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Mutations in Tetratricopeptide Repeat Domain 7A Result in a Severe Form of Very Early Onset Inflammatory Bowel Disease

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BACKGROUND & AIMS: Very early onset inflammatory bowel diseases (VEOIBD), including infant disorders, are a diverse group of diseases found in children younger than 6 years of age. They have been associated with several gene variants. Our aim was to identify the genes that cause VEOIBD. **METHODS:** We performed whole exome sequencing of DNA from 1 infant with severe enterocolitis and her parents. Candidate gene mutations were validated in 40 pediatric patients and functional studies were carried out using intestinal samples and human intestinal cell lines. **RESULTS:** We identified compound heterozygote mutations in the Tetratricopeptide repeat domain 7 (*TTC7A*) gene in an infant from non-consanguineous parents with severe exfoliative apoptotic enterocolitis; we also detected *TTC7A* mutations in 2 unrelated families, each with 2 affected siblings. TTC7A interacts with EFR3 homolog B to regulate phosphatidylinositol 4-kinase at the plasma membrane. Functional studies demonstrated that TTC7A is expressed in human enterocytes. The mutations we identified in *TTC7A* result in either mislocalization or reduced expression of TTC7A. Phosphatidylinositol 4-kinase was found to co-immunoprecipitate with TTC7A; the identified TTC7A mutations reduced this binding. Knockdown of TTC7A in human intestinal-like cell lines reduced their adhesion, increased apoptosis, and decreased production of phosphatidylinositol 4-phosphate. **CONCLUSIONS:** In a genetic analysis, we identified loss of function mutations in *TTC7A* in 5 infants with VEOIBD.

***Authors share co-first authorship; §Authors share co-senior authorship.**

Abbreviations used in this paper: **co-IP, co-immunoprecipitate; EFR3B, EFR3 homolog B; MIA, multiple intestinal atresia; PI4KIIIα, phosphatidylinositol 4-kinase IIIα; SCID, severe combined immunodeficiency; shRNA, short hairpin RNA; TPR, tetratricopeptide repeat; TTC7A, tetratricopeptide repeat domain 7; VEOIBD, very early onset inflammatory bowel diseases; WT, wild type.**

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