Girls homozygous for an IL-2-inducible T cell kinase mutation that leads to protein deficiency develop fatal EBV-associated lymphoproliferation.

The fatal immune dysregulation that sometimes follows EBV infection in boys has been linked to mutations in two X chromosome-encoded genes, SLAM-associated protein (SAP) and X-linked inhibitor of apoptosis (XIAP). In this study we describe 2 girls from a consanguineous Turkish family who died after developing severe immune dysregulation and therapy-resistant EBV-positive B cell proliferation following EBV infection. SNP array-based genome-wide linkage analysis revealed IL-2-inducible T cell kinase (ITK) as a candidate gene for this immunodeficiency syndrome. Both girls harbored a homozygous missense mutation that led to substitution of a highly conserved residue (R335W) in the SH2 domain of ITK. Characteristics of ITK deficiency in mouse models, such as absence of NKT cells and high levels of eomesodermin in CD8+ cells, were seen in either one or both of the girls. Two lines of evidence suggested that R335W caused instability of the ITK protein. First, in silico modeling of the mutant protein predicted destabilization of the SH2 domain. Additionally, Western blot analysis revealed that, unlike wild-type ITK, the R335W mutant was nearly undetectable when expressed in 293 T cells. Our results suggest that ITK deficiency causes what we believe to be a novel immunodeficiency syndrome that leads to a fatal
inadequate immune response to EBV. Because ITK deficiency resembles EBV-associated lymphoproliferative disorders in boys, we suggest that this molecular cause should be considered during diagnosis and treatment.