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Acid sphingomyelinase deficiency: Phenotypic, biochemical, and molecular heterogeneity in a series of 47 Iraqi patients from a single center

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ABSTRACT

Objectives: Acid sphingomyelinase deficiency (ASMD) is an inherited autosomal recessive disease caused by pathogenic variants in the sphingomyelin phosphodiesterase-1 *(SMPD1)* gene, which encodes acid sphingomyelinase (ASM). ASMD has 3 broad phenotypes (type A, type A/B, and type B) characterized by the age of onset, symptomatology, and the rapidity of disease progression. The diagnosis of ASMD can be delayed or missed because of the wide spectrum of severity and its variable manifestations. Analysis of genotype-phenotype correlations can help to determine ASMD disease type and inform management. Here, we describe the clinical presentation of 47 patients with ASMD referred to a single center in Iraq since 2007, whose diagnosis was confirmed by gene sequencing and ASM activity.

Study design: This was a retrospective observational cohort study of patients diagnosed with ASMD in Iraq.

Results: The cohort included 47 patients with ASMD. A positive family history and consanguinity were noted in 66% and 98% of these cases, respectively. Hepatosplenomegaly, anemia, and thrombocytopenia were present in 100%, 79%, and 44% of patients, respectively. Notably, dysmorphic features were observed in 23% of cases. Thirteen *SMPD1* variants were present in this cohort, the most common of which were c.1556A > G (p.Tyr519Cys), c.740delG (p.Gly247Alafs*10), c.967A > C (p.Ser323Arg), and c.1267C > T (p.His423Tyr). Three of the variants identified were novel, specifically c.967A > C (p.Ser323Arg), c.1579A > G (p.Asn527Asp), and c.905C > T (p.Thr302Ile).

Conclusions: Physicians assessing infants and children who present with hepatosplenomegaly or anemia and dysmorphic features should have a high index of suspicion for ASMD, particularly in regions with high rates of consanguineous unions.

1. Introduction

Acid sphingomyelinase deficiency (ASMD) is a rare lysosomal storage disorder (LSD) caused by loss-of-function variants in the sphingomyelin phosphodiesterase-1 gene (*SMPD1*) encoding acid sphingomyelinase (ASM) [1,2]. Deficient ASM activity leads to the pathological accumulation of sphingomyelin in tissues and organs, including the spleen, liver, lungs, and central nervous system (CNS) [3]. More than 250 pathogenic *SMPD1* variants have been identified, which together with genetic and epigenetic factors, give rise to a wide spectrum of clinical phenotypes [2,4]. Infantile neurovisceral disease (ASMD type A) progresses rapidly, resulting in death by 3 years of age and is characterized by prominent CNS involvement and visceral impairment [2]. Chronic neurovisceral disease (ASMD type A/B) is an intermediate phenotype with slowly progressing neurodegenerative symptoms and variable life expectancy [3,5]. Chronic visceral disease (ASMD type B) typically lacks neurological abnormalities, with patients often surviving into adulthood [6]. Hepatosplenomegaly and thrombocytopenia are common across subtypes [3,7].

ASMD diagnosis can be challenging and often delayed due to its rarity, phenotypic heterogeneity, and overlap of multiple symptoms with other LSDs [8,9]. Consensus guidelines recommend that diagnosis is based on reduced ASM activity followed by confirmatory genetic

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Glossary

ASM, acid sphingomyelinase
ASMD, acid sphingomyelinase deficiency
CNS, central nervous system
LSD, lysosomal storage disorder
lyso-SPM, lyso-sphingomyelin
Sap, sphingolipid activator protein
SMPD1, sphingomyelin phosphodiesterase 1

sequencing [2]. Identifying rare or novel *SMPD1* variants may not inform patient prognosis; therefore, genotype-phenotype correlations and ongoing clinical observation can help determine ASMD subtype and support patient management [7].

Here, we present a case series of 47 patients with ASMD referred to the Children's Welfare Teaching Hospital in Baghdad, Iraq, from 2007 to 2024. To our knowledge, this is the first description of ASMD in a large regional cohort from Iraq.

2. Methods

This observational retrospective study describes 47 patients referred from different governorates throughout Iraq to the Children's Welfare Teaching Hospital in Baghdad from 2007 to 2024. Patients were diagnosed with ASMD following comprehensive clinical evaluation and dried blood spot analysis (ArchimedLife, Vienna, Austria) of i) ASM activity by tandem mass spectrometry, ii) lyso-sphingomyelin (lyso-SPM) by tandem mass spectrometry, and iii) patient genotyping using next-generation sequencing of all coding exons and flanking intronic regions of the *SMPD1* gene. Subtype classification was determined by neurological manifestations and the overall severity and rate of disease progression.

This study was promoted by the Children's Welfare Teaching Hospital, Medical City, Baghdad, Iraq, and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients or the patients' legal guardian/next of kin prior to inclusion in the study.

3. Results

3.1. Patient demographics & clinical characteristics

Our case series was comprised of 47 patients (Table 1), including 22 males and 25 females who largely came from consanguineous families (46/47; 98% consanguinity), and two-thirds of patients demonstrated a positive family history of ASMD (31/47; 66% positive family history). In our cohort, 20/47 patients presented with type A, 4/47 type A/B, and 23/47 type B ASMD, respectively. Age of disease manifestation (in months) was, on average, 5.3 (range: birth to 1 year), 8 (range: 4–10 months), and 34.9 (2.9 years; range: birth to 18 years) for ASMD types A, A/B, and B, respectively. Two patients were identified via neonatal screening. The age of disease diagnosis (in months) was, on average, 13.4 (range: 1 month to 3 years), 35.3 (2.9 years; range: 9 months to 5 years), and 93.4 (7.8 years; range: 5 months to 22 years), for ASMD types A, A/B, and B, respectively. Seven patients died during this retrospective study; one of these individuals had ASMD type B, and the remaining deceased patients had ASMD type A. Death of the individual with ASMD type B was not ASMD-related, but due to the COVID-19 pandemic. Notably, one of the patients classified as having ASMD type A survived until age 4; however, this classification was based on early disease onset and severe neurological involvement. It is critical to note that because of the absence of disease-specific therapy, many patients were lost to follow-up, limiting the ability to determine survival outcomes and/or age at death.

Table 1
Clinical characteristics of patient cohort.

	Total n	Type A	Type A/B	Type B	All ASMD frequency (%)
Patients, *n*	47	20	4	23	
Sex (male/female)	47	(12/8)	(2/2)	(8/15)	
Age at onset[a] in months, mean, median, range	47	5.3, 6, 0–12	8, 9, 4–10	34.9 (2.9 years), 8, 0–216 (18 years)	
Age at diagnosis[a] in months, mean, median, range	47	13.4, 12, 1–36 (3 years)	35.3 (2.9 years), 36 (3 years), 9–60 (5 years)	93.4 (7.8 years), 72 (6 years), 5–264 (22 years)	
Deceased	7/47[b]	6	0	1	
Neurological manifestations (no/yes)	39[c,d]	(0/15)	(0/4)	(19/1)	20/39 (51%)
Hepatosplenomegaly (no/yes)	47	(0/20)	(0/4)	(0/23)	47/47 (100%)
Anemia (no/yes)	34[c]	(1/12)	(0/4)	(6/11)	27/34 (79%)
Thrombocytopenia (no/yes)	32[c]	(6/5)	(1/3)	(11/6)	14/32 (44%)
Cherry red spot (no/yes)	28[c]	(5/5)	(1/1)	(14/2)	8/28 (29%)
Respiratory manifestations (no/yes)	43[c]	(8/8)	(2/2)	(22/1)	11/43 (26%)
Jaundice (no/yes)	36[c]	(8/4)	(4/0)	(19/1)	5/36 (14%)

ASMD, acid sphingomyelinase deficiency.
[a] ASMD diagnosis was obtained for one type A and one type B patient at neonatal screening.
[b] Because there was no disease-specific treatment, the majority of patients were lost to follow-up at the time of analysis; therefore, age at death and/or survival status of many patients is unknown.
[c] Number of patients for whom data were recorded.
[d] Five patients with missing neurological data are deceased patients who had type A disease.

All patients with ASMD type A or type A/B demonstrated neurological symptoms (e.g., hypotonia, psychomotor delay) versus only one patient with type B, who exhibited a squint. The most commonly exhibited symptoms in this cohort were hepatosplenomegaly, anemia, and thrombocytopenia, which were documented in 100%, 79%, and 44% of all patients, respectively. Dysmorphic features were noted in 11 out of 47 patients (23%; Fig. 1), predominantly in those with ASMD type A (9/11; 82%). The most common findings included a flat nasal bridge and/or prominent eyes (4/11). Two patients displayed extensive Mongolian spots.

3.2. ASM activity & lyso-SPM levels

Deficient (ASM) enzyme activity was documented in all patients (Fig. 2A). Levels of the biomarker lyso-SPM (Fig. 2B) were available for 28 patients. Mean lyso-SPM was 373.65 ng/mL (range: 77–745.8). Lyso-SPM levels were positively associated with disease severity (i.e., lyso-SPM is significantly higher in ASMD type A than type B disease [$P = 0.030$]).

Fig. 1. Dysmorphic features and Mongolian spots were observed in Iraqi patients with ASMD. Two siblings with ASMD type A showing dysmorphic features (A and B). Two unrelated patients with ASMD type B displaying dysmorphic features (C and D). One sibling presenting with extensive Mongolian spots (E).

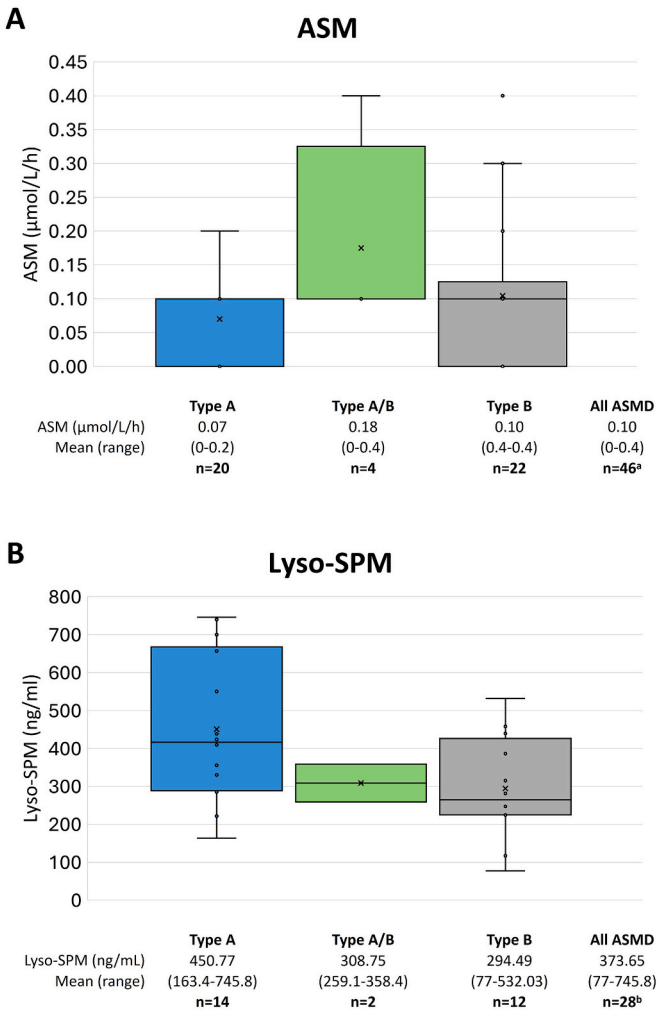

Fig. 2. ASM activity and lyso-SPM quantification in patients with ASMD subtypes. ASM activity (A) and lyso-SPM concentration (B) were quantified by tandem mass spectrometry of dried blood spot samples (ArchimedLife, Vienna, Austria). Box and whisker plot represents interquartile range (box), median (horizontal line), minimum and maximum values excluding outliers (whiskers), and mean (noted as 'X').
ASM, acid sphingomyelinase; lyso-SPM, lyso-sphingomyelin.
[a]Number of patients for whom ASM activity was recorded; one patient's ASM measurement was excluded, as it was performed using a different assay method.
[b]Number of patients for whom lyso-SPM concentration was recorded; one patient's lyso-SPM measurement was excluded, as it was performed using a different assay method.

3.3. Genetic findings

Across the study cohort, a total of 13 distinct *SMPD1* variants were identified (Table S1), including 9 unique missense and 3 frameshift variants. Missense variants constituted the majority, accounting for most alleles observed. Overall, 95.7% (45/47) of patients had a homozygous genotype (likely attributable to the high degree of consanguinity); among these, 2.2% (1/45) had mutations in the sphingolipid activator protein (Sap) domain, 53.3% (24/45) had mutations in the catalytic metallo-phosphatase domain, and 44.4% (20/45) had mutations in the C-terminal domain of the *SMPD1* gene (Fig. 3). Of the 2 patients with compound heterozygous mutations, one had both mutations in the catalytic metallo-phosphatase domain (c.[740delG];[905C > T]) and the other had one mutation in the catalytic metallo-phosphatase domain and one in the C-terminal domain (c.[967A > C];[1556A > G]).

The most common variant was missense variant c.1556A > G (p.Tyr519Cys), detected in 14 homozygous patients and one heterozygous patient, all of whom presented with chronic visceral (ASMD type B) disease. The second most frequent variant was frameshift c.740delG (p.Gly247Alafs*10), identified in 9 homozygous patients, all of whom exhibited ASMD type A. In addition, c.740delG was identified in one patient with a compound heterozygous genotype (c.[740delG];[905C > T]) and type B disease. Two recurrent missense variants, c.967A > C (p.Ser323Arg) and c.1267C > T (p.His423Tyr), were detected in 5 homozygous patients each. Three individuals homozygous for c.967A > C (p.Ser323Arg) exhibited type A disease, while 2 exhibited type A/B disease. One patient carrying this variant as part of a compound heterozygous genotype (c.[967A > C];[1556A > G]) was classified as having ASMD type B. The pathogenic missense variant c.1267C > T (p.His423Tyr) was present in 5 homozygous patients, including 4 with type A disease and one with type A/B disease (Table S1).

The remaining variants were observed less frequently. These included c.1244C > T (p.Ala415Val), a missense variant detected in 2 homozygous patients, both with type B disease, and the missense variant c.1492C > T (p.Arg498Cys), identified in 2 patients with homozygous genotypes, one classified as type A and one as type A/B. The homozygous missense variant c.1579A > G (p.Asn527Asp) was observed in 3 patients, all with type B disease. Two missense variants, c.1652T > C (p.Leu551Pro) and c.416T > C (p.Leu139Pro), were each identified in one

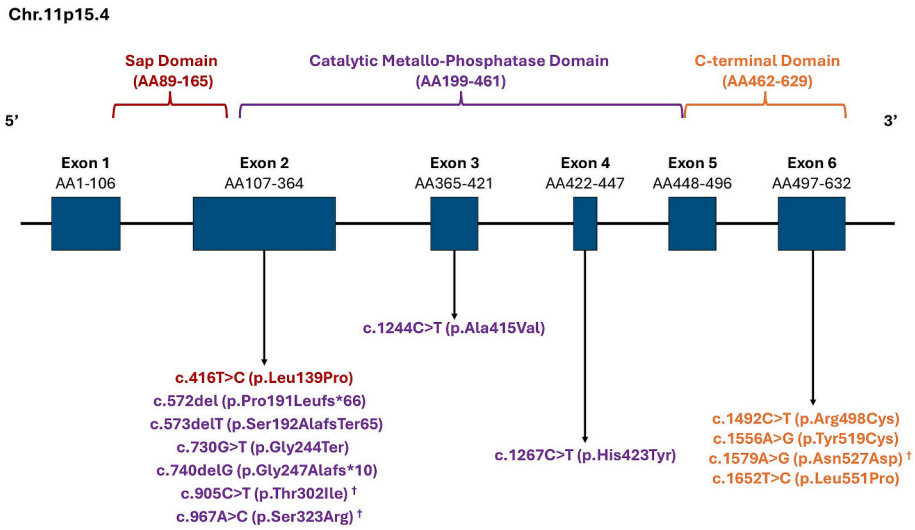

Fig. 3. Map of *SMPD1* mutations identified in Iraqi cohort. A schematic representation of the *SMPD1* gene is shown, with exons depicted as blue boxes. Domains with mutations identified are labeled according to the corresponding amino acid positions. The 13 individual mutations reported in this cohort are color-coded based on their domain location: the Sap domain (red), the catalytic metallo-phosphatase domain (purple), and the C-terminal domain (orange). Arrows indicate the specific exon where each mutation is located. †Denotes novel variant.

homozygous patient with type B disease, and 3 homozygous truncating variants were each observed in one homozygous patient with type A disease: c.572del (p.Pro191Leufs*66), c.573delT (p.Ser192AlafsTer65), and c.730G > T (p.Gly244Ter). Descriptions of each variant are listed in Table S1, and the distribution of ASMD subtypes for each genotype is shown in Fig. 4.

4. Discussion

This study describes the largest single-center cohort of patients with ASMD reported from Iraq and provides an integrated clinical, biochemical, and molecular characterization of the disease in a population with a high rate of consanguinity. Overall, the clinical phenotypes observed in this cohort are consistent with previously described ASMD subtypes, while also revealing notable observations that expand the current understanding of the clinical spectrum. Hepatosplenomegaly, anemia, and thrombocytopenia were the most frequent clinical manifestations across all ASMD subtypes, in line with prior descriptions [2,8]. However, notable findings in this cohort were the presence of dysmorphic features in nearly one-quarter of patients and Mongolian spots observed in 2 patients. These features are not classically associated with ASMD, but have been reported previously [10,11] and may represent underrecognized clinical clues. In settings where access to advanced diagnostic testing is limited, careful physical examination, including assessment for dysmorphic features, may contribute to earlier suspicion of LSDs such as ASMD.

In addition to clinical findings, biomarker analysis further supported patient characterization in our cohort. Deficient ASM activity was

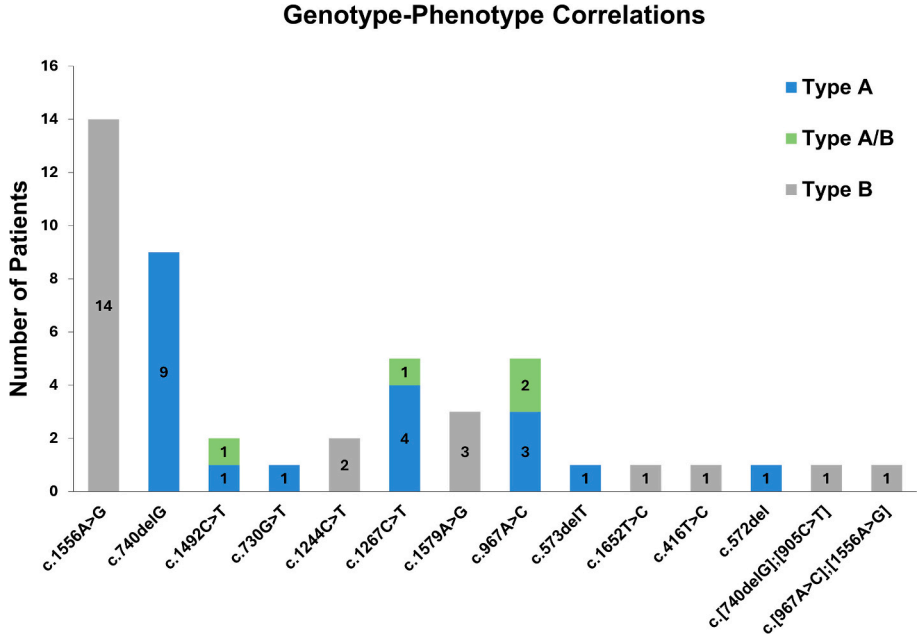

Fig. 4. Genotype-phenotype correlations in Iraqi patients with ASMD. Distribution of ASMD phenotypes (type A, type B, and intermediate type A/B) associated with *SMPD1* gene variants identified.

documented in all patients, and lyso-SPM levels were positively associated with disease severity, corroborating the work of others [12]. The ability to measure biomarkers such as lyso-SPM and ASM using dried blood spots makes these markers particularly suitable for newborn screenings, facilitating early diagnosis and aiding in differentiation of ASMD from other LSDs [13].

Our genetic findings are largely consistent with prior reports, while also revealing novel observations. Of the 13 *SMPD1* variants identified in this cohort, 10 have been described previously (c.740delG [14,15], c.1556A > G [10], c.1267C > T [10,16,17], c.416T > C [17], c.1244C > T [17], c.730G > T [18], c.1492C > T [16,17], c.1652T > C [Simonaro et al. 2002 reports c.1666T > C; L549P [19]], c.572del, and c.573delT [17,20]), whereas 3 variants are novel (c.967A > C, c.1579A > G, and c.905C > T). In addition, 2 compound heterozygous genotypes (c.[740delG];[905C > T] and c.[967A > C];[1556A > G]) have not been previously reported, further broadening the genotypic landscape associated with ASMD.

Consistent with previous studies [14,15], all 9 patients homozygous for the truncating variant c.740delG presented with severe neurovisceral disease (ASMD type A). In contrast, one patient with a compound heterozygous genotype, c.[740delG];[905C > T], exhibited a milder ASMD type B phenotype, highlighting the effect of the second allele on mitigating disease severity. The missense variant c.1556A > G, previously described in a single patient with a compound heterozygous genotype (c.[1556A > G];[1297T > C]) classified as having ASMD type A [10], was observed in 14 homozygous patients and one heterozygous patient in this study, all with ASMD type B. Variant c.1267C > T, previously described as pathogenic [10,16,17], was associated with type A disease in most patients in this cohort and type A/B disease in one patient. Similarly, variant c.1492C > T, previously associated with ASMD type A [16], was identified in 2 homozygous patients, one with ASMD type A and one with ASMD type A/B. Variant c.730G > T, previously reported in a compound heterozygous patient ([564delC];[730G > T]) with type A/B disease [18], was found in one homozygous patient with type A disease. Variants c.416T > C and c.573delT have been previously described as pathogenic [17,20], and were associated with type B and type A disease in this cohort, respectively. Variant c.572del was classified as pathogenic according to the ClinVar database (VCV001453617.6; accessed March 2026). Our observations align with this classification.

Although c.1829_1831del (p.Arg610del) is the most frequently reported *SMPD1* variant globally [17], it was not present among the patients screened in this study. Certain *SMPD1* variants are known to exhibit a higher prevalence within particular geographic regions; for example, c.1267C > T is most commonly found among patients with ASMD in Saudi Arabia [11] and was reported in 5 patients in this cohort. The majority of patients in this cohort (45/47) were homozygous for a specific *SMPD1* allele. This level of homozygosity may be attributed to the high rate of consanguinity [10,21]. Consanguineous marriage (between close biological relatives) is practiced in the Gulf region, including Iraq, where approximately 30% of marriages are between first cousins [22–24].

Together, these findings suggest that physicians who assess infants and children presenting with hepatosplenomegaly or anemia should consider ASMD/LSDs, especially in regions with high rates of consanguineous marriage. Dysmorphic features and Mongolian spots may provide additional diagnostic clues. Although some of the clinical observations reported here are consistent with previously described ASMD natural history, comprehensive cohort-level data from underrepresented regional populations remain an important contribution to the literature, particularly for a disease as rare as ASMD. These findings emphasize the need for thorough physical examination, particularly when genetic testing is limited. Future studies should investigate whether specific *SMPD1* variants are associated with a higher prevalence of dysmorphic features or Mongolian spots, which could provide further insight into genotype-phenotype correlations.

CRediT authorship contribution statement

Rabab Farhan: Conceptualization, Methodology, Validation, Investigation, Resources, Visualization, Data curation, Writing – review & editing. **Mays Al-Tai:** Conceptualization, Methodology, Validation, Investigation, Resources, Visualization, Data curation, Writing – review & editing. **Ikhlas Ali Ahmed:** Conceptualization, Methodology, Validation, Investigation, Resources, Visualization, Data curation, Writing – review & editing. **Adel Kareem:** Investigation, Writing – review & editing. **Saja Baheer:** Investigation, Writing – review & editing. **Bassam Musa Sadik:** Investigation, Writing – review & editing. **Matheel Mohamed Jafar:** Investigation, Writing – review & editing. **Marwa Sabah Alothman:** Investigation, Writing – review & editing.

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Declaration of competing interest

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2026.101328.

Data availability

The raw/processed data required to reproduce the findings below cannot be shared at this time due to legal/ethical reasons.

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