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Summary

CGNL1 CONTROLS VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE AND AUTOIMMUNE HEPATOBILIARY DISEASE

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Loss-of-function CGNL1 variants identified in siblings with very early onset IBD and PSC disrupt gut barrier integrity and activate ER stress in patient organoids and a novel knockout mouse model.

KEY POINTS

- Two rare loss-of-function CGNL1 variants were identified by whole exome sequencing in siblings with VEO-IBD diagnosed at age 3, both requiring early total colectomy and both developing PSC and additional autoimmune manifestations.
- Patient organoids formed smaller spheroids with skewed microvilli, impaired junctional complexes, and reduced barrier function; CGNL1 protein was diminished in patient intestinal epithelium and associated with spontaneous ER stress.
- Cgnl1-/- mice exhibited shortened microvilli, disrupted junctional complexes, enhanced epithelial ER stress, increased gut permeability, altered microbiome, and substantial vulnerability to DSS-induced colitis and C. difficile infection.
- Cgnl1-/- mice showed spontaneous periportal inflammation and fibrosis in the liver, establishing the model as novel for IBD-associated hepatobiliary disease.
- Chemical chaperones TUDCA and 4-PBA restored epithelial barrier integrity and alleviated ER stress in both patient organoids and Cgnl1-/- mice at steady state and during colitis or infection, warranting further investigation as therapies for IBD caused by primary intestinal barrier defects.
- CGNL1 protein was also reduced in unrelated UC and PSC patients, including in uninflamed UC tissues, suggesting broader relevance beyond the rare variants identified.

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