**Supplementary Results**

*Further observations on Families A-F*

In families A, B, C, D, F, and G, we observed unaffected and mildly affected individuals carrying heterozygous *TNFRSF13B* mutations. These observations can be attributed to the variable penetrance of these sequence variants and are consistent with previous reports (ref. 10,11,29). In families D, E, and F, however, we observed affected individuals with two wild-type *TNFRSF13B* alleles. In families A, B, and C, we found compound heterozygous *TNFRSF13B* mutations in a total of five patients (Table 4 and Figure 2), two of whom had an IgG subclass deficiency and three of whom had CVID.

In family A, two male siblings were affected with CVID and both carried a compound heterozygous mutation (C104R/C104Y).

In family B, a male and a female sibling carried the compound heterozygous mutation Y79C/I87N. Individual B.I.1 was shown to be slightly dysgammaglobulinemic without recurrent infections. The sister was affected by IgG subclass deficiency and suffered from recurrent infections requiring IVIG substitution therapy. Her brother developed splenomegaly.

In family C the index patient (C.II.1) was affected with CVID and had a compound heterozygous *TNFRSF13B* c.204insA/C104R mutation. Individual C.III.1 had a history of recurrent upper respiratory tract infections and one documented pneumonia by the age of 26, but her IgG levels were only slightly lowered.
In family D, the index patient carried a heterozygous C104 mutation and had CVID. Her Mother, individual D.I.2 was hypogammaglobulinemic and had four documented episodes of pneumonia when she was younger. During the last 20 years she had only recurrent upper respiratory tract infections but did not receive IVIG therapy. Individual D.II.1 also carried the C104R *TNFRSF13B* allele and had an IgG subclass deficiency and low IgA with recurrent upper respiratory tract infections. Individual D.III.2, however, had an IgG subclass deficiency but carried two wild-type alleles and had no increased rate of infections. The significance of this finding is uncertain because of his young age (4 years).

In family E, the index patient and one of his sisters had CVID, whereas his father and his other two sisters had a selective IgA deficiency. In family E, however, only the index patient is known to carry a C104R mutation.

Three individuals in family F carried heterozygous A181E mutations, but only one had developed CVID. Moreover, the mother in family F carried two wild-type alleles, but had CVID. Individual F.II.2 had been diagnosed with Crohn’s disease but had normal immunoglobulin levels.

In Family G the index patient had CVID and carried a double mutation (D41H;c.298insT). The index patient and his brother inherited both mutations from the mother, but both the brother and the mother were clinically healthy and had normal Ig levels.
**Analysis of TACI C104R in 293T cells**

To demonstrate that the impaired surface staining of the TACI C104R mutant EBV cell lines with a polyclonal anti-TACI antibody truly reflects impaired surface expression and is not solely due to the alteration of important epitope(s) recognized by the antibody, 293T cells were transfected with TACI full-length constructs or recombinant fusion proteins composed of the TACI extracellular domain fused to the C-terminal portion of TRAIL-R3. The fusion protein is GPI-anchored, and the TRAIL-R3 portion allows to monitor cell-surface expression in both wild type and C104R TACI. Transfected 293T cells expressing TACI C104R or wt TACI were stained either with the monoclonal anti-TACI antibody (1A1), or the polyclonal anti-TACI antibody or a monoclonal rat anti-human TRAIL-R3 antibody (clone 572.11) (Supplementary figure 3).

The stainings with monoclonal or polyclonal antibodies against full-length TACI or TACI C104R in 293T cells reflected the staining pattern observed in EBV cell lines (Supplementary figure 3 lower panels and Figure 3A and 3B). The staining with the monoclonal antibody 1A1 was also clearly reduced in the cells expressing the C104R mutant TACI/TRAIL-R3 fusion protein, which is consistent with the data in the EBV cell lines and is easily explained by the loss of the immunodominant epitope for this monoclonal antibody. In contrast, the staining with the polyclonal anti-TACI antibody was not reduced and the staining with the anti TRAIL-R3 antibody showed that both constructs were expressed equally well on the cell surface (Supplementary figure 3). We thus conclude that the reduced staining of full-length TACI C104R with the polyclonal anti-TACI antibody most likely reflects a reduced surface expression of TACI C104R.