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Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency

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To the Editor

Tumor necrosis factor (TNF)-like receptors are members of a superfamily of proteins involved in regulating maturation and survival of lymphocytes. One of these receptors, TACI (transmembrane activator and CAML interactor; encoded by *TNFRSF13B*), binds two ligands, BAFF and APRIL. Deletion of *Tnfrsf13b* in mice results in an impaired response to thymus-independent antigens¹ and virtually abolishes APRIL-induced switching to IgA, IgE and IgG1 (ref. ²). Conversely, lack of APRIL, owing to a targeted inactivation of *Tnfsf13* in mice, results in an impaired ability to switch to IgA production³.

Recently, two studies have reported that sequence variants in *TNFRSF13B* are associated with primary immunodeficiency diseases in humans^{4,5}. Specifically, common variable immunodeficiency (CVID) was found to be associated with homozygosity for several coding variants (S144X, C104R and A181E)⁴; in addition, heterozygous coding variants (C104R, A181E, S194X, R202H and ins204A) were identified in several individuals with CVID^{4,5}. Furthermore, Castigli *et al.*⁵ showed a strict correlation between the presence of heterozygous

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COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

coding variants (C104R, A181E and R202H) and CVID and selective IgA deficiency (IgAD) in members of their multicase families, suggesting a causal relationship. In our study⁴, one of the siblings of a CVID proband, who is heterozygous for the A181E variant, suffered from IgAD. However, her mother, who is also heterozygous for the A181E variant, had normal immunoglobulin levels, suggesting incomplete penetrance⁴.

Here we report that a significant proportion of the normal population carries heterozygous coding variants in *TNFRSF13B* (Table 1), necessitating a re-evaluation of the potential role of these variants in CVID/IgAD. Therefore, we analyzed *TNFRSF13B* in 115 Swedish, 154 German and 155 US individuals with CVID (Supplementary Table 1 online). We found a highly significant increase in the frequency of the C104R and A181E variants (Table 1) and a significant increase in the frequency of ins204A (Supplementary Table 1), suggesting that these variants, even in a heterozygous form, constitute risk factors for the development of CVID. However, other variants, including R72H, R122W, R202H, V220A and P251L, occurred at similar frequencies in affected individuals and controls (Supplementary Table 1), suggesting that these latter variants do not contribute to the risk of CVID.

Subsequently, we screened 254 Swedish adults with sporadic IgAD or probands in IgAD multicase families for genetic alterations in *TNFRSF13B*. In 55 randomly selected cases, we sequenced the entire gene but did not observe any additional mutations besides those present in controls and individuals with CVID (Supplementary Table 1). Using a SNP-based assay^{4, 6} (for primer sequences, see Supplementary Table 2 online), we did not find an overrepresentation of C104R, A181E or ins204A in our IgAD case series (Table 1 and Supplementary Table 1), nor did we identify any individuals who were homozygous or compound heterozygous for any of the coding variants. However, we found two individuals with IgAD who were heterozygous for the R202H variant, whereas we did not find any R202H heterozygotes among the Swedish controls (Table 1). Subsequently, we investigated the family members of the ten probands with IgAD who carried the C104R, A181E or R202H variants, five of whom belonged to multicase families. However, IgA deficiency did not cosegregate with the TACI coding variants (see families 1, 5, 7 and 10 in Supplementary Table 3 and Supplementary Fig. 1 online), and the transmission disequilibrium test (calculated using TRANSMIT) showed no linkage or association.

Thus, our sequence analysis of *TNFRSF13B* in a large number of cases and controls provides supporting evidence that heterozygous C104R, A181E and ins204A sequence variants in *TNFRSF13B* constitute risk factors for the development of CVID. However, our data suggest that these variants have only minor roles, if any, in the development of selective IgAD. We are currently examining the functional effects of the heterozygous TACI variants to better understand the mechanism by which these variants contribute to the development of CVID.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Frequency of selected TAC1 coding variants in individuals with CVID and IgAD^a

	C104R	A181E	R202H
CVID (all) ^b	16/846	22/844	16/844 ^d
Controls (all) ^c	17/4,208	20/3,924 ^e	20/3,924 ^e
<i>P</i> value	8.2×10^{-5}	3.9×10^{-8}	2.4×10^{-5}
OR	4.16 (1.98–8.74)	5.60 (2.99–10.51)	4.08 (2.07–8.04)
IgAD (Swedish)	1/478	7/464	2/480
Controls (Swedish)	8/2,038	12/1,730	0/2,082
<i>P</i> value	0.55	0.09	3.0×10^{-3}
OR	0.53 (0.07–4.12)	2.19 (0.88–5.47)	–

^a(Number of variant alleles)/(number of tested alleles).^bThe 'CVID (all)' group includes 115 Swedish, 154 German and 155 US individuals with CVID.^cThe 'Controls (all)' group includes 1,080 healthy Swedish blood donors and consecutive samples from the Swedish national neonatal screening program for phenylketonuria (PKU)⁶, 342 healthy German blood donors and 787 healthy US donors from the New York cancer project collection⁷.^dHomozygous sequence variants were excluded from the calculation.^eOne 'control' heterozygous for the A181E allele was found to be hypogammaglobulinemic (serum level of IgG = 3.7 g/l). The institutional review boards at the Karolinska Institute approved this study, and informed consent was obtained from all patients.