nerve. This disorder has multiple causes, such as noise over exposure, the use of ototoxic drugs, and genetic mutations in the cochlea or auditory

nerve pathways (1). Unfortunately, most cases of this disorder are irreversible and induce permanent hearing damage (1, 2). Currently, no clinical therapies are available to repair hearing function, and only rehabilitation tools like hearing aids and cochlear implantation with hearing training have effective roles in promoting hearing function (3-5).

Corresponding Author:

Ali Khajeh

Email: khajeha@zaums.ac.ir



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Over the last few decades, the discovery of cochlear hair cell regeneration in avians has spurred extensive research into stem cell-based therapies for SNHL in animal models (6). Research has been performed on cell injection into the inner ear using different types of stem cells through varied access routes, such as round window, lateral wall of cochlea and intravenous injection (6-9). Its efficiency has been usually evaluated by auditory brainstem response (ABR) threshold and morphological assessment (10). The success rate of cell transplantation in the cochlea, as in other organs, depends on the type and source of stem cells prepared, the timing of injection, and the dose of cells (11). Given the environment of the cochlea and its

complex structure, cell injection also depends on the degree and mechanism of damage and the route of cell injection (3). Some studies did not find the function integration of injected cells in the auditory system (9, 12), whereas other studies reported hearing restoration in animal models with ototoxic drugs that had local injection of exogenous stem cells, particularly mesenchymal stem cells (MSCs), and found improvement in ABR threshold (6, 13). A review article reported the efficacy of MSCs in repairing hearing damage, specifically caused by ototoxic drugs, despite the heterogeneity of the studies (14). This study has less investigated studies with animal models of noise-induced hearing loss (NIHL).

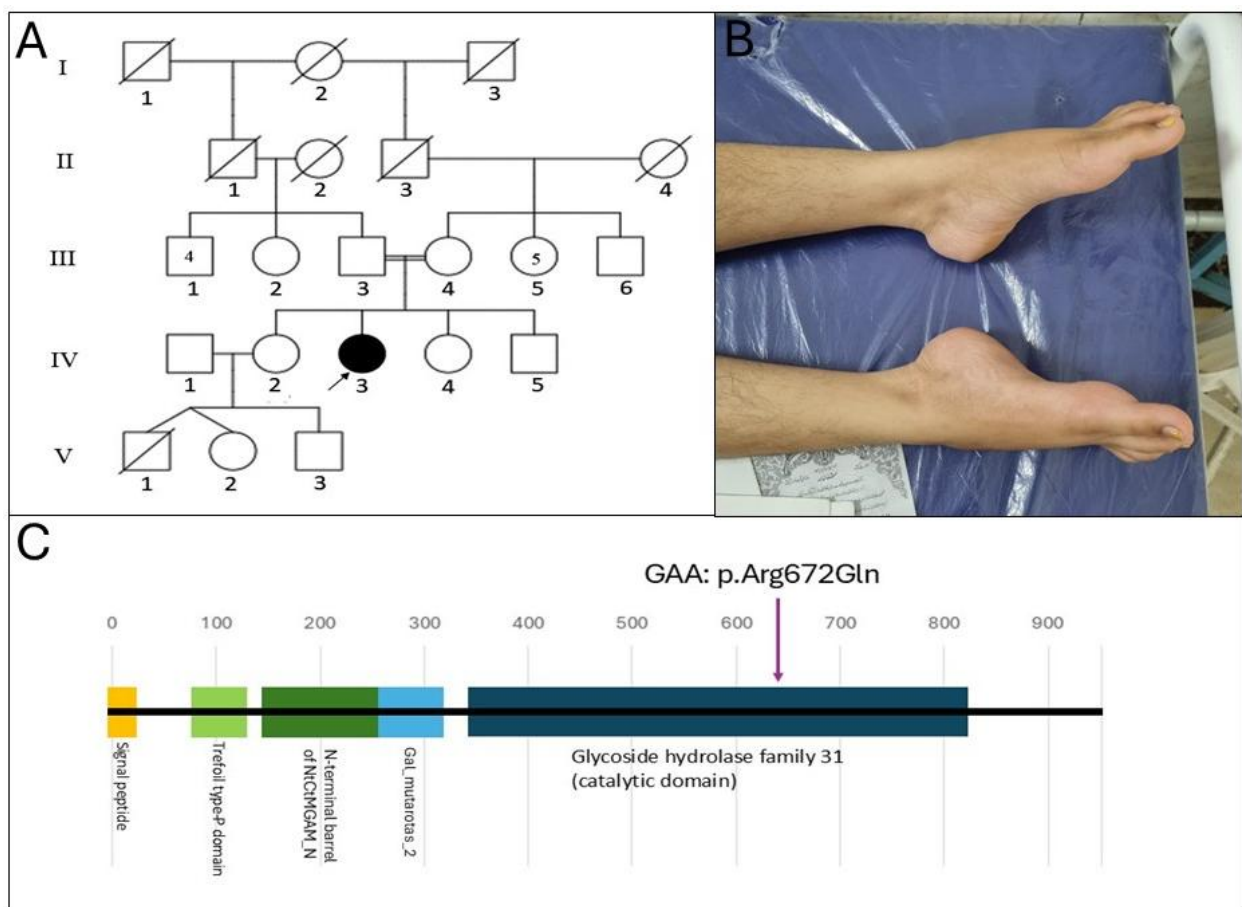


Figure 1. A, The pedigree of the studied family. B, Feet inversion and plantar flexion. C, 2D representation of the GAA protein, its domains, and the position of the amino acid substitution of the identified variant

Glycogen Storage Disease II (GSD2, MIM: 232300), also known as Pompe disease, is a lysosomal storage disorder inherited with an autosomal recessive pattern. Its frequency is estimated to be approximately 1 case per 40000 individuals (1, 2).

This rare genetic disorder is caused by mutations in the *acid α-glucosidase* (GAA, MIM: 606800) gene located on 17q25.3 (3).

This gene encodes the GAA protein, also known as acid maltase. GAA enzyme is needed for the hydrolysis of α-1, 4 and α-1, 6 glucosidic linkages in the lysosome. Therefore, the enzyme deficiency leads to glycogen accumulation in multiple tissues, specifically in organs such as the heart, muscles, and skeleton (4). Pompe has a broad clinical spectrum, from severe classic Infantile-Onset Pompe Disease (IOPD) to milder childhood, juvenile, and adulthood forms, all

considered Late-Onset Pompe Disease (LOPD). Classic IOPD starts before 12 months of age and is characterized by cardiomyopathy, hypotonia, respiratory failure, and early mortality. In contrast, LOPD, also known as non-classic Pompe disease, starts after 12 months of age or before, but without cardiac involvement. LOPD manifestations can be divided into two major groups: muscle weakness and exercise intolerance (5-8).

This case report presents a patient with LOPD who manifested unusual features, such as developing early cardiac involvement in infancy.

Case presentation

Clinical evaluation

A 16-year-old Iranian girl of Baloch ethnicity born to first-cousin parents (Figure 1A) was referred to the pediatric neurology clinic at the age of 11 with

complaints of progressive muscle weakness and difficulty in standing and walking.

The patient was a full-term third-born to a 22-year-old mother. In her prenatal history, a difficult forceps-assisted delivery was noted. She has three asymptomatic siblings.

She initially walked with a moderate delay but progressively developed a waddling gait. In her infancy and early childhood, she experienced recurrent respiratory infections. At the age of 6 months, after hospitalization due to an acute respiratory infection, she also underwent cardiovascular assessments, and echocardiography showed a mild increase in interventricular septal thickness (7.3 mm). At the age of 2 years, a second echocardiography clearly demonstrated overt interventricular septum (IVS) hypertrophy (thickness between 9.8 and 12 millimeters).

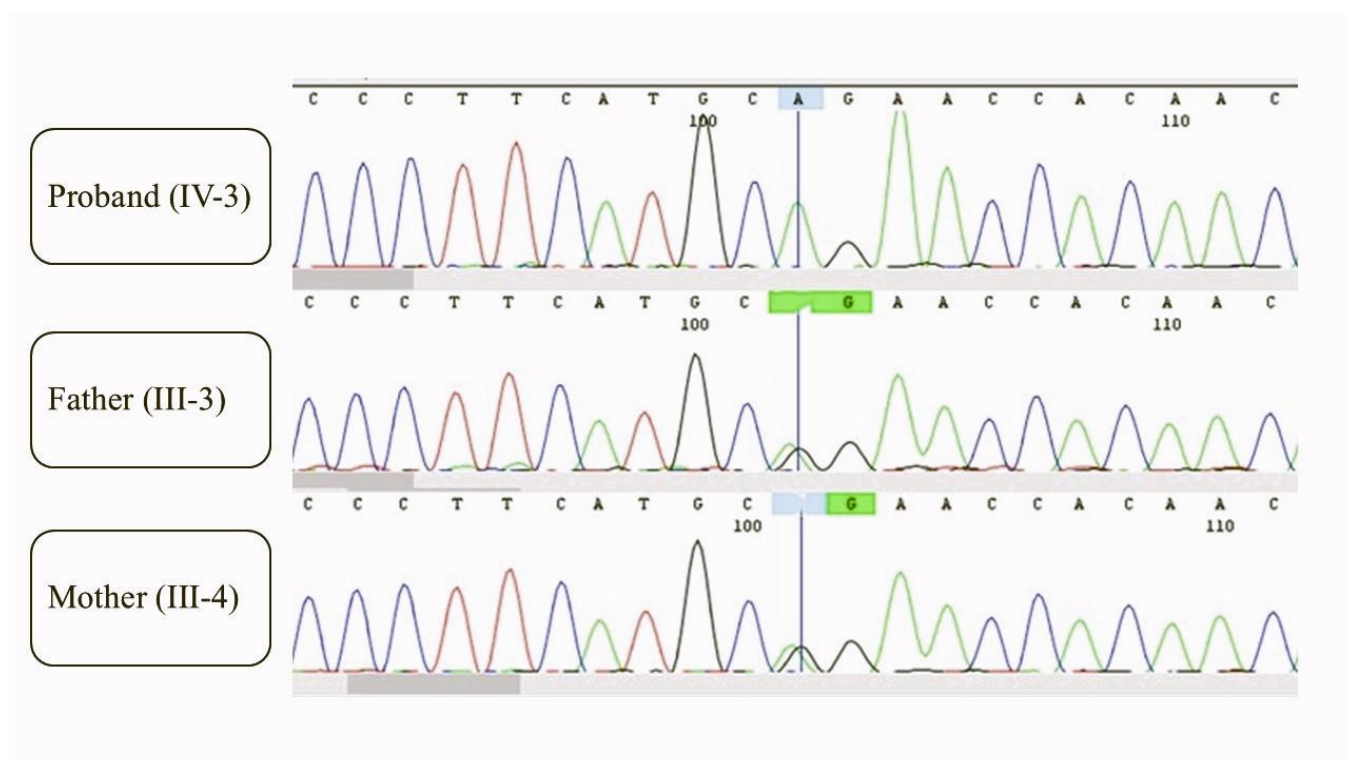


Figure 2. Sanger Sequencing Chromatogram showing the c.2015G>A variant, homozygous in the proband and heterozygous in both parents

She attended school up to 7th grade, at which point she dropped out due to slurred speech and tongue weakness. Her medical records also included dyspnea, mild to moderate dysphagia, and an audiometry showing a bilateral mild conductive hearing loss. Physical examination revealed decreased muscle tone of all four limbs, particularly in the proximal lower limb muscles, a positive Gowers' sign, decreased deep

tendon reflexes (DTRs), and mild lumbar scoliosis. The Medical Research Council score of proximal muscles was 2/5 to 3/5, but grip strength was normal. This study also noted an excessive supination of the feet, likely secondary to chronic compensatory use of the lateral border of the feet for rising from floor-level position (Figure 1B).

In the initial diagnostic investigation, the researchers discovered a significantly elevated level of creatine kinase (CPK = 830 IU/L) and lactate dehydrogenase (LDH = 1162 IU/L). Electromyography revealed a limb-girdle muscular dystrophy pattern. Given this clinical picture, a biochemical screening for Pompe disease was performed. GAA enzyme assay on DBS demonstrated enzyme activity of 0.42 nmol/spot/21h at pH 3.8 (normal reference range 1.5-10), enzyme activity of 5.62 nmol/spot/21h at pH 7 (normal reference range 1.8-17.1), and activity with inhibition of 0.08 nmol/spot/21h (normal reference range 0.9-7.2). These results revealed a significantly reduced enzyme activity at pH 3.8, both with and without the specific inhibitor.

Molecular investigations

Following a full clinical evaluation of the patient, this study provided genetic counseling to the proband and her immediate family to confirm the diagnosis. The patient underwent genetic analysis. With the construction of a detailed pedigree (Figure 1A), an autosomal recessive pattern of inheritance was suggested. The researchers obtained written informed consent from the patient and both parents for genetic testing and publication of anonymized results. After collecting 5 mL peripheral blood samples in EDTA-containing tubes from the proband and her parents, we extracted their genomic DNA using the FavorPrep mini kit (FAVORGEN Company, Taiwan) according to the manufacturer’s protocol.

Whole exome sequencing (WES) on the proband’s DNA sample was provided by ARCHIMEDLIFE laboratory (Vienna, Austria) on an Illumina® NovaSeq

6000 platform (Illumina Inc., USA) to achieve a minimum mean coverage depth of 100x across the target exome. We processed the raw sequencing data using standard bioinformatic methods, which included quality control with FastQC (Babraham Institute, UK), adaptor trimming with Trimmomatic (USA), alignment to the reference human genome (GRCh37/hg19) using BWA-MEM (Burrows-Wheeler Aligner), and variant calling using SAMtools and GATK HaplotypeCaller (Broad Institute, USA).

The current bioinformatic analysis aimed at finding variants in the GAA gene, given the confirmed biochemical diagnosis. We annotated all identified variants in GAA using ANNOVAR and thoroughly evaluated candidate variants against the patient’s detailed clinical picture. This case study classified the pathogenicity of the identified variant according to the consensus guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP).

The WES revealed a homozygous missense variant, c.2015G>A (p.Arg672Gln), located within exon 14 of the GAA gene. This variant is classified as likely pathogenic according to ACMG guidelines (Table 1). Sanger sequencing and co-segregation analysis of the patient and both parents confirmed the presence of this pathogenic variant (Figure 2). Specific primers for this variant were designed using the Primer3 online tool (Primer3web, version 4.1.0). Additionally, a two-dimensional model of the GAA protein and its constituent domains provided visualization of the location of the identified amino acid substitution (Figure 1C).

Table 1. In silico findings of c.2015G > A variant

Gene	RS ID	Genomic position	cDNA position	Protein change	Genome AD frequency	Iranome frequency	Pathogenicity line of evidence based on ACMG
GAA	rs778418246	chr17:80113002 (GRCh38.p14)	NM_000152.5 c.2015G>A	NP_000143.2 p.Arg672Gln	<0.001	Not found	PP5, PS3, PM5, PM1, PM2

Therapeutic intervention and follow-up

Following molecular confirmation of the diagnosis, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (alglucosidase alpha) was initiated at a standard dose of 20 mg/kg body weight administered via intravenous infusion every two weeks. Infusions were well tolerated, with no infusion-associated reactions or adverse events reported during the treatment course. The patient was monitored regularly through clinical examinations, functional

motor assessments, respiratory evaluations, and biochemical testing. Over a five-year follow-up period, ERT was associated with stabilization of disease progression and measurable functional gains, most notably improvement in proximal muscle strength, endurance, and mobility. The patient’s ability to perform activities of daily living improved, and no further deterioration in respiratory function or cardiac status was observed.

Discussion

Pompe disease is a rare inherited metabolic myopathy resulting from pathogenic variants of the GAA gene, which cause GAA enzyme deficiency and glycogen lysosomal accumulation (1). This gene contains 20 exons and 18,349 base pairs, and codes for 952 amino acids. At present, more than 600 mutations have been identified in the GAA (10, 11). The pathogenic variant c.2015G>A (p.Arg672Gln) revealed in this study is a missense mutation that was reported in 1998 for the first time in the USA, with different clinical features (12).

The current case report represents a patient with LOPD who manifests with progressive proximal muscle weakness, waddling gait, decreased DTRs, mild scoliosis, dysphagia, dyspnea, bilateral mild conductive hearing loss, and recurrent respiratory infections, all of which are well documented in the spectrum of LOPD presentations. Notably, echocardiography at 6 months of age showed mild septal hypertrophy. By 2 years of age, the patient had clear septal hypertrophy with IVS thickness reaching 12 mm, which is above the normal range for the age. This early cardiac involvement is atypical for LOPD and does not align with the classical phenotype, where cardiac manifestations are absent or minimal and occur after 12 months of age.

Assessment of GAA activity is a key diagnostic tool in Pompe disease, and its optimum activity is measured at an acidic pH of 3.7 to 4.5, reflecting its lysosomal function. The severity of disease symptoms depends on the GAA activity. Lower enzyme activity is associated with a more aggressive disease, and symptoms typically appear at a younger age. As previously mentioned, based on severity and initial presenting age, patients are divided into two categories: IOPD and LOPD. In IOPD, GAA activity is usually less than 1% of normal controls, and in LOPD, activity ranges from 2% to 40%. Cultured skin fibroblast and muscle biopsies are traditional specimens, with fibroblast considered as the gold standard. However, newer methods like DBS assays provide faster and less invasive options with high sensitivity (13, 14). In the present patient, the enzyme activity at pH 3.8 measured 0.42 nmol/spot/21h (normal reference range 1.5-10), which is approximately 7.3% of the normal mean activity and corresponds to the enzymatic pattern described for LOPD.

Although literature studies show a strong correlation between the clinical phenotype of Pompe disease and the specific type or location of GAA mutations, accumulating evidence indicates that this relationship is not always predictable. For instance, regarding the same c.2015G > A (p.Arg672Gln)

mutation, there were patients with variable age of onset, disease progression, and other presentations. In the study by Tokatly-Latzer et al. (2021), three children of Arab ethnicity who were homozygous for this mutation all presented with IOPD and showed early hypertrophic cardiomyopathy, pointing to a more severe form of disease than previously reported in Japanese and Korean groups. In contrast, data from a large German cohort reported by Herzog et al. (2012) demonstrate that disease severity varied significantly, even among patients with similar residual enzyme activity or shared variants. The exact reason for this phenomenon remains unclear, but it is likely due to additional modifying factors. The studied patient demonstrated a clinical presentation that lies between these two previously reported extremes. While the age of onset, enzyme activity level, and overall disease course were more in line with LOPD, the presence of early cardiac involvement is unusual for LOPD and resembles features described for IOPD. Therefore, the phenotype observed in the studied patient seems to be an intermediate expression of the c.2015G>A (p.Arg672Gln) variant (15-17).

In countries with high rates of consanguinity, such as Iran, particularly in the Sistan-Baluchestan Province, genetic counseling plays a crucial role in both diagnosis and prevention. This case highlights the importance of being more alert to Pompe disease in children who show unexplained muscle weakness. It also supports the increasing evidence for the benefits of early diagnosis and treatment of LOPD.

In Conclusion

This case expands the clinical spectrum of LOPD by demonstrating that atypical, early-onset cardiac involvement can manifest even in the absence of classic infantile-onset features. The obtained findings underscore the clinical necessity of routine cardiac evaluations in patients diagnosed with, or suspected of having, LOPD. Furthermore, in highly consanguineous populations such as Iran, a high index of suspicion and early diagnostic genetic screening are critical for patients presenting with combined neuromuscular and cardiac signs, enabling timely therapeutic intervention.

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Authors' Contributions

Atefeh Mir & Shadi Khedri: Recruitment of patients and family members, writing the first draft of the manuscript, reviewing and editing the manuscript, exome data analysis, and mutation screening; Zahra

Abbasi: Performing molecular experiments and segregation analysis in families by Sanger sequencing; Ali Khajeh: Patient identification and provision of clinical data, design and supervision of the research. The research was approved by the Ethics Committee of

the Zahedan University of Medical Sciences (ZAUMS), Iran (IR.ZAUMS. REC.1404.190).

Conflict of Interest

The authors declared no conflict of interest.

References

- 1.van der Ploeg AT, Reuser AJ. Pompe's disease. The lancet. 2008;372(9646):1342–53.
- 2.Ausems MG, Verbiest J, Hermans MP, Kroos MA, Beemer FA, Wokke JH, et al. Frequency of glycogen storage disease type II in The Netherlands: implications for diagnosis and genetic counselling. Eur J Hum Genet. 1999;7(6):713–6.
- 3.Martiniuk F, Mehler M, Pellicer A, Tzall S, La Badie G, Hobart C, et al. Isolation of a cDNA for human acid alpha-glucosidase and detection of genetic heterogeneity for mRNA in three alpha-glucosidase-deficient patients. Proc Natl Acad Sci U S A. 1986;83(24):9641–4.
- 4.Raben N, Plotz P, Byrne BJ. Acid alpha-glucosidase deficiency (glycogenosis type II, Pompe disease). Curr Mol Med. 2002;2(2):145–66.
- 5.Morales A, De Melo MHST, Anastasopoulou C, Anilkumar AC. Glycogen storage disease type II. StatPearls [Internet]: StatPearls Publishing; 2025.
- 6.Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr. 2006;148(5):671–6.
- 7.Teener JW. Late-onset Pompe's disease. Semin Neurol. 2012;32(5):506–11.
- 8.Winkel LP, Hagemans ML, van Doorn PA, Loonen MC, Hop WJ, Reuser AJ, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol. 2005;252(8):875–84.
- 9.Letunic I, Khedkar S, Bork P. SMART: recent updates, new developments and status in 2020. Nucleic Acids Research. 2020;49(D1):D458–D60.
10. GAA Gene - GeneCards | GAA Protein | GAA Antibody Weizmann Institute of Science: GeneCards®: The Human Gene Database ER; 2025 [updated 2025//. Available from: <https://www.genecards.org/cgi-bin/carddisp.pl?gene=GAA>.
11. National Center for Biotechnology I. ClinVar - GAA gene 2025 [updated 2025–08–07. Available from: <https://www.ncbi.nlm.nih.gov/clinvar/?term=GAA>.
12. Huie ML, Tsujino S, Sklower Brooks S, Engel A, Elias E, Bonthron DT, et al. Glycogen storage disease type II: identification of four novel missense mutations (D645N, G648S, R672W, R672Q) and two insertions/deletions in the acid alpha-glucosidase locus of patients of differing phenotype. Biochem Biophys Res Commun. 1998;244(3):921–7.
13. Umapathysivam K, Hopwood JJ, Meikle PJ. Correlation of acid alpha-glucosidase and glycogen content in skin fibroblasts with age of onset in Pompe disease. Clin Chim Acta. 2005;361(1-2):191–8.
14. Kishnani PS, Steiner RD, Bali D, Berger K, Byrne BJ, Case LE, et al. Pompe disease diagnosis and management guideline. Genet Med. 2006;8(5):267–88.
15. Herzog A, Hartung R, Reuser AJJ, Hermanns P, Runz H, Karabul N, et al. A cross-sectional single-centre study on the spectrum of Pompe disease, German patients: molecular analysis of the GAA gene, manifestation and genotype-phenotype correlations. Orphanet Journal of Rare Diseases. 2012;7(1):35.
16. Tokatly Latzer I, Sagi L, Bali DS, Rehder C, Orbach R, Fattal-Valevski A. Variable Genotype-Phenotype Correlation of Pompe's Disease Caused by a c.2015 G>A (p.Arg672Gln) Mutation in the GAA Gene. Neuropediatrics. 2021;52(6):475–9.
17. Luo JH, Qiu WJ, Fang D, Ye J, Han LS, Zhang HW, et al. [Clinical and gene mutation analysis of three children with late-onset glycogen storage disease type II with hypertrophic cardiomyopathy]. Zhonghua Er Ke Za Zhi. 2017;55(6):423–7.