



IgA deficiency: what is new?

Ning Wang and Lennart Hammarström

Purpose of review

To summarize recent publications on clinical and genetic aspects of IgA deficiency (IgAD).

Recent findings

Both major histocompatibility complex (MHC) and non-MHC genes contribute to susceptibility to the disease. The former genes appear to be located in different parts of the MHC region depending on the HLA haplotype. The latter show a marked overlap with genes associated with a variety of autoimmune disorders including Graves' disease, systemic lupus erythematosus, type 1 diabetes and celiac disease, suggesting common pathophysiological mechanisms. Various cytokines, recently shown to include interleukin 21, can induce IgA synthesis *in vitro* in cells from patients with IgAD, suggesting a regulatory basis of the disease.

Summary

IgAD is the most common primary immunodeficiency in the Western world with a prevalence of approximately 1 : 600 in the general population. It appears to be a polygenic disorder and several of the genes involved have recently been identified. The involvement of genes associated with autoimmunity may suggest that IgAD in itself is an autoimmune disease.

Keywords

genetics, IgA deficiency, immunodeficiency, MHC

INTRODUCTION

Selective IgA deficiency (IgAD), defined as serum IgA levels equal to or below 0.07 g/l with normal IgM and IgG levels in individuals of 4 years of age or older [1], is the most common primary immunodeficiency (PID) in Whites with an estimated frequency of 1:600 [2]. Its prevalence, however, varies from 1:155 [3] to 1:18 550 [4] in different ethnic groups.

Most individuals with IgAD are clinically asymptomatic; however, recurrent respiratory and gastrointestinal tract infections, allergies and autoimmunity have often been reported in association with the defect [5]. Moreover, concomitant IgG subclass deficiency may favor infection proneness in some IgAD patients [5]. There are a number of previously published reviews on IgAD [6–9] but in this article we will focus on recent publications within the field (from 2009 to 2012).

Update

The phenotypic feature of IgAD is a failure of B lymphocyte differentiation into plasma cells producing IgA. The challenge is to determine if the block reflects a defect in T helper cells, antigen-presenting cells or B cells themselves. The recent

demonstration of induction of IgA synthesis in cells from a majority of patients with IgAD by interleukin (IL) 21 [10[¶]] may point to a non-B-cell defect.

There are limited data available on B-lymphocyte subpopulation in patients with IgAD. One previous study [11] showed no significant abnormalities in the B-cell differentiation stages determined in IgAD patients including naive, IgM memory, switched memory or IgM⁺CD21⁺ B cells, as compared with healthy controls. However, a recent study [12[¶]] showed that there were two subgroups of patients with IgAD (switched memory B cells percentage: 0.34 ± 0.06 and $1.74 \pm 0.12\%$, respectively) as compared with healthy controls ($>0.4\%$) wherein the low-switched memory B cells subgroup of patients exhibited more severe clinical features, including pneumonia, autoimmune

Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden

Correspondence to Lennart Hammarström, Karolinska Institutet, Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden. Tel: +46 8 524 835 86; e-mail: Lennart.Hammarstrom@ki.se

Curr Opin Allergy Clin Immunol 2012, 12:000–000

DOI:10.1097/ACI.0b013e3283594219

KEY POINTS

- IgA deficiency is the most common primary immunodeficiency in the Western world, associated with considerable morbidity.
- The defect is associated with selected MHC haplotypes and, as shown recently, non-MHC genes.
- There is a marked overrepresentation of a variety of autoimmune diseases in patients with IgA deficiency, compatible with a common genetic link.
- Reversal of the phenotype can be induced *in vitro*, suggesting a regulatory (epigenetic?) cause.

diseases and bronchiectasis, than the latter. The authors suggested that the classification of patients with IgAD by assessment of switched memory B cells could aid physicians in determining the clinical prognosis for their patients. Nechvatalova *et al.* [13^{*}] also determined major lymphocyte subpopulations and B-lymphocyte subsets in patients with IgAD and confirmed the reduction in terminally differentiated B-lymphocyte subsets, similar to what has previously been found in patients with CVID, although less pronounced than in the latter.

Clinical picture

The clinical picture in patients with IgAD given above has recently been reconfirmed both in children [14–16] and adults [17]. Surprisingly, an increased frequency of malignancy (4.8%) was found among the Israeli children [15]. This, however, has previously not been noted in adult White patients [18]. Furthermore, although allergies have been suggested to be an integral part of the clinical picture, it should be noted that serum IgE levels are often reduced in individuals with IgAD and in a recent Italian study [19] in adults, atopy was not more prevalent in the IgAD group as compared with controls.

One of the remaining clinical questions regarding IgAD relates to individuals with subnormal levels of serum IgA, yet not deficient (IgAD light). Two recent studies have addressed this issue and in a small US-based cohort, a majority of the children investigated (11/13) complained of joint pain, joint swelling or morning stiffness [20]. However, in a large, population-based study [21^{*}] in Sweden, encompassing 2423 young children (4–8 years old), no increase in the prevalence of infections or allergies was found in children with subnormal serum levels of IgA, whereas the children with overt

IgAD showed symptoms usually associated with the defect.

Recently, 54 594 Canadian blood donations were screened for serum IgA levels and the prevalence of IgAD was 1:219 [22], which is higher than the prevalence reported previously in Whites [8]. In 2011, 22 609 healthy Chinese blood donors were also screened for IgA levels and 14 of them were shown to be IgAD, giving a prevalence of 1:1615 [23], markedly higher than that previously reported in China (1:4100) [24], suggesting that the prevalence of IgAD is probably slightly undervalued in the Chinese population.

Associated diseases

Autoimmune diseases are the most important concomitant clinical manifestations in patients with IgAD [9,25].

Graves' disease, one of the most prevalent autoimmune thyroid disorders, is characterized by lymphocytic infiltration of the thyroid gland and production of thyrotropin-receptor autoantibodies (TRAbs) that is found in more than 95% of newly diagnosed Graves' disease patients [26], leading to hyperthyroidism [27]. The association of IgAD and Graves' disease has previously been suggested in several small studies. In 2011, we investigated the association of IgAD with Graves' disease, which is defined by elevated serum levels of TRAb, in a large cohort of the Icelandic and Swedish patients [28]. The data showed a noticeably higher prevalence of IgAD in the Swedish cohort (1:60, $P=0.027$). Furthermore, the prevalence of TRAb positivity in IgAD patients was elevated in both patient cohorts, suggesting a significant association of IgAD with Graves' disease.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a diverse array of autoantibodies, immune complex deposition, complement activation and tissue injury. Many previous studies have reported an increased frequency of IgAD among SLE patients of different ethnical backgrounds [29^{*}]. Recently, 72 juvenile SLE patients in Brazil were analyzed for levels of immunoglobulin classes and three patients were IgAD [30], giving a prevalence of 1:24, suggesting that IgAD is overrepresented among juvenile SLE patients and may potentially contribute to lupus development.

Type 1 diabetes (T1D) is characterized by destruction of insulin-producing β cells in the pancreas, leading to reduced/absent insulin production. The prevalence of IgAD in T1D has been previously reported to range from 1:27 to 1:261 [29^{*}]. A recent Iranian study [31] has shown that the prevalence of

IgAD in juvenile patients with T1D is 0.7% (1:150), confirming its high prevalence among these patients as compared with the general population.

Celiac disease is characterized by villous atrophy, crypt hyperplasia and inflammation in the small bowel. IgAD was previously shown to be associated with celiac disease with a reported overall prevalence of 1:39 [29[¶]], indicating a 5-fold to 15-fold increase in the prevalence of IgAD among both children and adults with celiac disease. A recent study in New York [32] provided evidence that IgA deficiency/partial deficiency was present in 2% of celiac disease patients and was equally prevalent among adults and children. Interestingly, all four patients with celiac disease and IgAD who had persistently positive IgG celiac serological markers while on gluten-free diet were rebiopsied and showed a normal histology. In addition, 20 190 Turkish school children [33] were screened for celiac disease and IgAD and the prevalence was 1:212 and 1:108, respectively wherein celiac disease appeared overrepresented in the IgAD cohort, as four of them were positive for IgG antitransglutaminase (tTG) (3.7%). Furthermore, in a recent study [34]

on Swedish children, nine out of 278 were positive for antibodies against deamidated gliadin peptides (DGP) out of whom four were shown to have overt celiac disease. A newly developed dot immunoassay [35] provides simultaneous detection of IgA anti-tTG, anti-DGP and total IgA antibodies, which could improve the detection of IgA-deficient celiac disease patients (a prevalence of 3.6% in the published study) and furthermore, the efficacy of celiac disease serology.

Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory disease, mainly of the synovial joints that typically appears from 6 months to 16 years of age. The prevalence of IgAD among patients with JRA has been reported to be 1:37 [29[¶]] and a recent study on Iranian children [36] identified one IgAD patient out of the 83 tested children.

IgAD is also overrepresented among patients with a variety of chromosomal abnormalities, including the 22q11 deletion syndrome [37,38] and chromosome 18 aberrations [7]. Interestingly, autoimmune manifestations are also common in these patients [37,39], suggesting a common genetic/pathophysiological link. Five recent case

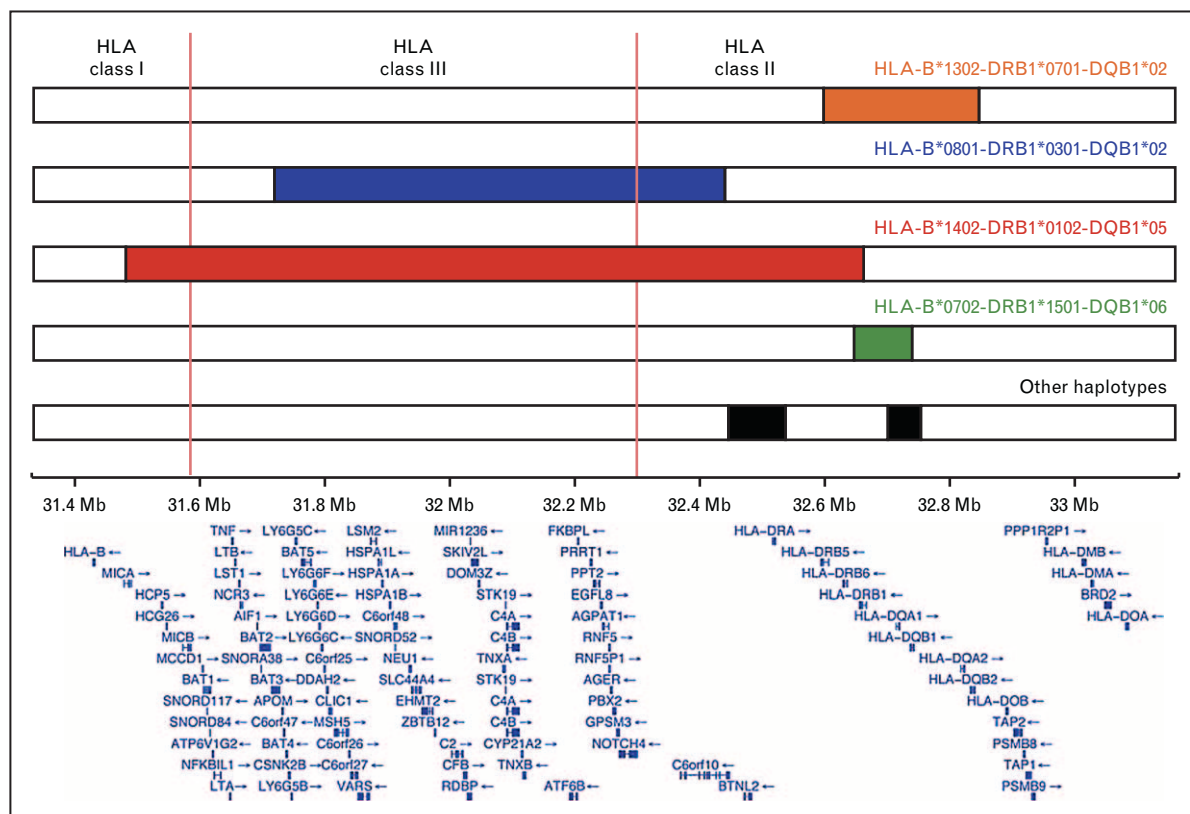


FIGURE 1. Summary of most significant independent association signals in the HLA locus. For each conserved haplotype background the critical region where the putative causal variant is more likely to be located is highlighted. Genomic positions on the x-axis are based on the NCBI Build 36 (hg 18) assembly. Mb, megabase pairs. Adapted from [53^{¶¶}]. Reprinted from PLoS Genetics under the Creative Commons Attribution License.

reports reinforce this notion, wherein IgAD in patients with the above chromosome aberrations were shown to be concomitant with Graves' disease [40–43], SLE [41], T1D [40] and JRA [44].

GENETICS

IgAD is a complex disease and although there are numbers of publications on the topic, its genetic basis has remained elusive. However, the MHC, in particular the ancestral HLA-A1, B8, DR3, DQ2 (8.1) haplotype and selected non-MHC genes have previously been reported to be associated with disease development.

MHC involvement

Up to 45% of IgAD patients carry at least one copy of the ancestral 8.1 haplotype as compared with 16% in the general population and homozygosity for this haplotype increases the risk of development of the disease even further [45]. The HLA-DR7, DQ2 and DR1, DQ5 haplotypes have also been shown to be risk factors for IgAD, whereas the DR15, DQ6 haplotype has been reported to confer an

almost complete protection against the disorder [46[■],47,48].

Interestingly, the 8.1 haplotype has also been reported to be associated with Graves' disease, SLE, T1D, celiac disease and, potentially, myasthenia gravis and rheumatoid arthritis [28,49] where the DRB1*1501 allele, which was confirmed as the protective factor for both IgAD and T1D, was found to be a risk factor for both SLE and multiple sclerosis [29[■],50]. However, due to the strong linkage disequilibrium within this region, the causative variants/mutations, except possibly for celiac disease, have not yet been identified.

We have previously suggested that genetic variation in the MSH5 encoding gene (mutS homolog 5) within the MHC class III region was associated with IgAD and common variable immune deficiency (CVID) [51]. Subsequently, however, Pozo *et al.* [52] argued that the MSH5 gene is not a genetic predisposing factor for IgAD but marks the HLA-DRB1*0102 subgroup carrying the susceptibility gene at least in the Spanish population.

Recently, we performed a high-density single nucleotide polymorphism (SNP) mapping of the MHC region in a combined sample of 772 IgAD

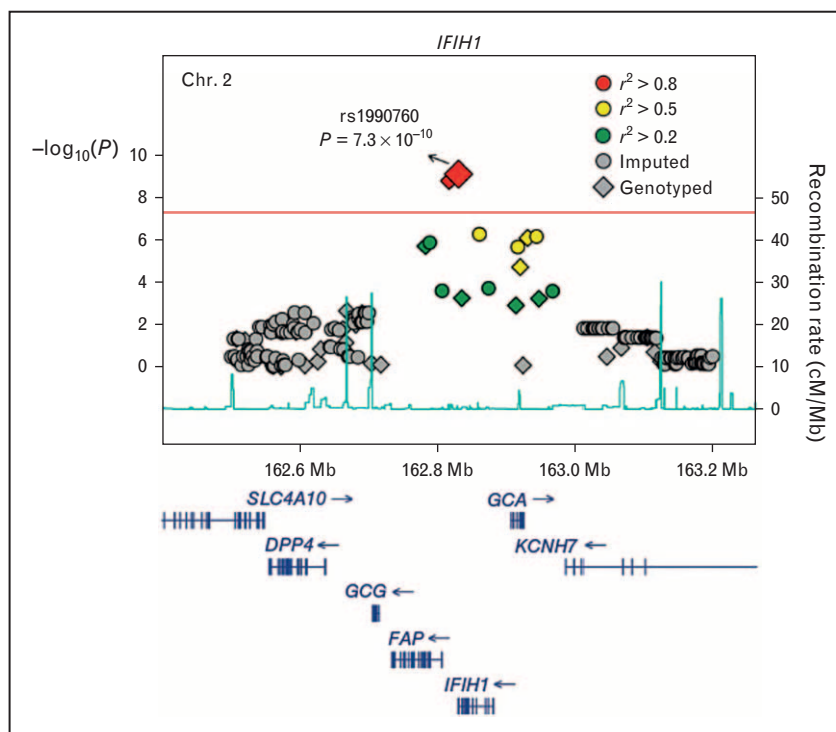


FIGURE 2. Linkage disequilibrium structure and combined association results at the IFIH1 locus. Chromosomal positions and gene loci on the x-axis are based on the NCBI Build 36 (hg 18) assembly. Combined *P*-values are shown for genotyped (diamonds) and imputed (circles) SNPs (left y-axis) and are shaded to reflect the extent of linkage disequilibrium with the most associated SNP. Recombination rates from the HapMap European CEU population are depicted in teal (right y-axis). The horizontal red line represents the genome-wide significance threshold of $P = 5 \times 10^{-8}$. Data shown represent 35 genotyped and 161 imputed SNPs. Reprinted from Nature Genetics [46[■]].

patients and 1976 matched controls from three independent European populations and confirmed the published IgAD risk and protective associated HLA haplotypes. We also provided evidence that the causative allele in the extended 8.1 haplotype is likely to be located in the telomeric end of the Class II region or in the Class III region (Fig. 1), which can guide future sequencing studies aimed at characterizing the precise functional variants contributing to disease pathogenesis [53[■]].

Non-MHC involvement

The MHC-associated genes, however, cannot explain the missing heritability of IgAD and some selected non-MHC genes, including *IFIH1* and *CLEC16A*, have recently been shown to be associated with IgAD [46[■]].

IFIH1 (also known as *MDA5*) is located on chromosome 2q24 and encodes the interferon induced with helicase C domain 1 protein. Together with RIG-1, it functions as a sensor for viral infections. We recently identified an association with a nonsynonymous variant in *IFIH1* [rs1990760 G>A, $P=7.3 \times 10(-10)$] in patients with IgAD (Fig. 2). This SNP was previously reported to be associated with T1D and SLE [54–56], suggesting that either another complementary antiviral pathway might be involved if patients carry loss of function variants or this SNP might just mark a particular haplotype with reduced expression of *IFIH1*.

CLEC16A (C-type lectin domain family 16, member A), another known locus associated with autoimmunity on chromosome 16, is widely expressed on B-lymphocytes, natural killer and dendritic cells [57]. Variants in *CLEC16A* showed suggestive evidence for association with IgAD [rs6498142 C>G, $P=1.8 \times 10(-7)$] and this SNP has previously been shown to be associated with several autoimmune diseases including T1D, SLE, celiac disease and multiple sclerosis [54,58–61].

Subsequently, our recent meta-analysis confirmed the association of IgAD and *IFIH1*, and provided evidence for an association with five additional novel non-MHC loci including *TNFAIP3*, *PVT1*, *FAS*, *CDH23* and *TM7SF3* [62].

Taken together, there is, thus, ample evidence for the implication of selected non-MHC genes in IgAD although the mechanism involved in the disease development remains elusive.

THERAPY

Stimulation with CD40L/anti-CD40 together with IL-4 and IL-10 has previously been shown to induce IgA synthesis in cells from IgAD patients

[63,64]. In addition, IL-21 has now also been shown to induce switching to IgA in cells from IgAD patients [10[■]], opening up novel avenues for potential therapy.

CONCLUSION

IgAD is the most common PID in Whites and its clinical consequences are well recognized. However, although much has been learned about the genetic basis of the disease during the past few years, the genes within the MHC that contribute to disease development have not yet been identified and finding the causative mutations/variants will, due to the marked linkage disequilibrium within the region, probably require full sequencing of the disease associated HLA haplotypes. Furthermore, although selected non-MHC genes have also been implicated in disease development, the mechanisms involved remain to be elucidated.

In terms of therapy, a variety of cytokines, including most recently IL-21, have been shown to induce IgA synthesis in cells from IgAD patients. In order to be able to translate these findings into clinically useful therapies, however, the pathways involved would need to be delineated and appropriate methods for delivery of the implicated cytokines developed.

Acknowledgements

None.

Conflicts of interest

The authors have declared no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Notarangelo LD, Fischer A, Geha RS, *et al.* Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol* 2009; 124:1161–1178.
2. Pan-Hammarström Q, Hammarström L. Antibody deficiency diseases. *Eur J Immunol* 2008; 38:327–333.
3. Pereira LF, Sapina AM, Arroyo J, *et al.* Prevalence of selective IgA deficiency in Spain: more than we thought. *Blood* 1997; 90:893.
4. Kano H, Mizumoto T, Yasuda N, *et al.* Selective IgA deficiency in Japanese blood donors: frequency and statistical analysis. *Vox Sang* 1986; 50:81–86.
5. Latiff AH, Kerr MA. The clinical significance of immunoglobulin A deficiency. *Ann Clin Biochem* 2007; 44:131–139.
6. Mestecky J, Hammarström L. IgA associated diseases. In: *Mucosal Immune Defense* (ed. CS Kaetzel) Springer, 2008. pp. 321–344.
7. Aghamohammadi A, Lougaris V, Plebani A, Hammarström L. Antibody deficiencies. In: *Primary Immunodeficiency Diseases, Definition, Diagnosis and Treatment* (ed. N. Rezaei) Springer, 2008. pp. 97–119.
8. Hammarström L, Smith CIE. Genetic approach to common variable immunodeficiency and IgA deficiency. In: *Primary Immunodeficiency Diseases, a molecular and genetic approach*, Oxford University Press, 2007. pp. 313–325.

9. Yel L. Selective IgA deficiency. *J Clin Immunol* 2010; 30:10–16.
10. Borte S, Pan-Hammarstrom Q, Liu C, *et al.* Interleukin-21 restores immunoglobulin production *ex vivo* in patients with common variable immunodeficiency and selective IgA deficiency. *Blood* 2009; 114:4089–4098.
- The first article describing in-vitro induction of IgA synthesis in cells from IgAD individuals using IL-21.
11. Litzman J, Vlkova M, Pikulova Z, *et al.* T and B lymphocyte subpopulations and activation/differentiation markers in patients with selective IgA deficiency. *Clin Exp Immunol* 2007; 147:249–254.
12. Aghamohammadi A, Abolhassani H, Biglari M, *et al.* Analysis of switched memory B cells in patients with IgA deficiency. *Int Arch Allergy Immunol* 2011; 156:462–468.
- Article giving a detailed analysis of surface markers on B cells from IgAD patients, showing an immature phenotype.
13. Nechvatalova J, Pikulova Z, Stikarovska D, *et al.* B-lymphocyte subpopulations in Patients with Selective IgA Deficiency. *J Clin Immunol* 2012; 32:441–448.
- Article describing surface markers on B cells from IgAD and CVID patients, showing similarities between them.
14. Aytekin C, Tuygun N, Gokce S, *et al.* Selective IgA Deficiency: Clinical and Laboratory Features of 118 Children in Turkey. *J Clin Immunol* 2012. [Epub ahead of print], doi: 10.1007/s10875-012-9702-3.
15. Shkalim V, Monselize Y, Segal N, *et al.* Selective IgA deficiency in children in Israel. *J Clin Immunol* 2010; 30:761–765.
16. Dominguez O, Giner MT, Alsina L, *et al.* Clinical phenotypes associated with selective IgA deficiency: a review of 330 cases and a proposed follow-up protocol. *An Pediatr (Barc)* 2012; 76:261–267.
17. Jorgensen G, Gardulf A, Sigurdsson MI, *et al.* Clinical symptoms in adults with selective IgA deficiency: a case-control study 2012: manuscript.
18. Mellemkjaer L, Hammarstrom L, Andersen V, *et al.* Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clin Exp Immunol* 2002; 130:495–500.
19. Franco A, Parrella R, Murru F, *et al.* Lack of association between IgA deficiency and respiratory atopy in young male adults. *In Vivo* 2011; 25:829–832.
20. Shakkottai A, Bupathi K, Patel AP, *et al.* Children with partial IgA deficiency: clinical characteristics observed in the pediatric rheumatology clinic. *Clin Pediatr (Phila)* 2012; 51:46–50.
21. Janzi M, Kull I, Sjöberg R, *et al.* Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. *Clin Immunol* 2009; 133:78–85.
- Article describing surface markers on B cells from IgAD and CVID patients, showing similarities between them.
22. Palmer DS, O'Toole J, Montreuil T, *et al.* Screening of Canadian blood services donors for severe immunoglobulin A deficiency. *Transfusion* 2010; 50:1524–1531.
23. Feng ML, Zhao YL, Shen T, *et al.* Prevalence of immunoglobulin A deficiency in Chinese blood donors and evaluation of anaphylactic transfusion reaction risk. *Transfus Med* 2011; 21:338–343.
24. Feng L. Epidemiological study of selective IgA deficiency among 6 nationalities in China. *Zhonghua Yi Xue Za Zhi* 1992; 72:88–90; 128.
25. Jacob CM, Pastorino AC, Fahl K, *et al.* Autoimmunity in IgA deficiency: revisiting the role of IgA as a silent housekeeper. *J Clin Immunol* 2008; 28 (Suppl 1):S56–S61.
26. Zophel K, Roggenbuck D, Schott M. Clinical review about TRAb assay's history. *Autoimmun Rev* 2010; 9:695–700.
27. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. *Endocr Rev* 2003; 24:802–835.
28. Jorgensen GH, Ormolfsson AE, Johannesson A, *et al.* Association of immunoglobulin A deficiency and elevated thyrotropin-receptor autoantibodies in two Nordic countries. *Hum Immunol* 2011; 72:166–172.
29. Wang N, Shen N, Vyse TJ, *et al.* Selective IgA deficiency in autoimmune diseases. *Mol Med* 2011; 17:1383–1396.
- Review summarizing published studies and own extensive screening data showing a clear association between IgAD and a variety of autoimmune diseases including Graves' disease, T1D, SLE and celiac disease.
30. Jesus AA, Liphaut BL, Silva CA, *et al.* Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients. *Lupus* 2011; 20:1275–1284.
31. Sayarifarid F, Aghamohammadi A, Haghi-Ashtiani MT, *et al.* Evaluation of serum IgA levels in Iranian patients with type 1 diabetes mellitus. *Acta Diabetol* 2012; 49:131–135.
32. Chow M. A., Lebwohl B., Reilly N. R., Green P. H. Immunoglobulin A deficiency in celiac disease. *J Clin Gastroenterol* 2012. [Epub ahead of print], doi: 10.1097/MCG.0b013e31824b2277.
33. Dalgic B, Sari S, Basturk B, *et al.* Prevalence of celiac disease in healthy Turkish school children. *Am J Gastroenterol* 2011; 106:1512–1517.
34. Olen O, Gudjonsdottir AH, Browaldh L, *et al.* Antibodies against deamidated gliadin peptides and tissue transglutaminase for diagnosis of pediatric celiac disease: diagnostic performance and cost in clinical practice. *J Pediatr Gastroenterol Nutr* 2012. [Epub ahead of print], doi: 10.1097/MPG.0b013e3182645c54.
35. Conrad K, Roggenbuck D, Ittenson A, *et al.* A new dot immunoassay for simultaneous detection of celiac specific antibodies and IgA-deficiency. *Clin Chem Lab Med* 2012; 50:337–343.
36. Moradinejad MH, Rafati AH, Ardalan M, *et al.* Prevalence of IgA deficiency in children with juvenile rheumatoid arthritis. *Iran J Allergy Asthma Immunol* 2011; 10:35–40.
37. Gennery AR, Barge D, O'Sullivan J J, *et al.* Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. *Arch Dis Child* 2002; 86:422–425.
38. Smith CA, Driscoll DA, Emanuel BS, *et al.* Increased prevalence of immunoglobulin A deficiency in patients with the chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Clin Diagn Lab Immunol* 1998; 5:415–417.
39. Dacou-Voutetakis C, Sertedaki A, Maniatis-Christidis M, *et al.* Insulin dependent diabetes mellitus (IDDM) and autoimmune thyroiditis in a boy with a ring chromosome 18: additional evidence of autoimmunity or IDDM gene(s) on chromosome 18. *J Med Genet* 1999; 36:156–158.
40. Jain N, Reitnauer PJ, Rao KW, *et al.* Autoimmune polyendocrinopathy associated with ring chromosome 18. *J Pediatr Endocrinol Metab* 2011; 24:847–850.
41. McGoe RR, Gedalia A, Marble M. Monosomy 18p and immunologic dysfunction: review of the literature and a new case report with thyroiditis, IgA deficiency, and systemic lupus erythematosus. *Clin Dysmorphol* 2011; 20:127–130.
42. Ohkubo K, Ihara K, Ohga S, *et al.* Hypothyroidism and levothyroxine-responsive liver dysfunction in a patient with ring chromosome 18 syndrome. *Thyroid* 2012. [Epub ahead of print], doi: 10.1089/thy.2011-0521.
43. Silva JM, Silva CP, Melo FF, *et al.* Graves disease and IgA deficiency as manifestations of 22q11.2 Kdeletion syndrome. *Arq Bras Endocrinol Metabol* 2010; 54:572–577.
44. Sato S, Kawashima H, Suzuki K, *et al.* A case of juvenile idiopathic polyarticular arthritis complicated by IgA deficiency in 22q11 deletion syndrome. *Rheumatol Int* 2011; 31:1089–1092.
45. Mohammedi J, Ramanujam R, Jarefors S, *et al.* IgA deficiency and the MHC: assessment of relative risk and microheterogeneity within the HLA A1 B8, DR3 (8.1) haplotype. *J Clin Immunol* 2010; 30:138–143.
46. Ferreira RC, Pan-Hammarstrom Q, Graham RR, *et al.* Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. *Nat Genet* 2010; 42:777–780.
- First article describing an association between IgAD and non-MHC genes (using three different European populations and matched controls). The authors show that, in addition to IFIH1 and CLEC16A, a variety of other genes implicated in autoimmune disorders are also associated with IgAD. The latter do, however, not reach genome wide significance.
47. Rioux JD, Goyette P, Vyse TJ, *et al.* Mapping of multiple susceptibility variants for the MHC region for 7 immune-mediated diseases. *Proc Natl Acad Sci U S A* 2009; 106:18680–18685.
48. Ramanujam R, Piehl F, Pirskanen R, *et al.* Concomitant autoimmunity in myasthenia gravis—lack of association with IgA deficiency. *J Neuroimmunol* 2011; 236:118–122.
49. Price P, Witt C, Allcock R, *et al.* The genetic basis for the association of the 8.1 ancestral haplotype (A1, B8, DR3) with multiple immunopathological diseases. *Immunol Rev* 1999; 167:257–274.
50. Cruz-Tapias P, Perez-Fernandez OM, Rojas-Villarraga A, *et al.* Shared HLA Class II in six autoimmune diseases in Latin America: a meta-analysis. *Autoimmune Dis* 2012; 2012:569728.
51. Sekine H, Ferreira RC, Pan-Hammarstrom Q, *et al.* Role for Msh5 in the regulation of Ig class switch recombination. *Proc Natl Acad Sci U S A* 2007; 104:7193–7198.
52. Pozo ND, Medrano LM, Cenit MC, *et al.* MSH5 is not a genetic predisposing factor for immunoglobulin A deficiency but marks the HLA-DRB1*0102 subgroup carrying susceptibility. *Hum Immunol* 2010; 71:861–864.
53. Ferreira RC, Pan-Hammarstrom Q, Graham RR, *et al.* High-density SNP mapping of the HLA region identifies multiple independent susceptibility loci associated with selective IgA deficiency. *PLoS Genet* 2012; 8:e1002476.
- The location of the IgAD predisposing/causing gene(s) within the MHC region has been a matter of debate (Class II versus Class III). In this article, the authors show that the IgAD associated regions differ depending on the MHC haplotype, thereby providing an explanation for the previous seemingly discrepant data.
54. Gateva V, Sandling JK, Hom G, *et al.* A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet* 2009; 41:1228–1233.
55. Liu S, Wang H, Jin Y, *et al.* IFIH1 polymorphisms are significantly associated with type 1 diabetes and IFIH1 gene expression in peripheral blood mononuclear cells. *Hum Mol Genet* 2009; 18:358–365.
56. Nejentsev S, Walker N, Riches D, *et al.* Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science* 2009; 324:387–389.
57. International Multiple Sclerosis Genetics Consortium (IMSGC). The expanding genetic overlap between multiple sclerosis and type I diabetes. *Genes Immun* 2009; 10:11–4.
58. Dubois PC, Trynka G, Franke L, *et al.* Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet* 2010; 42:295–302.

59. Martinez A, Perdignes N, Cenit MC, *et al.* Chromosomal region 16p13: further evidence of increased predisposition to immune diseases. *Ann Rheum Dis* 2010; 69:309–311.
60. Reddy MV, Wang H, Liu S, *et al.* Association between type 1 diabetes and GWAS SNPs in the southeast US Caucasian population. *Genes Immun* 2011; 12:208–212.
61. Zoledziewska M, Costa G, Pitzalis M, *et al.* Variation within the CLEC16A gene shows consistent disease association with both multiple sclerosis and type 1 diabetes in Sardinia. *Genes Immun* 2009; 10:15–17.
62. Bronson GP, Manoharan PA, Bhangale RT, *et al.* Selective immunoglobulin A deficiency is associated with IFIH1, TNFAIP3, PVT1, FAS, CDH23 and TM7SF3 in a genome-wide association study and meta-analysis, 2012: manuscript.
63. Marconi M, Plebani A, Avanzini MA, *et al.* IL-10 and IL-4 co-operate to normalize in vitro IgA production in IgA-deficient (IgAD) patients. *Clin Exp Immunol* 1998; 112:528–532.
64. Briere F, Bridon JM, Chevet D, *et al.* Interleukin 10 induces B lymphocytes from IgA-deficient patients to secrete IgA. *J Clin Invest* 1994; 94:97–104.