

ORIGINAL ARTICLE

Rare mutations in *TNFRSF13B* increase the risk of asthma symptoms in Swedish children

M Janzi¹, E Melén^{2,3}, I Kull², M Wickman^{2,4} and L Hammarström¹

¹Division of Clinical Immunology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden; ²Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ³Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden and ⁴Department of Paediatrics, Sach's Children's Hospital, Södersjukhuset, Stockholm, Sweden

TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) mutations seem to be associated with autoimmunity and common variable immunodeficiency in humans. Because of its role in immune responses, we investigated the association between TACI mutations and infection proneness/asthma symptoms in children. A total of 2372 children were genotyped for TACI mutations (I87N, C104R, S144X, A181E, R202H and ins204A). Serum IgA, IgG and specific IgE levels were determined in children with mutations. Data on parentally reported allergic diseases and infections were collected. In all, 55 individuals with TACI mutations were identified. Children with TACI mutations had a 2-fold increased risk of wheeze at 2 and 4 years of age and a 2.5-fold increased risk of asthma was seen at 4 years of age. None of the children with mutations suffered from IgA deficiency ($< 0.07 \text{ g l}^{-1}$). No significant differences in serum IgG levels or specific IgE were found. Common variants in asthma susceptibility genes may account for up to 40% of cases of childhood-onset asthma, indicating a high contribution, compared with other common disorders. The role of rare variants/mutations in the pathogenesis of asthma is less clear. We conclude that mutations in TACI are the contributing factors for asthma symptoms in Swedish children, although the mechanisms still remain elusive.

Genes and Immunity advance online publication, 18 August 2011; doi:10.1038/gene.2011.55

Keywords: TACI; IgA; asthma; children; allergy; genetics

Introduction

Despite the identification of hundreds of genetic variants associated with complex diseases, the results from candidate gene studies and genome-wide association studies to date only explain a small proportion of the heritability of many diseases. This fact has sparked questions about the 'missing heritability' and what genome-wide association studies actually can contribute to in terms of finding disease-causing genes and risk prediction.¹ Rare variants or mutations are, by design, not captured by current genome-wide association studies chips and have been suggested to be important for several complex diseases.² Few studies have addressed the role of rare variants in the pathogenesis of asthma to date. Reports on filagrin mutations and asthma in the context of eczema, and IL4 mutations and asthma in African Americans, however, point to a potentially important role.^{3,4}

The transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) is a tumor necrosis factor receptor (TNFR) mainly expressed as type III transmembrane protein not only on activated B cells,

but also on human macrophages, mediating their survival.⁵ TACI is part of a complex system of receptors and ligands with overlapping binding specificities.

It binds two ligands belonging to the TNF family, APRIL (a proliferation-inducing ligand) and BAFF (B-cell activating factor), both expressed as type II transmembrane proteins that can be cleaved and secreted.⁶ BAFF and APRIL are expressed by dendritic cells, monocytes and macrophages. APRIL is also expressed by activated T cell.⁷ It is believed that TACI has a central role in the activation of B cells and their differentiation into plasma cells. APRIL and BAFF seem to induce class switch recombination, and isotype switching can occur in naïve B cells.^{8,9}

TACI is encoded by TNFR superfamily member 13B (*TNFRSF13B*) on chromosome 17p11. *TACI*^{-/-} mice are IgA deficient despite normal B-cell development and have impaired ability to mount thymus-independent responses.¹⁰ This is due to lack of thymus-independent type II-specific plasma cells.¹¹ TACI also seems to have a negative effect on the regulation of B-cell homeostasis, as *TACI*^{-/-} mice have an increased number of circulating B cells.¹⁰ The mice also have an increase in lymphomas and autoimmunity, as fatal autoimmune glomerulonephritis, proteinuria and elevated levels of circulating autoantibodies are noted in mice with *TNFRSF13B* deletions.¹² Alternatively, the absence of TACI results in BAFF receptor-mediated hyperproliferation of autoreactive B cells.

Correspondence: Professor L Hammarström, Division of Clinical Immunology, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-14186 Stockholm, Sweden.

E-mail: lennart.hammarstrom@ki.se

Received 18 April 2011; revised 30 June 2011; accepted 7 July 2011

Several recent studies have shown an association between mutations in *TNFRSF13B* and common variable immunodeficiency (CVID) in humans,^{13–15} reporting TACI mutations in 8–10% of the patients.^{13,14} CVID has an estimated prevalence of 1/25 000 in Caucasians and is characterized by recurrent sinopulmonary infections. The patients have reduced serum levels of IgG and IgA, and reduced IgM levels in 50% of the patients.¹⁶ Patients with homozygous (C104R, S144X and A181E)¹³ as well as heterozygous (C104R, A181E, R202H, S194X and ins204A) mutations^{13,14} have all been reported. C104R and A181E account for more than 90% of TACI mutations. Additional rare mutations, including W40R, D41I, D41H, L69T, Y79C, C100L, I87N, C100L, C104Y, A149T, G152E, Y164X, D191G, C193X and V246F, have also been described.¹⁷ Heterozygous *TNFRSF13B* mutations (G76C, K154X, ins586A) are associated with selected cardiovascular diseases, including intracranial aneurysms and stroke.¹⁸ Because of its role in immune responses/inflammation, we investigated whether there was an association between TACI mutations and infection proneness, and asthma symptoms in children.

Results

In the present study, 55 children with TACI mutations were identified (Table 1) among 1979 successfully genotyped individuals in a population-based birth cohort. In all, 54 children carried heterozygote mutations, whereas one child carried a homozygous A181E mutation with a normal serum level of both IgA (1.1 g l⁻¹) and IgG (12 g l⁻¹). There was no significant difference in the allele frequency between the children and healthy adult blood donors (Table 1).

As TACI mutations have been reported in patients with defects in the immune system, we investigated whether there is an association between mutations in the TACI encoding gene and specific health outcomes during the first 8 years of life. The results are summarized in Table 2. Children with TACI mutations had an approximately two-fold increased risk of wheeze at 2 (OR (odds ratio), 1.85; 95% confidence interval (CI) 1.02–3.37) and 4 years of age (OR, 2.35; 95% CI 1.29–4.27). In addition, a

2.5-fold increased risk of asthma was seen at 4 years of age (OR, 2.53; 95% CI 1.21–5.29).

As TACI mutations are associated with CVID, we investigated the level of serum IgA at 4 years of age in all children in whom serum was available (1511 children without TACI mutations and 48 children with TACI mutations) and serum IgG in 47 children with TACI mutations. The proportion of children with subnormal IgA serum levels (<0.5 g l⁻¹; Karolinska University Laboratory, Stockholm, Sweden) were similar in children with and without TACI mutations (18.8 and 12.6%, respectively, *P*=0.27). The mean serum IgA level was slightly, albeit significantly, lower in the 4-year-old children carrying TACI mutations than in those who did not carry mutations (0.70 g l⁻¹ as compared with 0.99 g l⁻¹, *P*<0.001). None of the children with mutations suffered from IgA deficiency (<0.07 g l⁻¹) at 4 years of age (Figure 1), suggesting that selective IgA deficiency is not associated with TACI mutations. IgA levels were also determined at 8 years of age in the children with TACI mutations (*n*=47), giving a mean of 1.43 g l⁻¹, none suffering from IgA deficiency.

Six individuals with TACI mutations had serum IgG levels below the normal range (<6.1 g l⁻¹; Karolinska University Laboratory) at 4 years of age and 12 individuals at 8 years of age. No significant differences in IgG levels were seen in children with mutations with or without wheeze and asthma symptoms (Figure 2). IgE levels for common airborne and food allergens were determined at 4 and 8 years of age in all children included in the study. No significant difference was found between the children with and without TACI mutations at either 4 (OR, 0.95; 95% CI 0.49–1.83) or 8 years of age (OR, 0.63; 95% CI 0.33–1.19).

Discussion

TACI is mainly expressed on B cells and macrophages, mediating their survival. TACI^{-/-} mice are deficient in serum IgA and have an impaired ability to mount thymus-independent responses. The mice also have an increase in lymphomas and autoimmunity. In humans,

Table 1 Mutations in *TNFRSF13B* in a population-based cohort of Swedish children and adult Swedish blood donor controls

Protein ^a	cDNA ^b	Allele frequency		
		BAMSE children (population-based) ^c	Healthy adults ^d	P-values ^e
p.I87N	c.260T>A	1/3978 ^f	0/2076	NS
p.C104R	c.310T>C	11/4668	15/4116	NS
p.A181E	c.542C>A	43/4676 ^g	32/3798	NS
p.R202H	c.605G>A	1/4632	0/2082	NS

Abbreviations: BAMSE, the Children, Allergy, Milieu, Stockholm, Epidemiological survey; NS, not significant.

^aNCBI protein entry NP_036584. p.S144X and c.ins204A were not found in the present study.

^bNCBI nucleotide entry NM_012452.

^c54 heterozygous and one homozygous individual (A181E).

^dData extracted from Pan-Hammarström Q *et al.*¹⁵ including 1080 healthy Swedish blood donors and from 1039 additional healthy blood donors (for pC104R and pA181E), using MALDI-TOF.

^e χ^2 -test. The *P*-value was calculated comparing allele frequencies in the children with healthy adults.

^fOnly children with DNA samples available at 8 years of age were analyzed.

^gIncluding one child with a homozygous mutation.

Table 2 Clinical outcomes in children with mutations in the TAC1 encoding gene

Health outcomes	Any TAC1 mutation n (%) ^a	No mutation n (%)	OR	95% CI
Total number of children	55	1924		
Wheeze year 1 ^b	9 (16)	288 (15)	1.08	0.52–2.23
Wheeze year 2	16 (30)	355 (19)	1.85*	1.02–3.37
Wheeze year 4	16 (30)	287 (15)	2.35*	1.29–4.27
Wheeze year 8	9 (17)	212 (11)	1.68	0.81–3.49
Asthma year 1 and/or 2 ^c	8 (15)	164 (9)	1.84	0.85–3.97
Asthma year 4 ^d	9 (17)	138 (7)	2.53*	1.21–5.29
Asthma year 8 ^d	5 (10)	140 (7)	1.34	0.52–3.44
Sensitization year 4 ^e	12 (24)	404 (25)	0.95	0.49–1.83
Sensitization year 8	13 (26)	688 (36)	0.63	0.33–1.19
Pseudocroup year 1 ^f	1 (2)	104 (6)	0.31	0.04–2.31
Respiratory syncytial virus infection ^g	3 (6)	85 (5)	1.22	0.37–3.98

Abbreviations: CI, confidence interval; OR, odds ratios; TAC1, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Significant *P*-values are in bold.

^aI87N, C104R, A181E, R202H.

^bAt least one wheeze episode in the last 12 months.

^cParentally reported asthma at years 1 and 2 was defined as at least 3 episodes of wheezing in combination with treatment with inhaled steroids or signs of hyperactivity.

^dAt 4 and 8 years of age the definition included at least 4 episodes of wheezing in the last 12 months or at least 1 episode of wheezing combined with inhaled steroids treatment.

^eIgE-value for food mix and/or phadiatop ≥ 0.35 kU/l.

^fPhysician's diagnosis.

^gRespiratory syncytial virus infection was parent reported and defined as doctor's diagnosis during the 12 months prior to answering the questionnaire. **P* < 0.05. The results are presented as ORs and 95% CIs.

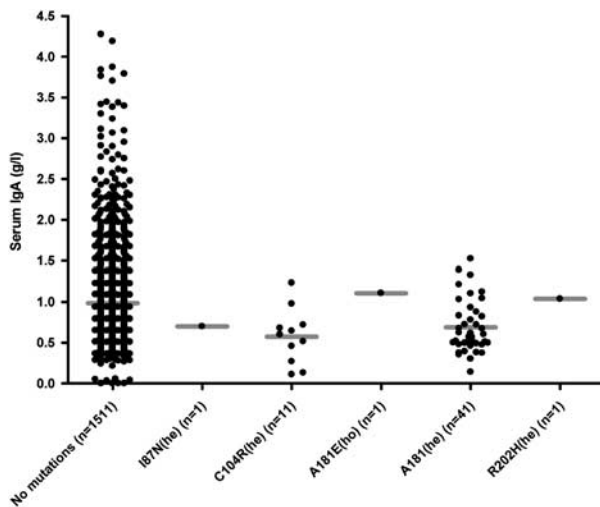


Figure 1 Serum IgA levels at 4 years of age in children, with ($n=55$) and without ($n=1511$) *TNFRSF13* mutations. Seven samples were not available at 4 years of age, and the IgA levels at 8 years of age are depicted instead: I87N(he), four C104R(he) and two A181E(he). Despite low levels in some individuals, none of the children with TAC1-mutations was found to be IgA deficient.

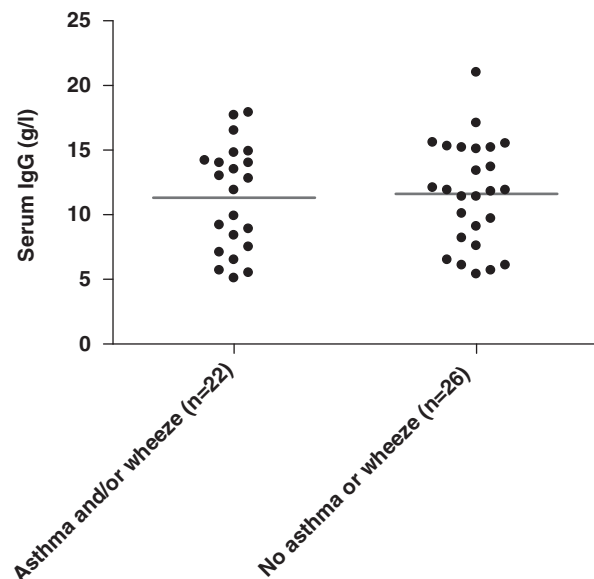


Figure 2 Serum IgG levels at 4 years in children with TAC1 mutations, with ($n=22$) or without ($n=26$) asthma at 4 years of age and/or wheeze at 2 and/or 4 years of age ($P=0.8$).

TAC1 mutations are associated with CVID, being present in 8–10% of all CVID cases.

In CVID patients, heterozygous TAC1 mutations constitute disease-predisposing rather than disease-causing factors. In contrast, homozygous mutations have been suggested to be exclusively found in CVID patients, and therefore disease-causing.^{13,17} Similar findings have been described in relatives of Spanish CVID patients three individuals with homozygous C104R mutations

were shown to have normal IgA levels (albeit somewhat low IgG levels in two of the cases (5.8 g l^{-1} and 5.3 g l^{-1})).¹⁹ Although it cannot be ruled out that these individuals may later develop CVID, it suggests that even homozygous TAC1 mutations are disease-predisposing rather than disease-causing. Bearing in mind the high frequencies of TAC1 mutations in the general population, one would expect approximately 1/5000–10000 to be homozygotes or compound heterozygotes

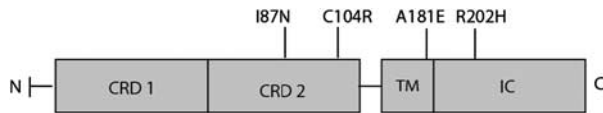


Figure 3 The location of TAC1 mutant. CRD, cysteine-rich domain; TM, transmembrane; IC, intracellular.

for disease-associated variants, corresponding to at least 1000 individuals in Sweden. As only 2 of 115 genotyped CVID patients are A181E homozygous (300 CVID patients are diagnosed in Sweden), it appears likely that even homozygous TAC1 mutations are merely disease-associated.

In the present study, we found individuals with four different TAC1 mutations (I87N, C104R, A181E and R202H; see Figure 3). TAC1 has an extracellular domain containing two cysteine-rich domains (CRDs), each with different functions. The first CRD is involved in the assembly of TAC1 into multimeric complexes,²⁰ the second CRD is involved in the binding of APRIL and BAFF. The C104R and the A181E mutation are the two most commonly seen variants in CVID patients. The C104R mutation is located in the second CRD, interfering with the binding of the ligands and therefore the receptor signaling.^{13,14} The A181E mutation is located in the transmembrane domain of TAC1 and thus, does not affect the binding of the ligands. However, it has been shown, both *in vitro* and *in vivo*, that the mutation severely impairs the ligand signaling.²¹ This mutation might affect the function of the receptor by changing the geometry of the intracellular domain.¹³

Although most individuals with the C104R and A181E mutations are heterozygotes, their B cells have impaired responses to TAC1 ligation *in vitro*.^{13,14} The mechanisms by which these two mutations affect the function of TAC1 are still unknown, but they seem to destroy the capacity of the receptor to activate nuclear factor κ B. The I87N mutation is located in the second CRD and is shown to result in residual BAFF binding, which increased with increasing concentrations of ligand, suggesting a decreased ligand-binding affinity of this mutant.²²

Signaling through TAC1 requires a trimerization of the receptor.^{23–25} It is thus possible that inclusion of even one mutant receptor might affect the signaling by the complex. This might suggest a route of action for the R202H mutation, which is situated in the intracellular part of the protein. The R202H mutation is located in the part of the receptor interacting with the calcium-modulator and cyclophilin ligand.²⁶

The binding of APRIL and BAFF induces class switch recombination.^{8,9} It is suggested that TAC1 is involved in the class switch recombination to both IgA and IgG in humans.¹³

As shown in Figure 4, children with TAC1 mutations and reported wheezing have somewhat higher mean IgA level than children with TAC1 mutations with no wheezing. This may suggest that the wheezing is associated with true asthma symptoms rather than only being triggered by infection. This is further supported by the lack of increase in respiratory syncytial virus infections in children with TAC1 mutations.

Children in the BAMSE (the Children, Allergy, Milieu, Stockholm, Epidemiological survey) study were recruited from the Stockholm area, and only 16% of the

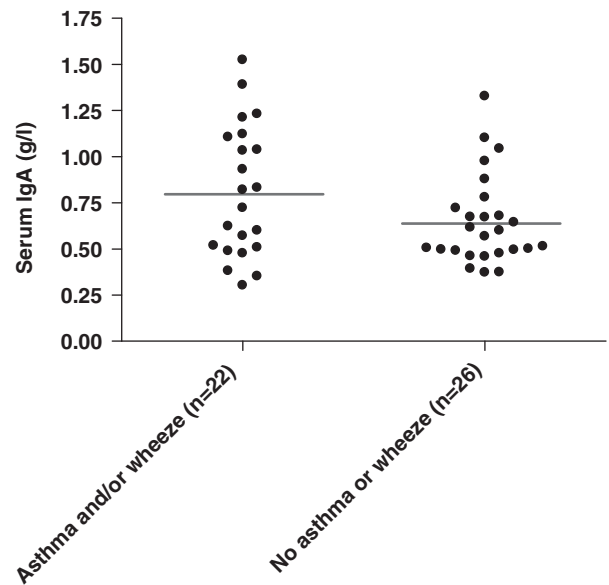


Figure 4 Serum IgA levels at 4 years in children with TAC1 mutations, with ($n = 22$) or without ($n = 26$) asthma at 4 years of age and or/wheeze at 2 and/or 4 years of age ($P = 0.07$).

children have one or two parents born outside Scandinavia.²⁷ We also included ethnicity in the analyses as a potential confounder, but it did not change the interpretation of our results. A subgroup of BAMSE children were also included in the multinational GABRIEL study, and based on genome-wide data, only 3.7% of the children were removed from the GABRIEL study because of potential extra-European ancestry.²⁸ Taken together, this indicates that population stratification very likely is a minor problem in BAMSE (although subtle stratification could still occur).

Wheeze and asthma symptoms in preschool children are usually triggered by viral infections and it is well established that patients with humoral immunodeficiency are prone to recurrent upper respiratory tract infections. We observed increased risk of early wheeze in children with TAC1 mutations, but no significant associations were seen with wheeze or asthma at school age (8 years). The lack of association between TAC1 mutations and sensitization might also argue against a strong role of these mutations in the development of allergy or allergic asthma. Thus, our results speak in favor of a more general immune effect of TAC1 mutations, affecting early wheeze, rather than atopy (i.e. sensitization) and asthma at later ages. The age limitation may suggest an association with infectious diseases occurring during this period, although no association was seen between TAC1 mutations and two conditions induced by viruses, pseudocroup and respiratory syncytial virus infection. However, there are numerous viruses affecting the respiratory tract that we did not have the possibility to test for. The observed association between mutations in TAC1 and early wheeze does not appear to be mediated through subnormal immunoglobulin levels. This is also supported by our previous study in which no association was found between low IgA levels (≥ 0.07 – 0.49 g l⁻¹) and wheeze/asthma symptoms in Swedish children.²⁹ Our findings

suggest that selective IgA deficiency is not associated with TACI mutations, which is in concert with the findings reported by Pan-Hammarström *et al.*¹⁵ and further work is needed to clarify the mechanisms by which TACI mutations may increase the risk of asthma symptoms early in life.

Asthma is a truly heterogeneous condition, and definitions in different age groups of children vary between countries. Our asthma definition is based on symptoms (wheezing) and prescription of inhaled steroids (by far the most common anti-inflammatory medication in Sweden at the time), and has been used in several previous studies.^{30–33} Yet, we acknowledge that some of these children may not have true asthma and rather transient wheezing.

In conclusion, we report an association of rare variants in an immunomodulatory gene to asthma symptoms in early childhood. Common variants in asthma susceptibility genes may account for up to 40% of cases of childhood-onset asthma, indicating a high contribution, compared with other common disorders.²⁸ The role of rare variants in the pathogenesis of asthma symptoms is, however, less clear, and very few studies on the role of rare mutations in asthma symptoms are available. Our results support the notion that rare variants in specific genes are also important for childhood asthma symptoms.

Patients and methods

Patient samples

The children included in this study are part of a large, population-based, prospective birth cohort (BAMSE) in a predefined area of Stockholm, Sweden. During 1994–1996, all newborns in a predefined area of Stockholm were invited to participate in the prospective BAMSE study. A total of 75% of all children in this area were included ($N=4089$). Details about the study design are described elsewhere.³⁴ At 4 years of age, all children were asked for a blood sample and 2614 samples (71%) were collected. DNA was available for 2372 children and these children were included in the present study.

Ethical approval was obtained from the local ethical review board in Stockholm.

Analysis of TNFRSF13B mutations

We screened the children for the most common TACI mutations (I87N, C104R, S144X, A181E, R202H and ins204A) using matrix-assisted laser desorption/ionisation-time of flight as described previously.³⁵ Out of 2372 children, 1979 were successfully genotyped and five mutations (I87N, C104R, A181E, R202H and ins204A) were found. Four mutations (I87N, C104R, A181E and R202H) (Table 1 and Figure 3) were confirmed by resequencing of the implicated exons as described previously.^{15,17} No significant difference in the allele frequency of different TACI variants was found between our population-based cohort of children and healthy adult blood donors (Table 1).

Definition of health outcomes

Data on parental allergies were collected from parent-answered questionnaires when the children were an average 2 months old. Questions regarding symptoms

related to allergic diseases and infections in their children were answered by the parents at years 1, 2, 4 and 8. Data on major exposure and confounding factors were collected prospectively, that is, at 2 months of age and for breastfeeding at 1 year of age. Pseudocroup and respiratory syncytial virus infection was parent-reported and defined as doctor's diagnosis during the 12 months prior to answering the questionnaire. Parentally reported pseudocroup is defined as a sudden spasm of the larynx that occurs in children and is marked by difficult breathing with prolonged noisy inspiration, normally caused by viral infection. Parentally reported asthma at years 1 and 2 was defined as at least three episodes of wheezing, in combination with treatment with inhaled steroids or signs of hyperactivity.³⁶ At 4 and 8 years of age, the definition included at least four episodes of wheezing in the last 12 months or at least one episode of wheezing combined with inhaled steroids treatment.³⁷ Parentally reported wheeze was defined as at least one episode of wheezing in the last 12 months. Sensitization to inhalant allergens was defined as positive Phadiatop (IgE-antibody levels $\geq 0.35 \text{ kU}_A \text{ l}^{-1}$; Phadia AB, Uppsala, Sweden) against cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* or *Cladosporium* species. Sensitization to food allergens was defined as positive fx5 (IgE-antibody levels $\geq 0.3 \text{ kU}_A \text{ l}^{-1}$; Phadia AB) against cow's milk, hen's egg, codfish, soybean, peanut or wheat.

Serum immunoglobulin levels

Serum IgA levels were previously determined in all included children at 4 years of age, using enzyme-linked immunosorbent assay.²⁹ The serum samples were available for 1511 children without mutations and 48 children with TACI mutations. The levels of serum IgA were also determined in all children with TACI mutations at 8 years of age, in whom serum was available ($n=47$), using the same procedure. For determination of IgG levels, 48 serum samples from children with TACI mutations, collected at 4 years of age and 47 serum samples at 8 years of age, were tested using ELISA. Polyclonal rabbit anti-human IgG antibodies (DAKO, Glostrup, Denmark) and alkaline phosphatase-conjugated rabbit anti-human serum IgG antibodies (DAKO) were added at a concentration of 0.6 mg l^{-1} and 1.1 mg l^{-1} , respectively. In addition, IgE levels for common airborne allergens (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *Cladosporium* species) were tested by Phadiatop (IgE-antibody levels $\geq 0.35 \text{ kU}_A \text{ l}^{-1}$; Phadia AB) and food allergens (cow's milk, hen's egg, cod fish, soy bean, peanut and wheat) by fx5 (IgE-antibody levels $\geq 0.35 \text{ kU}_A \text{ l}^{-1}$; Phadia AB) in all the successfully genotyped subjects ($n=1979$).

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Dr Qiang Pan-Hammarström at the Division of Clinical Immunology at Karolinska Hospital, Huddinge,

for TACI genotyping and valuable comments. We also thank all the children and parents participating in the BAMSE project. M Janzi was supported by an educational grant from the Health Care Sciences Postgraduate School. This research was supported by the Swedish Research Council and the EU (HEALTH-F2-2008-201549 EURO-PADnet). The BAMSE study was also supported by Stockholm County Council, The Swedish Heart and Lung Foundation and Centre for Allergy Research, Karolinska Institutet.

References

- Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorf LA, Hunter DJ *et al.* Finding the missing heritability of complex diseases. *Nature* 2009; **461**: 747–753.
- Pritchard JK. Are rare variants responsible for susceptibility to complex diseases? *Am J Hum Genet* 2001; **69**: 124–137.
- van den Oord RAHM, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; **339**: b2433.
- Haller G, Torgerson DG, Ober C, Thompson EE. Sequencing the IL4 locus in African Americans implicates rare noncoding variants in asthma susceptibility. *J Allergy Clin Immunol* 2009; **124**: 1204–1209.e9.
- Chang SK, Arendt BK, Darce JR, Wu X, Jelinek DF. A role for BlyS in the activation of innate immune cells. *Blood* 2006; **108**: 2687–2694.
- Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. *Annu Rev Immunol* 2003; **21**: 231–264.
- Ng LG, Mackay CR, Mackay F. The BAFF/APRIL system: life beyond B lymphocytes. *Mol Immunol* 2005; **42**: 763–772.
- Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP *et al.* TACI and BAFF-R mediate isotype switching in B cells. *J Exp Med* 2005; **201**: 35–39.
- Xu S, Lam KP. B-cell maturation protein, which binds the tumor necrosis factor family members BAFF and APRIL, is dispensable for humoral immune responses. *Mol Cell Biol* 2001; **21**: 4067–4074.
- Yan M, Wang H, Chan B, Roose-Girma M, Erickson S, Baker T *et al.* Activation and accumulation of B cells in TACI-deficient mice. *Nat Immunol* 2001; **2**: 638–643.
- Mantchev GT, Cortesão CS, Rebrovich M, Cascalho M, Bram RJ. TACI is required for efficient plasma cell differentiation in response to T-independent type 2 antigens. *J Immunol* 2007; **179**: 2282–2288.
- Seshasayee D, Valdez P, Yan M, Dixit VM, Tumas D, Grewal IS. Loss of TACI causes fatal lymphoproliferation and autoimmunity, establishing TACI as an inhibitory BlyS receptor. *Immunity* 2003; **18**: 279–288.
- Salzer U, Chapel HM, Webster AD, Pan-Hammarström Q, Schmitt-Graeff A, Schlesier M *et al.* Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nat Genet* 2005; **37**: 820–828.
- Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L *et al.* TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet* 2005; **37**: 829–834.
- Pan-Hammarström Q, Salzer U, Du L, Björkander L, Cunningham-Rundles C, Nelson DL *et al.* Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. *Nat Genet* 2007; **39**: 429–430.
- Primary immunodeficiency diseases. Report of a WHO scientific group. *Clin Exp Immunol* 1997; **109**(Suppl 1): 1–28.
- Salzer U, Bacchelli C, Buckridge S, Pan-Hammarström Q, Jennings S, Lougaris V *et al.* Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. *Blood* 2009; **113**: 1967–1976.
- Inoue K, Minerharu Y, Inoue S, Yamada S, Matsuda F, Nozaki K *et al.* Search on chromosome 17 centromere reveals TNFRSF13B as a susceptibility gene for intracranial aneurysm: a preliminary study. *Circulation* 2006; **113**: 2002–2010.
- Martínez-Pomar N, Detková D, Arostegui JJ, Alvarez A, Soler-Palacín P, Vidaller A *et al.* Role of TNFRSF13B variants in patients with common variable immunodeficiency. *Blood* 2009; **114**: 2846–2848.
- Garibyan L, Lobito AA, Siegel RM, Call ME, Wucherpfennig KW, Geha RS. Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). *J Clin Invest* 2007; **117**: 1550–1557.
- Lee JJ, Rauter I, Garibyan L, Ozcan E, Sannikova T, Dillon SR *et al.* The murine equivalent of the A181E TACI mutation associated with common variable immunodeficiency severely impairs B-cell function. *Blood* 2009; **114**: 2254–2262.
- Fried AJ, Rauter I, Dillon SR, Jabara HH, Geha RS. Functional analysis of transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) mutations associated with common variable immunodeficiency. *J Allergy Clin Immunol* 2011; **128**: 226–228.
- Hymowitz SG, Patel DR, Wallweber HJ, Runyon S, Yan M, Yin J *et al.* Structures of APRIL-receptor complexes: like BCMA, TACI employs only a single cysteine-rich domain for high affinity ligand binding. *J Biol Chem* 2005; **280**: 7218–7227.
- Ingold K, Zumsteg A, Tardivel A, Huard B, Steiner QG, Cachero CG *et al.* Identification of proteoglycans as the APRIL-specific binding partners. *J Exp Med* 2005; **201**: 1375–1383.
- Holler N, Tardivel A, Kovacsics-Bankowski M, Hertig S, Gaide O, Martinon F *et al.* Two adjacent trimeric Fas ligands are required for Fas signaling and formation of a death-inducing signaling complex. *Mol Cell Biol* 2003; **23**: 1428–1440.
- Xia XZ, Treanor J, Senaldi G, Khare SD, Boone T, Kelley M *et al.* TACI is a TRAF-interacting receptor for TALL-1, a tumor necrosis factor family member involved in B cell regulation. *J Exp Med* 2000; **192**: 137–143.
- Melén E, Neiberg F, Lindgren CM, Berglund N, Zuchelli M, Nordling E *et al.* Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. *Environ Health Perspect* 2008; **116**: 1077–1084.
- Moffatt MF, Gut IG, Demenais M, Strachan DP, Bouzigon E, Heath S *et al.* A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; **363**: 1211–1221.
- Janzi M, Kull I, Sjöberg R, Wan J, Melén E, Bayat N *et al.* Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. *Clin Immunol* 2009; **133**: 78–85.
- Ostblom E, Lilja G, Pershagen G, van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008; **38**: 1325–1332.
- Ostblom E, Egmar A-C, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy* 2008; **63**: 211–218.
- Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008; **63**: 418–424.
- Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to

- common foods in 4-year-old children. *Acta Paediatr* 2008; **97**: 85–90.
- 34 Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M *et al*. Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010; **125**: 1013–1019.
- 35 Mohammadi J, Liu C, Aghamohammadi A, Bergbreiter A, Du L, Lu J *et al*. Novel mutations in TACI (TNFRSF13B) causing common variable immunodeficiency. *J Clin Immunol* 2009; **29**: 777–785.
- 36 Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breast feeding and allergic diseases in infants-a prospective birth cohort study. *Arch Dis Child* 2002; **87**: 478–481.
- 37 Kull I, Almquist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004; **114**: 755–760.