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EDITORIAL

Plasmalemma Vesicle Associated Protein Truncation Causes Lethal Protein-Losing Enteropathy in Humans

Protein-losing enteropathy (PLE) is a syndrome that features excessive losses of serum proteins into the gastrointestinal (GI) tract. PLE elicits hypoproteinemia, often leading to severe edema, ascites, malnutrition, and fatality in affected infants. Although PLE is thought to be induced by several pathologic conditions, ranging from erosive or nonerosive GI disorders to increased intestinal pressure,[1] the genetic and molecular ontogenesis of PLE remains unclear. Current treatment comprises primarily supportive measures, including dietary modification and maintenance of nutritional status. The mortality that accompanies PLE would be greatly reduced if we understood the underlying causes and could effectively identify the affected patients by screening.

Elkadri et al[2] used whole exome sequencing to identify a homozygous nonsense mutation in the plasmalemma vesicle-associated protein (*PLVAP*) gene in an infant who died from a severe PLE condition. This identified 1072C>T mutation causes a premature stop codon that truncates 84 amino acids off *PLVAP*'s C terminus. Surprisingly, the primary pathologic defects were not found in the patient's intestinal epithelial cells but rather in the intestinal vascular endothelial cells. This finding differs somewhat from most cases of enteropathy that affect young children, including microvillus inclusion disease[3] and congenital tufting enteropathy.[4] In these latter conditions, genetic abnormalities cause cellular abnormalities that primarily affect the intestinal epithelial structure and function. In contrast, the *PLVAP* p.R358 patient reported in this study showed virtually no histologic abnormality in the intestinal epithelium. Rather, the ultrastructural analyses present evidence supporting a collapse of the intestinal vascular endothelium, probably caused by a lack of diaphragms in the fenestrae. This structural abnormality is believed to impair the gatekeeping function of endothelium, causing the leakage of plasma proteins.

Remarkably, a similar phenotype has been described in *Plvap* knockout mice, with additional vascular endothelium defects in several organs.[5] The phenotypic features of the endothelium in the *PLVAP* p.R358 patient largely resemble those of *Plvap* knockout mice at both ultrastructural and biochemical levels, strongly supporting a critical involvement of *PLVAP* in PLE pathogenesis. It thus becomes possible to screen infants for this genetic mutation and to prevent severe complications at an early stage of the disease. The recent promise of gene therapy[6] makes targeted correction of *PLVAP* mutations plausible in future to cure affected patients.

This novel monogenic lethal defect discovered by Elkadri and colleagues sheds fresh light on new focus points that must be explored by future studies. In particular, it will be interesting to examine the molecular basis of leaky fenestrated capillaries in the intestinal endothelial cells lacking *PLVAP*. Moreover, *PLVAP* mutations may result in congenital malformation in other tissues besides intestines. This study holds the key to insight into the endothelial barrier function and intestinal homeostasis. As we move into the era of precision medicine, more studies extrapolating genetic causes of GI and hepatic disorders are needed to guide the effective identification and treatment of patients. A combination of basic research and clinical investigation, as finely exemplified by this work, will help achieve improved patient outcomes.

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Conflicts of interest
The authors disclose no conflicts.

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