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X-linked recessive Galloway-Mowat syndrome 2 caused by a specific
LAGE3 variant

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Short Communication

**Introduction**

Galloway-Mowat syndrome (GAMOS) is a rare genetically heterogeneous disorder presented with early-onset steroid-resistant nephrotic syndrome in combination with microcephaly and brain anomalies. It was originally described in two siblings by Galloway and Mowat in 1968.¹ Recently, novel causative mutations for GAMOS have been identified in the genes encoding the four KEOPS (kinase, endopeptidase, and other proteins of small size) subunits: LAGE3, OSGEP, TP53RK, and TPRKB.² Braun et al. revealed that knocking down genes encoding KEOPS subunits in human podocytes results in impaired cell proliferation and translation, endoplasmic reticulum stress, activation of DNA damage response signaling, increased apoptosis, and defects in actin regulation, all of which play a major pathogenic role in the development of GAMOS.²

Recessive OSGEP mutations appears to represent the most typical and common subtype of GAMOS. Through an international collaborative effort, 91 individuals with GAMOS were collected and studied.³ In total, 37 patients with mutations of four KEOPS complex genes were diagnosed. OSGEP mutations accounted for 28 of these 37 patients, including 9 out of 10 GAMOS patients of Taiwanese ethnic origin.³ Our previous study suggested that these patients had a highly concordant clinical phenotype of typical GAMOS comprising facial and extremity dysmorphism, early-onset nephrotic syndrome, primary microcephaly with abnormal gyri and migration anomalies, severe developmental delay, a propensity for seizure, and death in early childhood (< six years). The “aged face” and arachnodactyly or camptodactyly may be important clues for diagnosis.³

**Case report**
A six-month-old facial dysmorphic boy was diagnosed with GAMOS by the criteria of early-onset steroid-resistant nephrotic syndrome in combination with microcephaly and brain anomalies. His clinical presentations are shown in figure 1. Tracing his history, primary microcephaly was diagnosed with head circumference of 27.5 cm at birth. Psychomotor retardation, feeding difficulties, failure to thrive, hypotonia, and intermittent spasticity had been exhibited since birth. Epilepsy was identified at age 2 months. Proteinuria was noted at 3 months and nephrotic syndrome developed at 6 months old. The patient died due to multiple episodes of sepsis and spontaneous bacterial peritonitis at 8 months old. Diffuse sclerosing glomerulopathy (11/12 glomeruli) without immune complex deposition was discovered through renal biopsy. Electron microscopy indicated extensive effacement of podocyte foot process (Fig. 1). Our patient was included in the study conducted by Braun et al., who identified the genetic cause of GAMOS and reported genetic results and rudimentary clinical data (case ID: 16M0417). Whole-exome sequencing was performed with Agilent SureSelect human exome capture arrays (Thermo Fisher Scientific) with next-generation sequencing on an Illumina platform. The coding regions of OSGEP, TP53RK, TPRKB, and LAGE3 were screened. A hemizygous G-to-A transition in intron 1 (c.188+1G>A, NM_006014.4) of the LAGE3 gene on chromosome Xq28 was identified, which was inherited from the unaffected mother. Thus, X-linked recessive inheritance was demonstrated. The mutation affects the canonical sequence of the splice donor site and may result in a truncated protein (p.Phe63LeufsTer63).

Discussion and conclusions

Our present patient was affected by X-linked GAMOS. Four GAMOS families (five patients) with different LAGE3 mutations were reported in literature. The
families were from Europe, Japan (two brothers), the United States, and Taiwan (our patient). Primary microcephaly was noted in all 5 patients (5/5) after birth. The following minor dysmorphic features were noted but not uniform: narrow forehead (3/3), micrognathia (3/3), mid-face hypoplasia (1/5), hypertelorism (1/5), flat nasal bridge (1/5) and arachnodactyly (2/5). The neurologic presentations include developmental delay with intellectual disability (5/5), seizures (3/5), hypotonia (5/5), spasticity (1/5), swallowing difficulties (3/5), and esotropia (2/5). Various brain imaging findings include: abnormal gyri and migration disorders (2/5), cerebellar atrophy (3/5), cerebral atrophy (2/5), and thin corpus callosum (1/5). The timing of the onset of proteinuria ranged from 3 months in our patient to 2-3 years in Japanese siblings. When aggressive dialysis therapy was not applied, the patients’ age of death ranged from 8 months in our patient to 8-25 years in Japanese siblings. Renal pathology indicated minimal change nephrotic syndrome (1/4), focal segmental glomerulosclerosis (2/4), and diffuse mesangial sclerosis (1/4). Unlike other patients with GAMOS who have a highly consistent phenotype, interfamilial variability was noted in LAGE3 mutations among patients with different dysmorphic pictures, clinical presentations, imaging findings, and outcomes. The clinical heterogeneity may be related to different pathogenic mutations in LAGE3 gene. In our patient and the patient evaluated by Baker et al., splice site mutations indicated earlier onset of proteinuria (3 and 9 months) and poorer outcome (death at 8 and 14 months), compared with the Japanese siblings, who had a missense mutation (c.410T>C). The hypothesis should be evaluated through additional cases and functional studies.

**Declarations of competing interest**

None declared.
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2. This manuscript was edited by Wallace Academic Editing.

References


Figure 1

(1A) Anterior and lateral view of the patients with peculiar facial dysmorphisms, microcephaly, flat occiput, mid-face hypoplasia, hypertelorism, flat nasal bridge, esotropia, narrow forehead and micrognathia.

(1B) Brain MRI showed mild prominence of the subarachnoid space in bilateral frontal, temporal and parietal area, suggesting brain atrophy. No abnormal neuronal migration or cerebellar atrophy was noted.

(1C) Renal pathology on light microscopy of glomeruli show diffuse mesangial sclerosis with diffuse sclerosing glomerulopathy, increased mesangial matrix and hypercellularity, tubular ectasia, and tubulointerstitial scarring. Electron microscopy showed extensive effacement (arrowhead) of the foot processes.
This certifies that the paper **X-linked recessive Galloway–Mowat syndrome caused by LAGE3 variant** has been edited by Hannah Fox on June 27, 2022 and is considered to be improved in grammar, punctuation, spelling, verb usage, sentence structure, conciseness, general readability, writing style, and native English usage to the best of the editor’s ability.

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