THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0141

The Mechanism Underlying Galloway-Mowat Syndrome Caused by LAGE3 Deficiencies

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Case Study : Objective：Galloway-Mowat Syndrome (GAMOS) (MIM 251300) is a rare disorder characterized by the combination of congenital nephrotic syndrome, microcephaly, brain abnormalities, growth retardation, and various clinical manifestations. Mutations in LAGE3 genes of the KEOPS complex have been found. This study aims to identify LAGE3 mutations in Chinese pediatric patients and explore the pathogenic mechanisms. Methods：Based on the Chinese Children Genetic Kidney Disease Database, patients with LAGE3 variants were screened. The consequence of the LAGE3 intron variant was assessed using minigene technology. Furthermore, the stability of the KEOPS complex with the LAGE3 variants was examined through immunoprecipitation. Results： 1. A total of 3 cases carry suspected pathogenic LAGE3 variants in an X-linked recessive inheritance pattern were identified: Patient #1: Male, 4-year-old. Clinical Presentation: Proteinuria with renal biopsy showed FSGS. Developmental delay is observed. Several male family members in this lineage developed kidney disease and passed away during childhood. Genetic Variant: c.188+1 G>A (maternal). Multiple females in the lineage carry this mutation in LAGE3. Patient #2: Male, 8-year-old. Clinical Presentation: SRNS with renal biopsy showed FSGS. Genetic Variant: c.193C>A, p.Leu65Ile (maternal). Patient #3: Male, 9-year-old. Clinical Presentation: SRNS with renal biopsy showed MCD. Genetic Variant: c.389T>G, p.Val130Gly (maternal). His brother shares the same genotype and presents with proteinuria. 2. Minigene experiments confirmed that c.188+1 G>A causes abnormal mRNA splicing (c.189-1_189-6insCCCCAG), resulting in altering the amino acid sequence p.63_64insPheSer). Co-immunoprecipitation results suggest this variant weakens the binding between LAGE3 proteins that can affect the stability of the KEOPS complex. Conclusion: Our study underscores that LAGE3 mutations, following X-linked recessive inheritance patterns, result in GAMOS. The prominent clinical features include SRNS, FSGS, with or without neurodevelopmental defects. Intronic variant of c.188+1 G>A affects the stability of the KEOPS complex. These findings contribute to the understanding of the molecular mechanisms underlying GAMOS.

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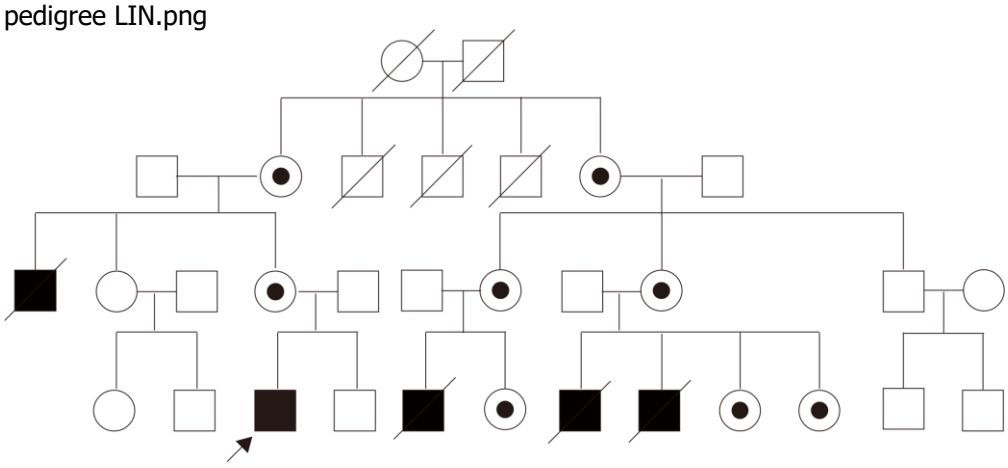

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