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The TACI gene is mutated in common variable immunodeficiency and IgA deficiency. The tumor necrosis factor receptor (TNFR) family member TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) mediates isotype switching in B cells. Five of 20 unrelated patients with common variable immunodeficiency (CVID) and one of 16 patients with IgA deficiency (IgAD) were found to have a missense mutation in one TACI allele. One of the 4 CVID patients had a single nucleotide insertion in the other TACI allele. None of these mutations were present in 50 healthy subjects. TACI mutations co-segregated with the phenotype of CVID or IgAD in family members of four index patients studied. B cells from patients with TACI mutations expressed TACI, but failed to undergo isotype switching to IgG and IgA in response to the TACI ligand APRIL. These results suggest that TACI mutations can result in CVID and IgAD.