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TNFRSF13B Variants in SLE and Immunodeficiency

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Abstract

Background: The co-existence of autoimmunity and primary antibody deficiency in some individiuals is intriguing. The transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) gene (TNFRSF13B) has been implicated in both autoimmunity and primary antibody deficiency to varying extents in mice and humans. However, the phenotype described in mice with TNFRSF13B polymorphisms has not been entirely consistent with patients with similar orthologous polymorphisms.

Objective: To further understand the relationship between TNFRSF13B variants and PAD and autoimmunity, we set out to determine the association of the two most common TNFRSF13B polymorphisms with autoimmunity and immunodeficiency, in patients with primary antibody deficiency and SLE.

Method: We genotyped the C104R and A181E polymorphisms of TNFRSF13B in193 individuals and 144 controls from the Australian and New Zealand Antibody Deficiency Allele (ANZADA) Study, 107 patients from the Australian Point Mutation in Systemic Lupus Erythematosus (APOSLE) study, 169 patients with SLE from a European population, and 263 European controls. We were also able to determine TNFRSF13B genotypes for family members for nine of twelve pedigrees with primary antibody deficiency identified with TNFRSF13B variants.

Results: The total number of TNFRSF13B variants in the primary antibody deficiency cohort was significantly higher than in the control group (p=0.0089; OR 9.481 [95% CI 1.218−73.81]). Similar results were obtained when patients with systemic lupus erythematosus were analysed. TNFRSF13B variants were strongly associated with SLE (p=0.0161, OR 3.316 [95% CI 1.245-8.836]). Familial analysis revealed incomplete penetrance of the TNFRSF13B variants.

Conclusion: Taken together, the two most common TNFRSF13B variants are associated with primary antibody deficiency and systemic lupus erythematosus.

Introduction

Non-congenital primary antibody deficiency (NCPAD) includes common variable immunodeficiency (CVID), selective IgA deficiency (sIgAD), immunoglobulin G subclass deficiency (IgGSD) and specific antibody deficiency (SAD). Shared genetic aetiology amongst these conditions is suggested by observations that different forms of NCPAD cluster within the same kindred, and that in some individuals, less severe forms of immunoglobulin deficiency can progress to complete antibody deficiency [1-3]. In many patients, there is evidence of additional immunological defects in the form of autoimmune disease ranging from autoimmune haematological disease, which is the most common, occurring in approximately 11% of patients, to solid organ-specific autoimmunity and systemic conditions, which also occur in up to 11% of patients [4-7]. These systemic autoimmune diseases include rheumatoid arthritis, sicca syndrome, vasculitis and in particular for this paper, systemic lupus erythematosus (SLE).

A number of studies have identified an increased incidence of antibody defects among patients with autoimmune disease. In a retrospective study of 33 children with an array of autoimmune diseases including systemic diseases such as systemic lupus erythematosus, autoimmune cytopenias and organ specific autoimmune conditions such as Hashimoto's thyroiditis, autoimmune hepatitis and alopecia areata, 12% of children with autoimmune diseases have some form of NCPAD [8]. Another study established that 4.6% of SLE cases and 4.3% of juvenile idiopathic arthritis cases have sIgAD, which is 10-20 times greater than the prevalence in the general population [9]. There have also been reports of SLE preceeding the onset of hypogammaglobulinemia [10,11]. Furthermore, in a series of 326 patients with CVID, clinical evidence of autoimmunity appeared prior to the onset of immunodeficiency in 54% of patients with autoimmune haematological manifestations [7]. Similarly, Michel and co-workers described a cohort where the initial manifestation in 62% of the 21 patients with CVID and ITP was thrombocytopenia [12].

One explanation for this intriguing association is that immune dysregulation contributes to both immunodeficiency and autoimmunity. We will consider the underlying mechanisms including some of own data and a review of published literature to set these findings in context. In particular, we describe genetic variants that appear to be shared between SLE and CVID.

Polymorphisms in the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) gene (TNFRSF13B) have been identified in patients with primary antibody deficiencies [13,14]. Disease associated variants include C104R, A181E, R202H, S114X and S194X [13,14]. Polymorphisms of TNFRSF13B also occur in people with no evidence of immune deficiency, including healthy relatives of CVID patients [13,15,16].

The most robust associations appear to be between polymorphisms encoding C104R and A181E and CVID [17]. Together, these variants have been identified in up to 10% of individuals with CVID, compared with up to 2% of immune competent controls [13,14,18,19]. While one study found an increased prevalence of TNFRSF13B variant in patients

with sIgAD [14], this has not been replicated in other studies [15,20]. In summary, C104R and A181E polymorphisms appear to act dominantly to increase the risk of antibody deficiency.

The mechanism that accounts for this association remains unclear. Total serum immunoglobulin levels were not impaired in TACI$^{-/-}$ mice [21,22]. Indeed, these mice developed features of autoimmunity (diffuse membranoproliferative glomerulonephritis, positive antinuclear antibodies and double stranded DNA antibodies consistent with systemic lupus erythematosus (SLE)), lymphoproliferation and splenomegaly, and 15% went on to develop lymphoma [22,23]. Autoimmunity, lymphoproliferation and splenomegaly were not seen in all individual mice with TNFRSF13B polymorphisms.

The amino acid sequences surrounding both the C104R and A181E variants are highly conserved between humans and mice. The C104R variant in the extracellular domain disrupts the cysteine-rich region that is vital for ligand binding [24,25]. More recently, Lee and colleagues produced evidence of TACI haploinsufficiency in mice heterozygous for the orthologous variant to human C104R (C76R) [26]. Although the mice had evidence of defective T cell-independent responses to polysaccharides and decreased serum IgM, serum IgG and IgA levels were normal [26]. There was no evidence of B cell lymphoproliferation or splenomegaly. Mice with the A144E variant, the murine ortholog of human A181E variant, exhibited reduced serum IgA and IgM as well as impaired responses to T cell-independent antigens [27], but did not develop B cell lymphoproliferation or anti-DNA antibodies.

Here, we report the association between between the A181E and C104R polymporphisms of TNFRSF13B in patients with primary antibody deficiency and SLE.

Method

Subjects

We genotyped 193 individuals and 144 controls from the Australian and New Zealand Antibody Deficiency Allele (ANZADA) Study, 107 patients from the Australian Point Mutation in Systemic Lupus Erythematosus (APOSLE) study, 169 patients with SLE from a European population, and 263 European controls. The controls consisted of individuals without a personal or family history of immunodeficiency or autoimmunity, drawn from the same population. Ethics approval was obtained from each participating institution.

Genotyping

Genomic DNA was extracted from saliva collected from subjects using the Oragene DNA collection kit (DNA Genotek, Ontario, Canada), based on the protocol provided by the manufacturer. Allele-specific forward primers and the common reverse primer for both C104R (GAAGGTCGGAGTCAACGGATTCCCTAAGCAATGTGCA TACTTCC, GAAGGTGACCAAGTTCATGCTACCCTAAGCAATGT GCATACTTCT and TGGGCTCCTGAGCTTGTT) and A181E (GAAGGTGACCAAGTTCATGCTTCTGCTGCTTCCTGGTGGA, A AGGTCGGAGTCAACGGATTTGCTGCTTCCTGGTGGC and GAC TTTGACGGGGCCTT) single nucleotide polymorphisms (SNP) were designed using Amplifluor® Assay Architect Software (www.apps.serologicals.com/AAA, Millipore, MA, USA).

A cocktail consisting of water, deoxynucleotide triphosphates, platinum TAQ polymerase (Invitrogen, Carlsbad,Calif), 20Amplifluor SNP FAM primer, 20Amplifluor SNP JOE primer, SNP-specific primers, and 10reaction mix S plus is added to individual DNA samples and a PCR program was run on a thermocycler. Subsequent to the completion of the PCR procedure, samples were cooled to room temperature and analyzed on the FLUOstar OPTIMA microplate reader (BMG Labtech, Offenburg, Germany). Results obtained from the microplate reader were transferred to a Microsoft Excel macro provided by Millipore and analysed.

Sequencing was also used to confirm subsets from each Amplifluor genotype. Thus, DNA from representative samples from each Amplifluor® run, encoding the wild-type and heterozygous and homozygous variants, was sequenced after the region was amplified by PCR using the conventionally designed primers (C104R - 5'-CTTTGT GGTCAAACCCAGAG-3' and 5'-CTGGGCTTCATGCATTGTGG-3'; A181E - 5'-TTGAGCCTAATGACGGGAAG-3' and 5'-CTGCCAGGA TGTCTTAACCTG-3') to confirm the validity of the Amplifluor® results.

DNA from patients with NCPAD that were found to have either the C104R or A181E variant was amplified by PCR and sequenced by conventional sequencing to exclude the possibility of biallelic TNFRSF13B variants, using the following primers (Exon 1 - 5'-GGGTGTGGCTGATTTACAT-3' and 5'-CTTTGCACCTGCTGGAC-3'; Exon 2 - 5'-GCCCCAGGCCCCTAGCAAGTG-3' and 5'TCTCCTCCT GCCACCCTTTCCTCA-3'; Exon 3 - 5'-CTTTGTGGTCAAACCCAGA G-3'and 5'-CTGGGCTTCATGCATTGTGG-3'; Exon 4 - 5'-TTGAGC CTAATGACGGGAAG-3' and 5'-CTGCCAGGATGTCTTAACCTG-3'; Exon 5 - 5'-GTGATTGCCCTTAGCTCCTG-3' and 5'-TCTCCATCTC TCCCTCCTC-3').

Statistics

Genotypic and allelic frequencies were compared using the Fisher exact test. These tests, together with the OR, relative risk and 95% CI were performed with GraphPad Prism 5.0 software (Graph-Pad Software, La Jolla, Calif). Comparisons were considered significant at p< 0.05.

Results

Frequency of C104R and A181E in NCPAD

We assessed the prevalence of the TNFRSF13B C104R and A181E encoding polymorphisms in 193 patients with NCPAD from the ANZADA cohort, including 171 with a diagnosis of CVID. The remainder had a diagnosis of IgG subclass deficiency (IgGSD, n=11), specific antibody deficiency (SAD, n=6) or immunoglobulin A deficiency (IgAD, n=5).

In the NCPAD cohort, 12 individuals (6.22%) possessed either A181E (n=6) or C104R (n=6) TNFRSF13B polymorphisms. No homozygous variants were detected in the cohort. The prevalence of C104R in the NCPAD cohort was not significantly different to the controls, p=0.2458, but the prevalence of A181E was significantly higher, p=0.0389 (Table 1). The total number of TNFRSF13B variants in the NCPAD cohort was also significantly higher than in the control group (p=0.0089; OR 9.481 [95% CI 1.218–73.81]) (Table 2).

Similar results were obtained when we analysed according to CVID rather than all NCPAD. Here, C104R was not significantly more common in the patient group (4/171 [2.33%]) than the controls (1/144 [0.69%]), p=0.3803 (Table 1). The result was similar for A181E (p=0.0651), with five CVID patients (2.92%) possessing the variant compared to none of the controls (Table 1). However, the association between CVID and the two TNFRSF13B polymorphisms combined was significant (p=0.0240; OR 7.944 [95% CI 0.9938–63.51]) (Table 2). The other two subjects with C104R variants in this cohort had a diagnosis of IgGSD while the other patient with A181E had a diagnosis of SAD. None of the patients had biallelic variants in TNFRSF13B.

Frequency of C104R and A181E in autoimmunity

We next tested the association between C104R and A181E polymorphisms and autoimmunity in the NCPAD cohort. In the Australian NCPAD cohort, 43/193 (22%) individuals had one or more manifestations of autoimmunity, including autoimmune haematological cytopenia, arthritis, autoimmune thyroid disease, Sjogren's syndrome, vitiligo, psoriasis, autoimmune Addison's disease and alopecia areata [5]. Of the six individuals with the C104R variant, only one patient (with a diagnosis of CVID) had features of autoimmunity (pernicious anaemia and Sjogren's syndrome) while three out of six individuals who were heterozygous for A181E had features of autoimmunity. These three individuals with CVID had histories of autoimmune thyroiditis (one individual) and autoimmune cytopenias (two individuals). No association was found between C104R or A181E in NCPAD patients with autoimmunity (p=0.871 and p=0.246 respectively). There was also no association when both variants were combined (p=0.5538).

The frequencies of C104R and A181E were next determined in patients with SLE (Australian Point Mutation in SLE, APOSLE cohort). The C104R variant was more prevalent than the A181E variant in the Australian SLE cohort. 4/107 (3.74%) SLE patients possessed the C104R polymorphism while none had the A181E polymorphism. Although the C104R polymorphism was more prevalent than in the Australian control cohort (3.74% vs 0.69%), this difference did not reach statistical significance (p=0.1668).

These analyses were repeated in a second SLE cohort. In the European SLE cohort, 6/169 (3.55%) individuals possessed a C104R polymorphism while only 3/167 (1.80%) individuals possessed the A181E variant. Two samples from the European cohort and one control from the European control cohort did not amplify with the A181E Amplifluor® assay or by direct PCR and these samples were excluded from our analysis. The C104R polymorphism was 3.12 times more common in the European SLE cohort than the European control cohort (3.55% vs. 1.14%) while A181E was 2.36 times more common (1.80% vs. 0.76%) in the European SLE cohort compared to the European control cohort. In this European SLE cohort, the C104R mutation was 1.98 times more common than the A181E polymorphism (Table 3).

When the results from Australian and European SLE cohorts were combined, C104R was significantly associated with SLE (p=0.0249, OR 3.797, [95% CI 1.178-12.24]) compared to combined Australian and European control cohorts (Table 4), while A181E was not (p=0.3965) (Table 5). Similarly the C allele in C104R was strongly associated with SLE (p=0.0256, OR 3.745 [95% CI 1.168-12.01]). Furthermore, when both heterozygous variants were combined in the analysis, they were associated with SLE (p=0.0161, OR 3.316 [95% CI 1.245-8.836]) (Table 6).

C104R			Controls	NCPAD	Controls	CVID
Genotype	TT		143 (99.31)	187 (96.89)	143 (99.31)	167 (97.67)
	CT		1 (0.69)	6 (3.11)	1 (0.69)	4 (2.33)
	CC		0	0	0 (0.0)	0 (0.0)
Genotypic *p* OR (95% CI)	2 x 2			*p*=0.2458 4.59 (0.55-38.56)		*p*=0.3803
C alleles	TT		287	380	287	338
	CT + CC		1	6	1	4
Allelic *p* OR (95% CI)	2 x 2			*p*=0.2483 4.53 (0.55-37.87)		*p*=0.3822
A181E						
	CC		144 (100)	187 (96.89)	144 (100)	166 (97.08)
	CA		0 (0)	6 (3.11)	0 (0)	5 (2.92)
	AA		0	0	0 (0.0)	0 0)
	2 x 2			*p*=0.0398 10.02 (0.56-179.4)		*p*=0.0651
A alleles	CC		288	380	288	380
	CA + AA		0	6	0	5
	2 x 2			*p*=0.0406 9.857 (0.55-175.80)		*p*=0.0747
Data in parentheses show percentage prevalence or 95% CI						

Table 1: C104R and A181E genotypes in NCPAD, CVID and controls.

	Controls	NCPAD	Controls	CVID
Wildtype	143 (99.31)	181 (93.78)	143 (99.31)	162 (94.74)
Heterozygotes	1 (0.69)	12 (6.22)	1 (0.69)	9 (5.26)
Genotypic *p*		*p*=0.0089		*p*=0.0240
OR (95% CI)		9.481 (1.218-73.81)		7.944 (0.9938-63.51)
Data in parentheses show percentage prevalence or 95% CI				

Table 2: *TNFRSF13B* variants in NCPAD, CVID and controls.

	European SLE	Controls	*P* value
C104R	6/169 (3.55%)	3/264 (1.14%)	0.1632
A181E	3/167 (1.80%)	2/263 (0.76%)	0.3810
Data in parentheses show percentage prevalence.			

Table 3: C014R and A181E genotypes in a European population.

		Controls	SLE
Genotype	TT	404 (99.02)	266 (96.38)
	CT	4 (0.98)	10 (3.62)
	CC	0 (0.0)	0 (0.0)
Genotypic *p*	2 x 2		*p*=0.0249
Odds ratio			3.797 (1.178-12.24)
C allele carriers	TT	812	542
	CT + CC	4	10
Allelic *p*	2 x 2		*p*=0.0256
Odds ratio			3.745 (1.168-12.01)
Data in parentheses show percentage prevalence or 95% CI.			

Table 4: C104R genotypes in the combined Australian and European SLE and control cohorts.

		Controls	SLE
Genotype	CC	405 (99.51)	271 (98.91)
	CA	2 (0.49)	3 (1.09)
	AA	0 (0.0)	0 (0.0)
Genotypic *p*	2 x 2		*p*=0.3965
A allele carriers	CC	812	545
	CA + AA	2	3
Allelic *p*	2 x 2		*p*=0.3971
Data in parentheses show percentage prevalence or 95% CI.			

Table 5: A181E genotypes inthe combined Australian and European SLE and control cohorts.

	Controls	CVID
Wild-type	401 (98.53)	262 (95.27)
Heterozygotes	6 (1.47)	13 (4.73)
Genotypic *p*		*p*=0.0161
OR (95% CI)		3.316 (1.245-8.836)
Data in parentheses show percentage prevalence or 95% CI.		

Table 6: C104R and A181E inthe combined Australian and European SLE and control cohorts.

Familial segregation

We were able to determine TNFRSF13B genotypes for family members for nine of twelve pedigrees identified with TNFRSF13B variants. These are shown together with nine other pedigrees within the cohort (Figure 1). While 12/18 pedigrees contain at least one family member with autoimmunity, overall the prevalence in those with TNFRSF13B single nucleotide variants is too low to assess for evidence of transmission disequilibrium. In 8/18 pedigrees, at least one relative had clinical evidence of autoimmunity. In some pedigrees, multiple relatives of probands with antibody deficiency had evidence of autoimmunity alone.
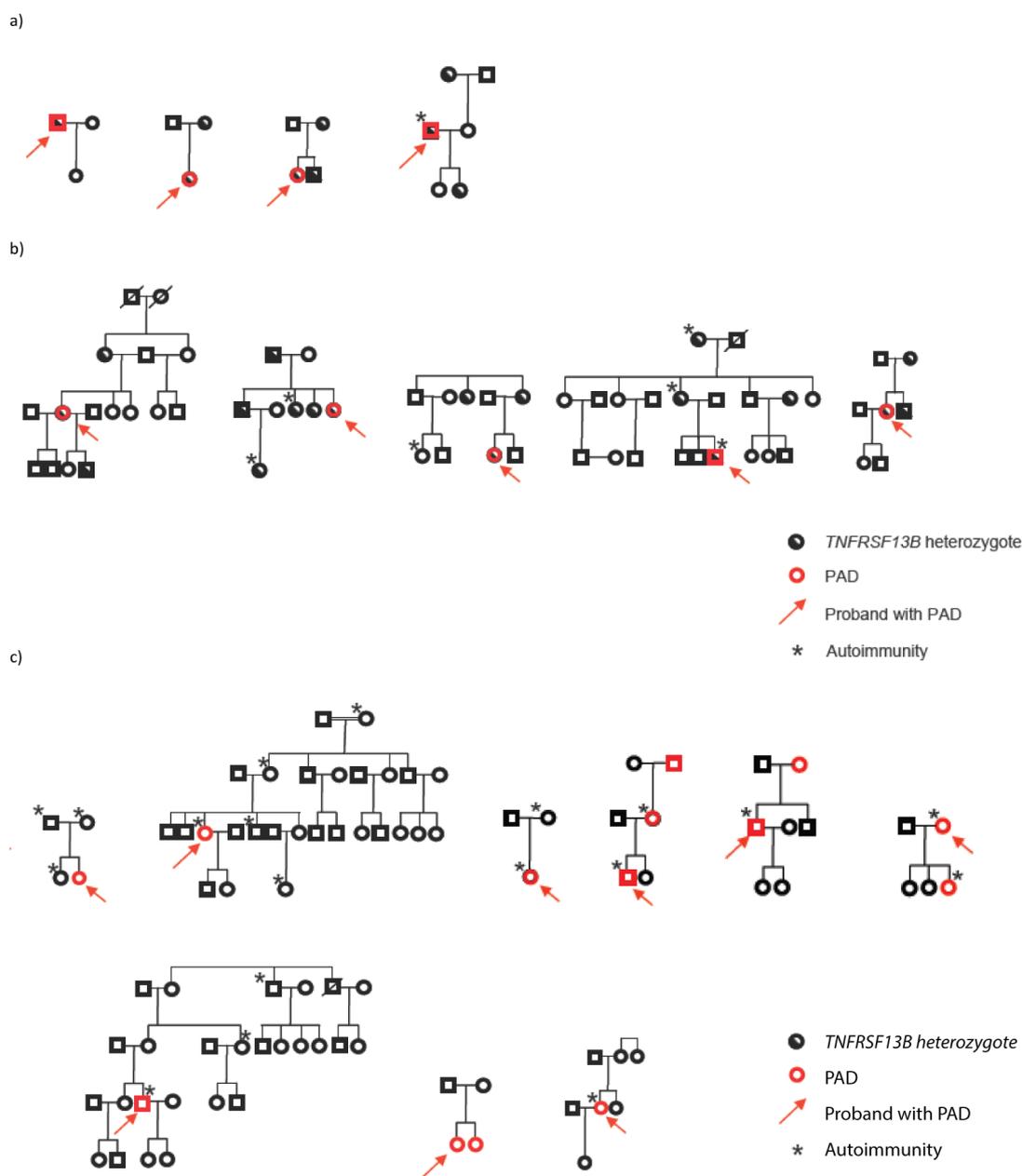
Figure 1: Pedigrees of patients with antibody deficiency with coexisting a) C104R polymorphism of *TNFRSF13B*; b) A181E polymorphism of *TNFRSF13B*; c) wild-type *TNFRSF13B*.

Discussion

With regard to antibody deficiency, our results are similar to those reported for other cohorts. In a large cohort of 564 patients with hypogammaglobulinemia (predominantly CVID, 94.5%) and 675 controls, Salzer and colleagues [16] found the two most common variants to be C104R (4.6%) and A181E (2.3%). Only one patient from each group had homozygous variants. In the control cohort, 1% had the A181E polymorphism while 0.9% possessed the C104R polymorphism. We report a similar prevalence of these genotypes in the Australian (ANZADA) cohort, in both patients and controls, yielding a similar association with disease (A181E, p=0.0398, OR, 10.02; 95% CI, 0.56-179.4; C104R, p=0.2458, OR, 4.59; 95% CI, 0.55-38.56). When both polymorphisms were analysed together, the association between NCPAD and TNFRSF13B variants became significant (p=0.0089; OR, 9.481; 95% CI, 1.22-73.81). In isolation, the results from this study would not achieve a high level of statistical

certainty but the association and magnitude of effect is similar to that reported elsewhere [16]. Taken together, we conclude that our NCPAD population is similar with regard to these TNFRSF13B single nucleotide variants.

Salzer and colleagues also found evidence to suggest that autoimmune manifestations in NCPAD were more common in cases with TACI deficiency, particularly with the heterozygous C104R variant [16]. This is in contrast to the findings in the Australian cohort, where there was no association between C104R or A181E alone or in combination in individuals with both antibody deficiency and autoimmunity.

By contrast, we found an association between TNFRSF13B and autoimmunity in the absence of antibody deficiency. The C104R polymorphism was more common in SLE (p=0.0249; OR, 3.797, 95% CI 1.18- 12.24), but A181E was not (p=0.3965). When both these variants were combined, the association of TACI with SLE reached statistical significance (p=0.0161; OR, 3.316, 95% CI 1.17 - 12.01]). This is at odds with another study in which 190 SLE subjects were analysed and no association was found between C104R or A181E and SLE [28].

A review of the literature regarding murine models of TNFRSF13B did not clarify these conflicting findings seen in human studies. Features of SLE are present in TACI knockout mice [21] but not mice with the C76R or A144R polymorphisms (murine equivalents of C104R and A181E respectively) [26,27]. Both TACI knockout mice [21] and mice with the C76R polymorphism [26] demonstrated impaired T cell-independent responses, but total serum IgG was not reduced in either model. Mice with the A144E variant did not have evidence of autoimmunity but had evidence of impaired antibody responses, with reduced total serum IgA and IgM levels, and defective responses to T cell-independent antigens [27].

The high prevalence of autoimmunity in the relatives of patients with NCPAD irrespective of whether they are immunodeficient or whether they possess TNFRSF13B variants, suggest that the risk of autoimmunity exists in families with NCPAD (Figure 1). These preliminary findings suggest that independent genetic modifiers might act to promote either autoimmunity or immune deficiency.

Other PAD have been described with SLE. A number of series report the association between selective IgA deficiency (IgAD) and SLE [29-33]. There is a shared association between the HLA-B8, DR3, DQ2 haplotype of IgAD and autoimmunity. Polymorphisms in non-MHC regions, interferon induced helicase 1 (IFH-1) and the C-type lectin family domain have been detected in recent genome wide association study [34]. A small number of case reports associating SLE and NCPAD with a toll-like receptor signalling defect [35], mannose binding lectin gene polymorphisms [36] and thymoma [37] have been reported. The mechanism underpinning these associations is unclear but has led to the suggestion that IgAD may itself be an autoimmune disease [33].

In summary, the incomplete penetrance revealed by familial analysis and the modest effect of TNFRSF13B polymorphisms on the risk of antibody deficiency and autoimmunity suggest that other interacting factors may play a role in determining whether an individual with a TNFRSF13B variant develop antibody deficiency or autoimmunity. The association between autoimmunity and immunodeficiency reminds us to not disregard the possibility of immunodeficiency in the setting of SLE.

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