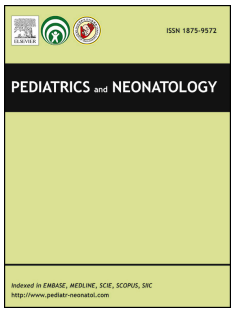


X-linked recessive Galloway- Mowat syndrome 2 caused by a specific LAGE3 variant

Tsai-Ling Liu, Shuan-Pei Lin, Martin Zenker, Tung-Ying Chen, Jui-Hsing Chang, ChunChen Lin, Jeng-Daw Tsai

PII: S1875-9572(22)00218-2

DOI: https://doi.org/10.1016/j.pedneo.2022.09.005

Reference: PEDN 1413

To appear in: *Pediatrics & Neonatology*

Received Date: 18 January 2022

Revised Date: 3 July 2022

Accepted Date: 27 September 2022

Please cite this article as: Liu T-L, Lin S-P, Zenker M, Chen T-Y, Chang J-H, Lin C, Tsai J-D, X-linked recessive Galloway- Mowat syndrome 2 caused by a specific LAGE3 variant *Pediatrics and Neonatology*, https://doi.org/10.1016/j.pedneo.2022.09.005.

Title Page (with Author Details)

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

Tsai-Ling Liu [a,b], Shuan-Pei Lin [a,c], Martin Zenker [d], Tung-Ying Chen [e], Jui-Hsing Chang [a], ChunChen Lin [a], Jeng-Daw Tsai [a,b,c]

a Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan

b Department of Pediatrics, Taiwan Adventist Hospital, Taipei, Taiwan

c Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

d Institute of Human Genetics, University Hospital Magdeburg, Magdeburg, Germany

e Department of Pathology, MacKay Memorial Hospital, Taipei, Taiwan

* Corresponding authors: Jeng-Daw Tsai

Address: No. 92, Sec. 2, Chung-Shan North Road., Taipei City 10449, Taiwan

Tel: +886-2-2543-3535

Fax: +886-2-2543-3642

E-mail address: Jeng-Daw Tsai (tsaijd@yahoo.com.tw)

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.,[2] who identified the genetic cause of GAMOS and reported genetic results and rudimentary clinical data (case ID: 16M0417).[2] 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).[2]

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.[2,4,5] The

families were from Europe, Japan (two brothers),[4] the United States,[5] 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.

Acknowledgement

1. We wish to express particular appreciation to Dr. Friedhelm Hildebrandt for his great contribution for the genetic study of this patient.[3]

2. This manuscript was edited by Wallace Academic Editing.

References

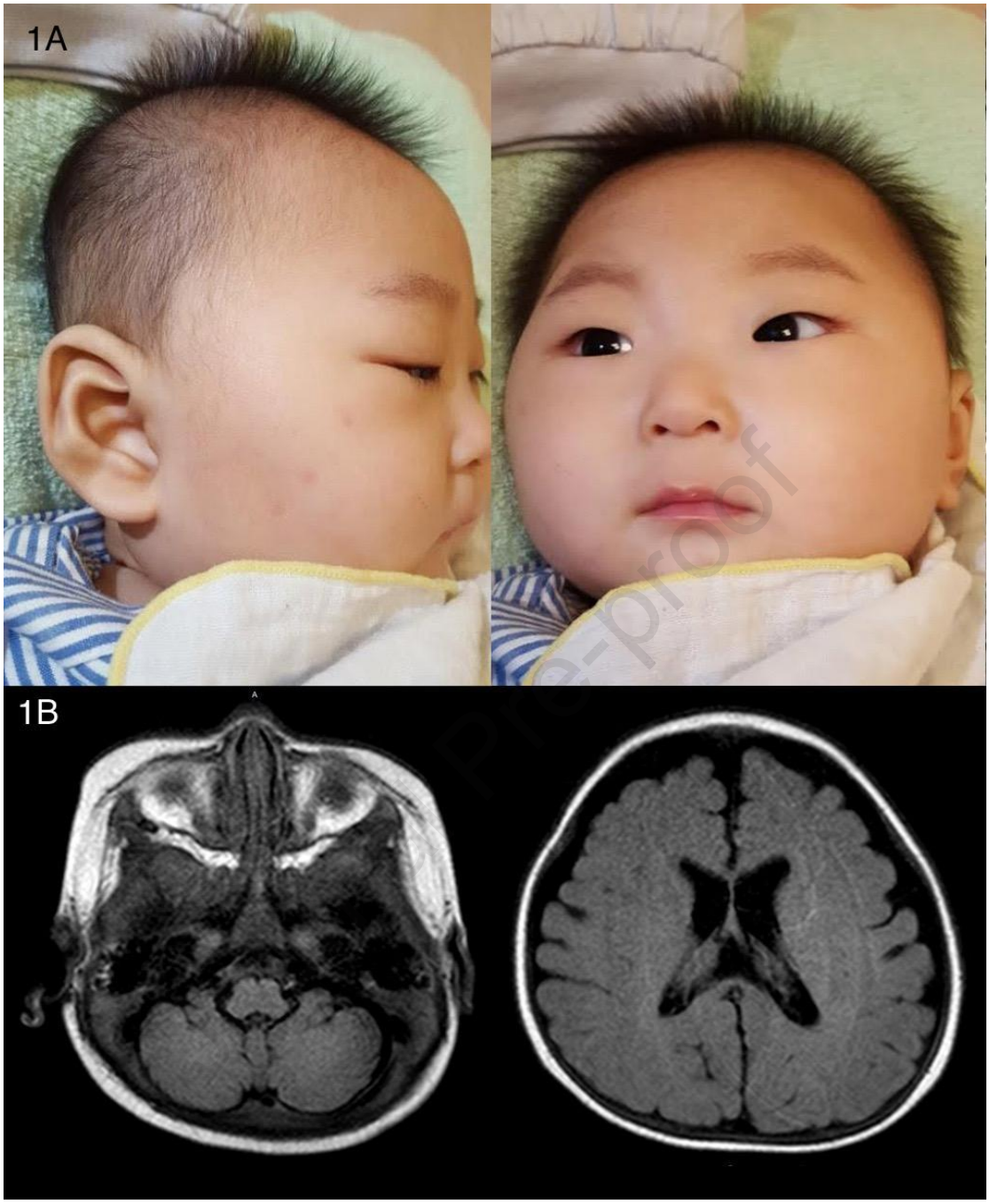
1. Galloway WH, Mowat AP. Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet. 1968; 5(4):319–321

2. Braun DA, Rao J, Mollet G, Schapiro D, Daugeron MC, Tan W, et al. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly. Nat Genet. 2017; 49(10):1529-1538.

3. Lin PY, Tseng MH, Zenker M, Rao J, Hildebrandt F, Lin SH, et al. Galloway-Mowat syndrome in Taiwan: OSGEP mutation and unique clinical phenotype. Orphanet J Rare Dis. 2018; 13(1):226

4. Shiihara T, Kato M, Kimura T, Matsunaga A, Joh K, Hayasake K. Microcephaly, Cerebellar Atrophy, and Focal Segmental Glomerulosclerosis in Two Brothers: A Possible Mild Form of Galloway-Mowat Syndrome. J Child Neurol. 2003; 18(2):147-149

5. Baker E, Weaver D, Massengill S, Mittag D, Juusola J, Demmer L. An unusual case of nephrotic syndrome in a microcephalic infant: Answers. Pediatr Nephrol. 2019; 34:2327-2329


1A
1B

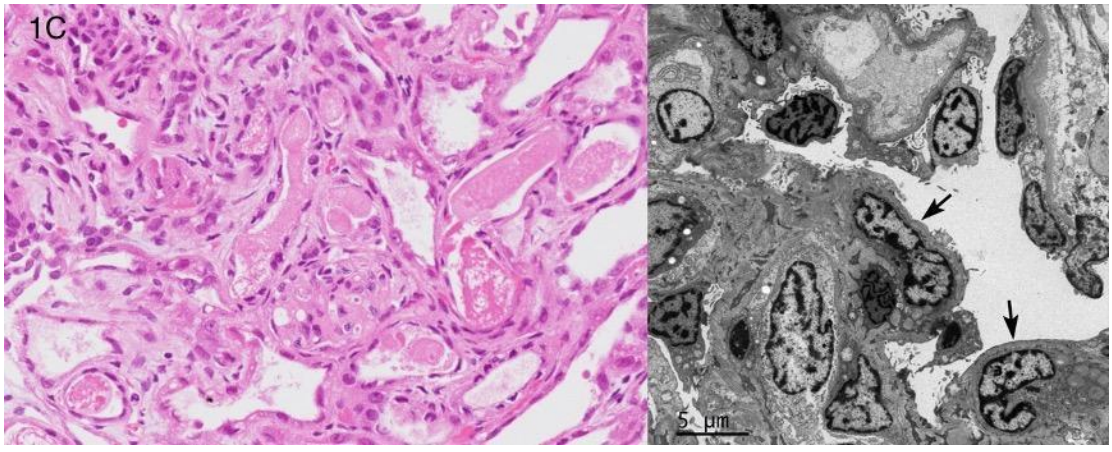

1C
5 μm

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.

Wallace Academic Editing

English Editing Certificate

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.

Best regards,
Wallace Academic Editing

Phone No.: +886-2-2555-5830
Website: http://www.editing.tw
Email: editing@editing.tw
Address: 3F., No.180, Chang'an W. Rd., Datong Dist., Taipei City

Pediatrics and Neonatology

AUTHORSHIP &

CONFLICTS OF INTEREST STATEMENT

Manuscript title (please type):

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

AUTHORSHIP

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication. Indicate the specific contributions made by each author (list the authors' initials followed by their surnames, e.g., Y.L. Chang). The name of each author must appear at least once in each of the three categories below.

Category 1

Conception and design of study (typed): Jeng-Daw Tsai, Shuan-Pei Lin, Tsai- Ling Liu , Martin Zenker.

acquisition of data (typed): Jeng-Daw Tsai ,Shuan-Pei Lin, Martin Zenker ,Tung-Ying Chen.

analysis and/or interpretation of data (typed): Tung-Ying Chen, Jui-Hsing Chang, Chun-Chen Lin.

Category 2

Drafting the manuscript (typed): Tsai-Ling Liu.

revising the manuscript critically for important intellectual content (typed): Jeng-Daw Tsai .

Category 3

Approval of the version of the manuscript to be published (names of all authors must be typed below):

Tsai-Ling Liu, Martin Zenker, Tung-Ying Chen, Jui-Hsing Chang, Chun-Chen Lin, Shuan-Pei Lin, Jeng-Daw Tsai.

Acknowledgments

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgments and have given us their written permission to be named. If we have not included an Acknowledgments, then that indicates that we have not received substantial contributions from non-authors.

CONFLICTS OF INTEREST

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. PEDN Editors strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

Section I

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Author names (typed): nil

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript. Please specify the nature of the conflict on a separate sheet of paper if the space below is inadequate.

Author names (typed):nil