Mutations in tetratricopeptide repeat domain 7A result in a severe form of very early onset inflammatory bowel disease.

Abstract:
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. 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. 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. In a genetic analysis, we identified loss of function mutations in TTC7A in 5 infants with VEOIBD. Functional studies demonstrated that the mutations cause defects in enterocytes and T cells that lead to severe apoptotic enterocolitis. Defects in the phosphatidylinositol 4-kinase-TTC7A-EFR3 homolog B pathway are involved in the pathogenesis of VEOIBD.