A homozygous mucosa-associated lymphoid tissue 1 (MALT1) mutation in a family with combined immunodeficiency.

Combined immunodeficiency (CID) is characterized by severe recurrent infections with normal numbers of T and B lymphocytes but with deficient cellular and humoral immunity. Most cases are sporadic, but autosomal recessive inheritance has been described. In most cases, the cause of CID remains unknown. We wanted to identify the genetic cause of CID in 2 siblings, the products of a first-cousin marriage, who experienced recurrent bacterial and candidal infections with bronchiectasis, growth delay, and early death. We performed immunologic, genetic, and biochemical studies in the 2 siblings, their family members, and healthy controls. Reconstitution studies were performed with T cells from mucosa-associated lymphoid tissue lymphoma-translocation gene 1-deficient (Malt1(-/-)) mice. The numbers of circulating T and B lymphocytes were normal, but T-cell proliferation to antigens and antibody responses to vaccination were severely impaired in both patients. Whole genome sequencing of 1 patient and her parents, followed by DNA sequencing of family members and healthy controls, showed the
presence in both patients of a homozygous missense mutation in MALT1 that resulted in loss of protein expression. Analysis of T cells that were available on one of the patients showed severely impaired I?B? degradation and IL-2 production after activation, 2 events that depend on MALT1. In contrast to wild-type human MALT1, the patients' MALT1 mutant failed to correct defective nuclear factor-?B activation and IL-2 production in MALT1-deficient mouse T cells. An autosomal recessive form of CID is associated with homozygous mutations in MALT1. If future patients are found to be similarly affected, they should be considered as candidates for allogeneic hematopoietic cell transplantation.