Clin. Lab. 2026;72:XXX-XXX

CASE REPORT

Early-Onset Wolman Disease in an Infant with Novel Compound Heterozygous *LIPA* Variants

Tingting Zhu [1, 2], Yue Pu [1], Dongliu Wei [1], Tao Wang [1, 2]

[1] *Xizang Region Child Development Clinical Medical Research Center, Women and Children's Hospital of Tibet Autonomous Region, Lhasa, China*
[2] *Key Laboratory of Obstetrics & Gynecology, Pediatric Diseases, and Birth Defects of The Ministry of Education, West China Second Hospital, Sichuan University, Chengdu, China*

ABSTRACT

Background: **Wolman disease is a rare autosomal recessive lysosomal storage disorder caused by lysosomal acid lipase deficiency, with fewer than 150 cases reported. It often presents in infancy with hepatosplenomegaly and adrenal calcification.**
Methods: **We report a 2-month-old female with abdominal distension, vomiting, hepatosplenomegaly, and bilateral adrenal calcification.**
Results: **Laboratory findings showed anemia, thrombocytopenia, hypoalbuminemia, and elevated liver enzymes. Genetic testing revealed novel compound heterozygous *LIPA* variants: a paternal frameshift (c.731_732del, p.Gly244Aspfs*24) and a maternal missense (c.605C>G, p.Pro202Arg).**
Conclusions: **This case expands the *LIPA* variant spectrum and emphasizes the importance of combining clinical data for early diagnosis and counseling.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250940)

Correspondence:
Tao Wang
West China Second Hospital
Sichuan University
Wuhou District
People's South Road Three Sections No. 17
Chengdu, 610000
China
Phone: +86 18180600868
Email: zk930406@163.com

Case Report accepted September 22, 2025

KEYWORDS

Wolman disease, lysosomal acid lipase, *LIPA* gene, compound heterozygote, infant

INTRODUCTION

Wolman disease is a rare autosomal recessive lysosomal storage disorder caused by deficiency of lysosomal acid lipase (LAL), encoded by the *LIPA* gene [1-3]. It presents in early infancy with vomiting, abdominal distension, hepatosplenomegaly, adrenal calcification, and growth retardation, and carries a poor prognosis if untreated [4,5]. Variants in *LIPA*, including missense, nonsense, deletions, and insertions, lead to partial or complete loss of LAL function, resulting in either severe Wolman disease or the milder cholesterol ester storage disease (CESD). Early diagnosis is essential for timely intervention with enzyme replacement therapy and dietary management [6]. This study reports two previously unreported *LIPA* variants presenting in a compound heterozygous infant, expanding the mutational spectrum and providing valuable insights for precise

molecular diagnosis, genetic counseling, and future research on Wolman disease.

CASE PRESENTATION

A 2-month-old female infant was admitted to the General Pediatrics Department of the Women and Children's Hospital of Tibet Autonomous Region with a one-month history of progressive abdominal distension and a three-day history of fever. Initial symptoms included constipation and recurrent vomiting, while bowel movements remained normal and no jaundice was observed. She had received brief treatment at Lhasa People's Hospital without clinical improvement. Three days prior to admission, she developed unexplained fever up to 38°C accompanied by cough. Owing to persistent abdominal distension and concern for a potential underlying metabolic or genetic disorder, she was admitted for further evaluation.

Personal history

The patient was born at Lhasa People's Hospital to a G2P2 mother via full-term vaginal delivery with a birth weight of 3.1 kg and had no significant medical history. Both parents and a 5-year-old brother are healthy, with no known family history of genetic or infectious diseases, and no relevant environmental or infectious exposures.

Physical examination

The patient was alert, weighing 4.0 kg and measuring 55.0 cm. Vital signs included temperature: 37°C, heart rate: 169 bpm, respiratory rate: 34 breaths/minute, blood pressure: 81/42 mmHg, and SpO_2: 78% on room air. The abdomen was markedly distended with prominent abdominal wall veins and a reducible 1 cm umbilical mass. The liver was palpable 7 cm below the costal margin and 5 cm below the xiphoid process, and the spleen was palpable 7.5 cm below the left costal margin, both firm. Bowel sounds were reduced. Heart sounds were strong and regular. Coarse breath sounds were noted bilaterally. Other findings, including jaundice, rash, lymphadenopathy, and neurological examination, were unremarkable.

Laboratory and imaging findings

Laboratory tests showed mild anemia (Hb 97 g/L), thrombocytopenia (PLT 136 x 10^9/L), and elevated hs-CRP (74.14 mg/L). Liver function revealed hypoalbuminemia (29.6 g/L; reference 40 - 55 g/L) and markedly elevated transaminases (ALT 172 U/L, AST 477 U/L; reference 9 - 50 U/L), with total bilirubin of 15.5 µmol/L (0 - 21 µmol/L) and direct bilirubin of 7.2 µmol/L (0 - 3.4 µmol/L). Chest X-ray indicated mild bilateral pulmonary inflammation. Abdominal X-ray showed increased upper abdominal density with intestinal gas, without wall thickening. Ultrasound revealed hepatosplenomegaly with increased echogenicity. Abdominal CT confirmed hepatomegaly with fatty infiltration, splenomegaly, bilateral adrenal enlargement with diffuse calcification, widened and hypodense abdominal and pelvic fat spaces with focal fat accumulation, abdominal and pelvic effusion, markedly thickened mesentery, and an umbilical hernia (Figure 1).

Genetic analysis

Genetic testing for hereditary hyperlipidemia (Supplementary Table 1) was performed using a targeted sequencing panel (Kingmed Diagnostics Group). Genomic DNA was sequenced on an Illumina platform, and data were analyzed via the GATK pipeline with alignment to the UCSC hg19 reference genome. Single nucleotide variants, small insertions/deletions (indels), and selected copy number variants (CNVs) were annotated using Variant Effect Predictor and cross-referenced against ClinVar, OMIM, HGMD, and gnomAD databases. Variants were classified according to ACMG/AMP guidelines, and CNVs were evaluated with internal software per ACMG/ClinGen recommendations [7]. The proband was found to carry compound heterozygous variants in the *LIPA* gene, both of which have not been previously reported, and were confirmed by Sanger sequencing to be inherited from both parents (Figure 2). She harbored a heterozygous paternal frameshift variant in exon 7 (c.731_732del, p.Gly244Aspfs*24), predicted to cause premature termination or nonsense-mediated mRNA decay and classified as likely pathogenic, along with a maternal heterozygous missense variant in exon 6 (c.605C>G, p.Pro202Arg) of uncertain clinical significance.

Treatment

Upon admission, the patient underwent comprehensive auxiliary examinations and continuous electrocardiogram monitoring. Ceftriaxone sodium was administered for infection control, compound glycyrrhizin for liver protection, and vitamin K1 to prevent coagulopathy. On hospital day 2, prior genetic testing from an external hospital revealed compound heterozygous *LIPA* variants, prompting abdominal contrast-enhanced CT and confirming a diagnosis of Wolman disease based on integrated genotype and clinical phenotype. Consultations with the Departments of Critical Care Medicine and Genetic Metabolism at West China Second University Hospital recommended further evaluations, including lipid profile, coagulation function, CMV/EBV testing, adrenal corticosteroid levels, bone marrow smear, and lysosomal acid lipase activity; however, the family declined invasive testing. During hospitalization, recurrent fever persisted, antibiotics were escalated to meropenem, and the patient was transitioned to a low-fat formula. By day 8, abdominal distension and fever remained significant, and the family, informed of the poor prognosis, elected discharge.

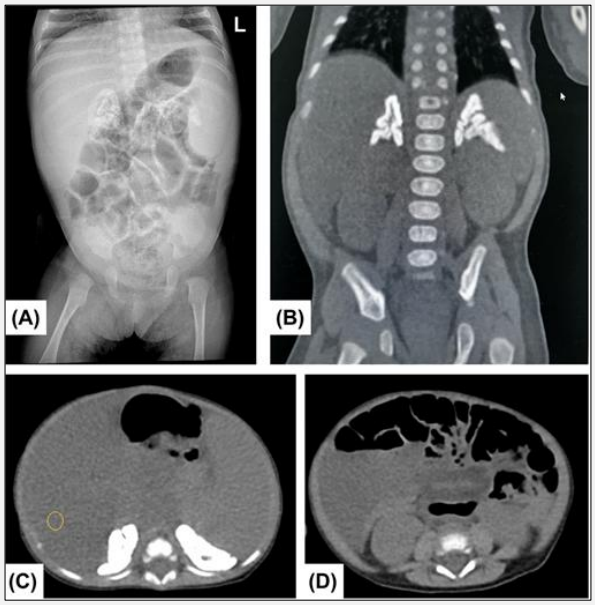

Figure 1. Imaging findings.

A: Abdominal X-ray showing calcification shadows in both adrenal glands, B: CT coronal reconstruction demonstrating bilateral adrenal enlargement and diffuse calcification, C: CT axial image showing hepatomegaly with fatty infiltration and enlarged adrenal glands with diffuse calcification, D: CT axial image showing markedly thickened mesentery.

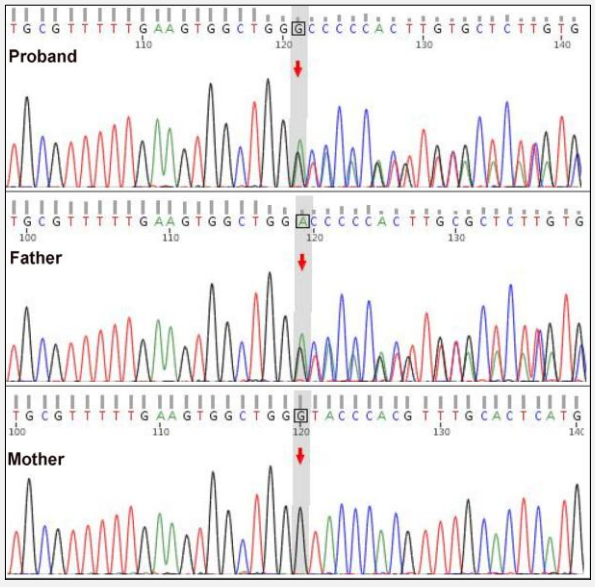

Figure 2. Sanger sequencing confirmation of LIPA variants.

The heterozygous frameshift variant (c.731_732del, p.Gly244Aspfs*24) was inherited from the father, and the heterozygous missense variant (c.605C>G, p.Pro202Arg) was inherited from the mother.

DISCUSSION

Wolman disease, first reported by Dr. Wolman in Israel in 1956, is a rare autosomal recessive disorder with an incidence of approximately 1:350,000, more common among Jews [1,8,9]. It results from a deficiency of LAL, encoded by the *LIPA* gene located at 10q23.2-q23.3, which spans 36 kb with 10 exons. HGMD lists over 100 *LIPA* variants, including > 50% missense/nonsense, 15% splicing, 15% small deletions, and fewer insertions or large deletions. These variants cause partial or complete loss of LAL function [10]. LAL deficiency presents in two phenotypes [1]: severe Wolman disease, with < 1% enzyme activity, leads to lysosomal inability to degrade low-density lipoproteins, cholesterol esters, and triglycerides, causing lipid accumulation in the liver, spleen, lymph nodes, adrenal glands, bone marrow, small intestine, and lungs. Major lesions occur in the reticuloendothelial system, small intestinal mucosa, and adrenal cortex, with lipid deposition causing adrenal necrosis and calcification; and mild CESD, with 1 - 12% residual activity, usually due to exon 10 missense or deletion variants, resulting in hepatomegaly, liver fibrosis, hypercholesterolemia, or liver failure. Wolman disease typically manifests within 2 - 4 months of birth with vomiting, diarrhea, abdominal distension, hepatosplenomegaly, growth retardation, and adrenal insufficiency. Hematologic abnormalities and hemophagocytic lymphohistiocytosis (HLH) may occur, with HLH caused by lipid-activated macrophages transforming into foam cells and releasing proinflammatory cytokines, triggering acute systemic inflammation, a key diagnostic feature of Wolman disease [11,12].

In this case, the patient developed symptoms within the first month of life, initially presenting with vomiting and constipation, followed by progressive abdominal distension, hepatosplenomegaly, abnormal liver function, hypoalbuminemia, elevated bilirubin levels, and mild anemia, all characteristic features of Wolman disease. Abdominal CT demonstrated hepatomegaly with fatty infiltration, bilateral adrenal enlargement with calcification, and otherwise normal adrenal morphology, supporting the clinical suspicion of Wolman disease. Genetic analysis revealed compound heterozygous previously unreported variants in the *LIPA* gene (c.731_732del, p.Gly244Aspfs*24 and c.605C>G, p.Pro202Arg), confirmed by Sanger sequencing to be inherited from each parent. These results not only confirmed the clinical diagnosis of Wolman disease but also significantly expanded the mutational spectrum of LIPA, providing valuable information for future genetic counseling and molecular diagnosis.

Wolman disease carries a poor prognosis, and management has traditionally focused on symptomatic supportive care, including low-fat or fat-free formula feeding, intravenous nutrition, and supplementation with fat-soluble vitamins [13]. Hematopoietic stem cell transplantation (HSCT) has been reported as a potentially curative approach, providing normal LAL through donor-derived cells, thereby restoring the ability to hydrolyze cholesterol esters and triglycerides [14]. The first successful pediatric bone marrow transplantation was reported in 2000, followed by a case of umbilical cord blood transplantation in 2007, both resulting in normalized liver function, blood lipids, and LAL activity with long-term survival. However, HSCT carries substantial risks, and most patients succumb to treatment-related complications; liver transplantation alone does not prevent disease progression, and mortality remains high. Typical Wolman disease, if untreated, generally results in death within the first year of life, with an average age of 3.7 months. In recent years, enzyme replacement therapy (ERT) with recombinant sebelipase α has emerged as a promising intervention. Combined with a low-lipid diet, ERT aims to restore LAL activity and reduce lysosomal lipid accumulation. Early initiation, ideally before 2 - 3 months of age, is critical, and patients with Wolman disease require higher infusion doses than do those with CESD. Clinical trials have shown that 67% of ERT-treated infants survive to 12 months, with improvements in growth, liver function, and hepatosplenomegaly [15]. ERT combined with dietary substrate reduction may stabilize patients, reduce complications, and serve as an effective early intervention for Wolman disease.

CONCLUSION

In conclusion, this case demonstrates a typical early-onset presentation of Wolman disease, with vomiting, abdominal distension, hepatosplenomegaly, abnormal liver function, and adrenal calcification. Genetic analysis revealed two previously unreported *LIPA* variants (c.731_732del, p.Gly244Aspfs*24 and c.605C>G, p.Pro202Arg) in this compound heterozygous infant, inherited from each parent, expanding the mutational spectrum. This underscores the importance of combining clinical, imaging, and molecular data for timely diagnosis. Unfortunately, due to family decisions, the patient did not receive treatment, and long-term follow-up was not possible. Early identification supports enzyme replacement therapy and dietary management and informs genetic counseling.

Acknowledgment:
The authors would like to thank the patient and her parents for their cooperation and consent to this study. We thank Medjaden Inc. for scientific editing of this manuscript.

Ethics Approval and Consent to Participate:
This study was approved by the Ethics Committee of the Women and Children's Hospital of Tibet Autonomous Region (Approval No. qfeyy-2025001). All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki. Written informed

consent to participate was provided.

Data Availability:
The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Source of Funds:
This work was supported by the Tibet Autonomous Region Science and Technology Plan project (XZ202501 YD0006).

Declaration of Interest:
All authors declare that they have no conflict of interest.

References:

1. Pericleous M, Kelly C, Wang T, Livingstone C, Ala A. Wolman's disease and cholesteryl ester storage disorder: the phenotypic spectrum of lysosomal acid lipase deficiency. Lancet Gastroenterol Hepatol 2017;2(9):670-9. (PMID: 28786388)

2. Saito S, Ohno K, Suzuki T, Sakuraba H. Structural bases of Wolman disease and cholesteryl ester storage disease. Mol Genet Metab 2012;105(2):244-8. (PMID: 22138108)

3. Witeck CDR, Schmitz AC, de Oliveira JMD, Porporatti AL, De Luca Canto G, Pires MMS. Lysosomal acid lipase deficiency in pediatric patients: a scoping review. J Pediatr (Rio J) 2022;98(1): 4-14. (PMID: 33964214)

4. Menon J, Shanmugam N, Srinivas S, et al. Wolman's Disease: A Rare Cause of Infantile Cholestasis and Cirrhosis. J Pediatr Genet 2022;11(2):132-4. (PMID: 35769959)

5. Bay L, Canero Velasco C, Ciocca M, et al. Liver disease and dyslipidemia as a manifestation of lysosomal acid lipase deficiency (LAL-D). Clinical and diagnostic aspects, and a new treatment. An update. Arch Argent Pediatr 2017;115(3):287-93. (PMID: 28504497)

6. Korbelius M, Kuentzel KB, Bradić I, Vujić N, Kratky D. Recent insights into lysosomal acid lipase deficiency. Trends Mol Med 2023;29(6):425-38. (PMID: 37028992)

7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-24. (PMID: 25741868)

8. Pasta A, Borro P, Cremonini AL, et al. Effect of a common missense variant in LIPA gene on fatty liver disease and lipid phenotype: New perspectives from a single-center observational study. Pharmacol Res Perspect 2021;9(5):e00820. (PMID: 34476902)

9. Jackson J, Farajzadeh J, Turner R, et al. Prevalence of p.G87V and p.Gln298=Variations in LIPA Gene Within Middle Eastern Population Living Around Los Angeles. Genet Test Mol Biomarkers 2023;27(10):319-24. (PMID: 37903030)

10. Elaraby NM, Galal ER, Abdel-Hamid M, et al. First LIPA Mutational Analysis in Egyptian Patients Reveals One Novel Variant: Wolman Disease. J Mol Neurosci 2023;73(7-8):598-607. (PMID: 37470904)

11. Alabbas F, Elyamany G, Alanzi T, Ali TB, Albatniji F, Alfaraidi H. Wolman's disease presenting with secondary hemophagocytic lymphohistiocytosis: a case report from Saudi Arabia and literature review. BMC Pediatr 2021;21(1):72. (PMID: 33568092)

12. Baronio F, Conti F, Miniaci A, et al. Diagnosis, treatment, and follow-up of a case of Wolman disease with hemophagocytic lymphohistiocytosis. Mol Genet Metab Rep 2022;30:100833. (PMID: 35242567)

13. Eskandari SK, Revenich EGM, Pot DJ, et al. High-Dose ERT, Rituximab, and Early HSCT in an Infant with Wolman's Disease. N Engl J Med 2024;390(7):623-9. (PMID: 38354141)

14. Potter JE, Petts G, Ghosh A, et al. Enzyme replacement therapy and hematopoietic stem cell transplant: a new paradigm of treatment in Wolman disease. Orphanet J Rare Dis 2021;16(1):235. (PMID: 34020687)

15. Jones SA, Rojas-Caro S, Quinn AG, et al. Survival in infants treated with sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multicenter, dose-escalation study. Orphanet J Rare Dis 2017;12(1):25. (PMID: 28179030)

Additional material can be found online at:
http://supplementary.clin-lab-publications.com/250940/