Pathogenic LAMA5 Variants and Kidney Disease

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The manuscript by Nagano et al. (1) describes four children with the nephrotic syndrome and biallelic pathogenic variants in LAMA5. Three of the children, each with two truncating variants, presented within the first year of life and developed kidney failure by the age of 4 years. The other child, with two missense variants, was 7 years old at presentation and still had functioning kidneys 2 years later. Their kidney biopsies demonstrated diffuse mesangial sclerosis or FSGS, with a glomerular basement membrane (GBM) that was thinned or thickened and “moth eaten”. One child also had hypoplastic kidneys and a congenital cataract, but none of the others had extrarenal abnormalities.

The three biallelic truncating LAMA5 variants were considered pathogenic by the ACMG/AMP criteria on the basis of their truncating effect, analysis of multiple computational tools, and low population frequencies in gnomAD. Pathogenicity was confirmed by demonstrating immunohistochemically that the corresponding GBM lacked the laminin α5-chain (1). The truncating variants were also examined in an in vitro heterotrimer assay, where they formed shortened chains that nevertheless included most of the main carboxy terminus β1- and γ1-binding sites that allowed all three chains to polymerize. These truncated but still functional laminin α5-chains were thought to be responsible for the kidney-limited phenotype. The manuscript authors commented that biallelic truncating LAMA5 variants in mice are embryonic lethal and that only embryos with truncating variants that allow polymerization survive.

There have been previous reports of biallelic LAMA5 variants associated with the nephrotic syndrome. However, most have been variants of uncertain significance whose pathogenicity has not been confirmed independently with, for example, reduced expression in affected tissues, altered function, an animal model that recapitulates the clinical features, or incomplete recovery when the variant is used to rescue a knockout.

The effects of the truncating variants contrast with those in a 2-year-old child with a homozygous pathogenic LAMA5 missense variant, c.857G>T or p.(Arg286Leu), who presented with the nephrotic syndrome and whose features were reproduced in a CRISPR-generated mouse model (2). The substituted Arg residue is adjacent to the PLENGE sequence in the laminin α5-chain through which individual chains of the laminin-αβγ trimer polymerize. The pathogenic variant was demonstrated to result in defective polymerization in vitro and, a syndromic disorder with neurodevelopmental, ocular, skeletal, and skin abnormalities.

In addition, there are reports of a homozygous LAMA5 missense variant associated with a presynaptic congenital myasthenic syndrome (3) and of a heterozygous LAMA5 variant associated with skin and skeletal defects, and myopathy but normal kidney function without proteinuria (4).

These observations are all consistent with laminin-α5 domain-specific roles affecting embryonic development and kidney function (5). They are also consistent with truncating variants resulting in earlier onset and more severe disease than missense variants. However, specialized tests, such as MRI, EMG, or ocular examinations, may be required to identify subtle extrarenal features, and the consequences may only be apparent at a later age.

Basement membranes are not only mechanical barriers but also metabolically active scaffolds for cells and other proteins. The laminins are a family of basement membrane proteins that are important in embryogenesis and contribute to membrane assembly, cell-matrix interactions, and tissue differentiation and function (6). Laminin forms a lattice-like network that binds to agrin and nidogen and through nidogen to the collagen IV network and perlecian. The laminin network is anchored to cell surfaces via dystroglycan and through integrins to the cytoskeleton and intracellular signaling pathways.

Each laminin molecule is a glycoprotein comprising α-, β-, and γ-chains that form a cruciform structure with three short arms and one long arm (Figure 1). The amino termini of the three chains form the short arms, the carboxy termini contribute to the long arm, and the carboxy terminus of the α-chain forms the long-arm globular domain that bind to cells.

Five α-chains, four β-chains, and three γ-chains have been described that assemble into multiple different laminin molecules. These isoforms are functionally distinct and expressed in a developmental and tissue-specific manner. Four laminins (111, 511, and 521 and small amounts of 332) are found in the kidney (Table 1).

Laminin 111 comprises the α1-, β1-, and γ1-chains and is the first isoform expressed in the developing embryo, where it is important in organogenesis, neural development, and angiogenesis. In adults, laminin
111 is found in kidney, brain, and blood vessels. Laminin 511 (α5β1γ1) replaces laminin 111 during glomerulogenesis at the capillary loop stage and is required for GBM cell adhesion. It is also present in the skin and smooth muscle. Laminin 521 (α5β2γ1) is expressed in the GBM, neuromuscular system, various ocular structures, and vascular tissue. Laminin 332 (α3β3γ2) is found in the skin but also, in small amounts in the kidney, and it is mainly involved in cell adhesion to the underlying connective tissue.

Thus, the laminin-α5 chain is highly expressed in embryonic development and in the adult kidney, where it is critical for glomerular filtration barrier integrity, as well as in the neuromuscular system, eye, and vascular tissue (7) (8). Because laminin 521 is the main laminin found in the adult kidney, pathogenic variants in both LAMA5 and LAMB2 might result in similar clinical features. Pierson syndrome (Online Mendelian Inheritance in Man 609049), an autosomal recessively inherited disease caused by two pathogenic LAMB2 variants, is well described. It too is characterized by the nephrotic syndrome and sometimes, neurologic and ocular abnormalities. Most reported pathogenic variants

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**Figure 1.** Each laminin molecule comprises three short arms formed from the amino termini of the α-, β-, and γ-chains, the long arm from the carboxy termini, as well as the long arm globular domain from the α chain.

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**Table 1.** Phenotypes of human disease and mouse models corresponding to pathogenic variants in the genes for the kidney laminin chains

<table>
<thead>
<tr>
<th>Gene</th>
<th>Human Disease (Online Mendelian Inheritance in Man)</th>
<th>Tissues Affected in Mouse Model (Mouse Genome Informatics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMA1</td>
<td>Poretti–Boltshauser syndrome (AR; OMIM 615960) due to truncating variants. Cerebellar vermis atrophy, cerebellar cysts, high myopia, retinal dystrophy, abnormal eye movements, delayed motor development and speech</td>
<td>Brain, eye</td>
</tr>
<tr>
<td>LAMA3</td>
<td>Epidermolysis bullosa of various types (AR; OMIM 226650, 226700) due to truncating variants</td>
<td>Skin, skeletal, respiratory</td>
</tr>
<tr>
<td>LAMA5</td>
<td>Congenital nephrotic syndrome, FSGS; ? congenital myasthenia gravis (AR; OMIM 601462)</td>
<td>Brain, eye, skeletal, respiratory, kidney (cyts, FSGS, proteinuria, abnormal podocyte foot processes)</td>
</tr>
<tr>
<td>LAMB1</td>
<td>Lissencephaly (AR; OMIM 615191), loss-of-function mutations with cobblestone cortex, hydrocephalus, seizures, delayed psychomotor development</td>
<td>Brain, muscle</td>
</tr>
<tr>
<td>LAMB2</td>
<td>Nephrotic syndrome with or without ocular abnormalities (AR; OMIM 614199) probably due to missense variants. Pierson syndrome (AR; OMIM609049) probably due to truncating variants. Nephrotic syndrome, ocular abnormalities (typically microcoria), possibly also congenital myasthenia</td>
<td>Brain, eye, kidney (proteinuria, abnormal GBM)</td>
</tr>
<tr>
<td>LAMB3</td>
<td>Amelegenes imperfecta type 1A (AD; OMIM 104530) due to truncating variants; epidermolysis bullosa of various types (AR; OMIM 226700 and 226650)</td>
<td>Skin, skeleton, respiratory, kidney (cyts)</td>
</tr>
<tr>
<td>LAMC1</td>
<td>? Dandy–Walker malformation</td>
<td>Brain, eye, muscle, respiratory, kidney (cyts, reduced glomerular number, kidney agenesis)</td>
</tr>
<tr>
<td>LAMC2</td>
<td>Epidermolysis bullosa of various types (OMIM 226700 and 226650; AR); often due to truncating variants</td>
<td>Skin, skeleton, respiratory, kidney (cyts, obstruction)</td>
</tr>
</tbody>
</table>

Data are from OMIM (www.omim.org) and Mouse Genome Informatics (www.informatics.jax.org). AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man; GBM, glomerular basement membrane.
are truncating, but missense variants are often associated with isolated nephrotic syndrome and later disease onset. Severe neurodevelopmental defects, including developmental delay, congenital myopathy or myasthenia, and ocular abnormalities, occur (7). Mouse models demonstrate a similar phenotype with severe glomerular disease and neurologic and ocular features (9) (Table 1).

Although kidney disease has only been described with pathogenic variants in LAMB2 and LAMA5 in humans, mouse models suggest that it also occurs with LAMBS3, LAMC1, and LAMC2 variants but may be less common or less severe than the neurologic, skin, and skeletal defects.

There are parallels between the effects of pathogenic variants in the genes for the laminin and collagen IV chains. Like laminin, there are multiple genes for collagen IV that have arisen by reduplication from a shared ancestor. The six COL4A1–COL4A6 genes code for the collagen IV α1–6 chains, which form three heterotrimers and networks (α1α1α2, α3α4α5, and α5α5α6), each with different roles in embryogenesis and different tissue distributions. At birth, the main basement membrane collagen IV in the kidney, ear, and eye is an α1α1α2 heterotrimer, but this switches to the α3α4α5 heterotrimer in infancy, which persists throughout life.

Pathogenic variants affecting COL4A3–COL4A5 result in different forms of Alport syndrome, with X-linked (COL4A5), AR (two variants in COL4A3 or COL4A4), AD (heterozygous variants in COL4A3 or COL4A4), or digenic disease (variants in two of COL4A3–COL4A5). In addition, modifying variants in other podocyte or GBM genes exacerbate the effects of COL4A3–COL4A5 variants.

Pathogenic variants in LAMA5 share some consequences for the kidney with those affecting the COL4A3–COL4A5 genes. These include GBM thinning and the moth-eaten appearance, the development of proteinuria and FSGS, the association with kidney cysts (10), and, possibly, kidney dysplasia (11) and the hearing loss (2).

Pathogenic COL4A3–COL4A5 variants are the single most common cause of FSGS, which appears to occur because substitution of the α1α1α2 for the damaged α3α4α5 network results in an abnormal GBM that is less able to support the overlying podocytes (12). The resulting podocyte loss causes secondary FSGS and renal impairment. Interestingly, the same phenomenon is present in the corneal cells overlying the Descemet membrane in Alport eyes (13).

Pathogenic COL4A3–COL4A5 variants are also associated with kidney cysts in mice and humans (2). These occur at a younger age than in polycystic kidney disease, are fewer in number, do not distort kidney size, and are associated with proteinuria but not necessarily impaired kidney function (14). It is unclear whether cysts result from a developmental anomaly or from localized distension of Bowman’s capsule or the tubules. There is a single report of kidney dysplasia in a canine model of Alport syndrome, but this has not been studied further in human disease (11).

Finally, there are now several reports of LAMA5 variants acting as modifiers that exacerbate the clinical features seen with pathogenic changes in COL4A3–COL4A5 (15).

The story of laminin in inherited kidney disease is only just beginning.

Disclosures

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Author Contributions

P. Harraka and J. Savidge conceptualized the study; J. Savidge was responsible for project administration; P. Harraka was responsible for resources; P. Harraka was responsible for software; P. Harraka was responsible for visualization; J. Savidge provided supervision; P. Harraka and J. Savidge wrote the original draft; and J. Savidge reviewed and edited the manuscript.

References


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