Selective IgA Deficiency in Autoimmune Diseases

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Selective immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency in Caucasians. It has previously been suggested to be associated with a variety of concomitant autoimmune diseases. In this review, we present data on the prevalence of IgAD in patients with Graves disease (GD), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), celiac disease (CD), myasthenia gravis (MG) and rheumatoid arthritis (RA) on the basis of both our own recent large-scale screening results and literature data. Genetic factors are important for the development of both IgAD and various autoimmune disorders, including GD, SLE, T1D, CD, MG and RA, and a strong association with the major histocompatibility complex (MHC) region has been reported. In addition, non-MHC genes, such as *interferon-induced helicase 1* (*IFIH1*) and *c-type lectin domain family 16, member A* (*CLEC16A*), are also associated with the development of IgAD and some of the above diseases. This indicates a possible common genetic background. In this review, we present suggestive evidence for a shared genetic predisposition between these disorders.

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INTRODUCTION

Selective immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency with a frequency of 1 in 600 in Caucasians (1). The prevalence in various ethnic groups ranges from 1:155 in Spain (2) to 1:18,550 in Japan (3) (for additional data, see refs. 4 and 5). The current definition, established by the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies, defines the disorder as serum IgA levels <0.07 g/L with normal IgM and IgG levels in individuals ≥4 years of age (6).

Most individuals with IgAD are clinically asymptomatic, but the defect may be associated with recurrent respiratory and gastrointestinal tract infections/disorders, autoimmunity and allergies. Patients with IgAD are usually more prone to infections when concomitant IgG subclass deficiency is present (7).

IgAD is strongly associated with the major histocompatibility complex (MHC) region, in particular with the human leukocyte antigen (HLA)-B8, DR3, DQ2 (8.1) haplotype (8,9), and up to 45% of IgAD patients have at least one copy of this haplotype compared to 16% in the general population (10). Homozygosity for the ancestral 8.1 haplotype increases the risk of development of the disease even further (10). Other haplotypes, including HLA-DR7, DQ2 and DR1, DQ5 are also associated with IgAD (11). In contrast, the DR15, DQ6 haplotype has been shown to confer an almost complete protection against the disorder (12–14). Polymorphisms in the non-MHC genes *interferon-induced helicase 1* (*IFIH1*) and *c-type lectin domain family 16, member A* (*CLEC16A*) genes have also been shown to be associated with IgAD in a recent genome-wide association study (GWAS) (13).

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Interestingly, the ancestral 8.1 haplotype is also reported to be associated with Graves disease (GD), systemic lupus erythematosus (SLE), type 1 diabetes (T1D) and celiac disease (CD) (15,16). In addition, telomeric portions of this haplotype have also been shown to contain a risk factor for myasthenia gravis (MG) (17) and rheumatoid arthritis (RA) (18). Moreover, there are several non-MHC genes in common that have also been shown to be associated with these autoimmune disorders. It is therefore possible that IgAD and selected autoimmune disorders share some of the predisposing genes, thus explaining the increased prevalence of IgAD in certain patient groups.

Table 1. Prevalence of IgAD among GD patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1994	37	Finland	NM	52	0	NM
1999	38	Italy	25–69	23	0	NM
1999	39	Italy	19–79	18	0	NM
2005	36	UK	NM	111	3 (1:37)	<0.1-0.6
2011	15	Sweden	NM	841[a]	14 (1:60)	<0.07
Total				1,045[b]	17 (1:61)[b]	

NM, not mentioned.
[a]TRAb-positive patients.
[b]Summing up total screened GD patients and IgAD individuals, the prevalence of IgAD is equal to the total number of IgAD individuals divided by the total number of screened GD patients (this also applies to Tables 2–6).

IgAD and Graves Disease

GD is one of the most prevalent autoimmune thyroid disorders (19). GD is characterized by lymphocytic infiltration of the thyroid gland and production of thyrotropin-receptor autoantibodies (TRAbs), leading to hyperthyroidism (20). TRAb, which is found in >95% of newly diagnosed GD patients (21), has been shown to be the main contributor to the onset and maintenance of GD. The incidence rates of GD have increased significantly and are roughly 29–30/100,000 annually in Caucasians (22), while an incidence of 14/100,000 has been reported in China (23). The seasonal trend and the geographical variation in the incidence of GD suggest that infections might be an important contributing factor to the pathogenesis of the disease (20). Twin studies have reported a concordance rate of 35% in monozygotic (MZ) compared to 3% in dizygotic (DZ) twins (reviewed in [24]), and the sibling risk ratio for GD is increased (25), indicating a strong genetic influence on the development of the disease.

GD was initially found to be associated with the HLA-B8 allele in Caucasians (24,26). However, subsequent study suggested that the primary susceptibility allele is the DR3 allele (27), with a frequency of approximately 40–55% in GD patients (26). However, because of the pronounced linkage disequilibrium, the exact location on the extended HLA-A1, B8, DR3 haplotype cannot be pinpointed. In addition, the HLA-DQA1*0501 allele was also shown to be associated with GD in Caucasians (28,29), as have non-MHC genes, including *cytotoxic T-lymphocyte-associated protein 4* (*CTLA4*); *CD40*; *protein tyrosine phosphatase, non-receptor type 22* (*PTPN22*); *thyroglobulin* and *thyroid stimulating hormone receptor* (TSHR) (30,31).

An association between GD and IgAD was previously suggested in various case reports (32–35), and a small screening study showed that IgAD is overrepresented among GD patients (36) (Table 1), although this could not be confirmed by other groups (37–39).

We recently investigated the association of IgAD with GD, defined by elevated serum levels of TRAb, in Icelandic and Swedish patients (15). The data showed a markedly higher prevalence of IgAD in the Swedish cohort (see Table 1). Furthermore, the prevalence of TRAb positivity in IgAD patients was increased in both cohorts (1:60, $P = 0.006$), suggesting a significant association of IgAD with GD. In addition, of the five GD patients with IgAD where DNA could be obtained, four carried the HLA-DR3, DQ2 haplotype (15).

IgAD and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that is characterized by a diverse array of autoantibodies, immune complex deposition, complement activation and tissue injury, influenced by multiple genetic and environmental factors. It predominantly affects women (prevalence ratio of women to men is 9:1), particularly during the childbearing years (40). The prevalence of SLE varies among different ethnic groups, ranging from 7 to 71 cases per 100,000 people of European descent (68/100,000 in Sweden [41]), 31 to 70 cases per 100,000 people among Chinese populations (40) and >200 per 100,000 people of African descent (42). The concordance rates within pairs of MZ twins range from 20% to 40% compared with 2% to 5% for DZ twins (43,44). Furthermore, the risk of SLE is increased both in first- and second-degree relatives (43,44), suggesting a strong genetic basis of the disease.

An association with the HLA-DR region, in particular, the HLA-DRB1*0301 and HLA-DRB1*1501 alleles (12,45,46), was reported in SLE patients of European ancestry, whereas DR2 (DRB1*1501) was overrepresented among Asian patients (47–49). Genes within the class III region of the MHC, including *mutS homolog 5* (*MSH5*) (50) and *superkiller viralicidic activity 2-like* (*SKIV2L*) (51), have also been suggested to constitute risk factors for the disease. Furthermore, SLE is associated with a variety of non-MHC genes, including *three prime repair exonuclease 1* (*TREX1*); *tumor necrosis factor, alpha-induced protein 3* (*TNFAIP3*); *interferon regulatory factor 5* (*IRF5*); *integrin, alpha M* (*ITGAM*); *signal transducer and activator of transcription 4* (*STAT4*); *B lym-*

phoid tyrosine kinase (*BLK*); *B-cell scaffold protein with ankyrin repeats 1* (*BANK1*); *PTPN22*; *tumor necrosis factor superfamily, member 4* (*TNFSF4*); *PX domain containing serine/threonine kinase* (*PXK*) and *interleukin-1 receptor-associated kinase 1* (*IRAK1*) (reviewed in [52]).

Previous studies have reported an increased frequency of IgAD among SLE patients, ranging from 1:19 in the USA to 1:130 in Spain (Table 2) (53–63). There have also been several case reports on the association between IgAD and SLE (64–72). However, the total number of patients screened for IgAD is still quite limited, and the criteria used to define IgAD have been variable. We thus determined the frequency of IgAD among 3388 SLE patients in Sweden, the UK, the USA and China, using an enzyme-linked immunosorbent assay to measure the serum IgA levels (for protocol, see [5]). IgAD was identified in a total of 44 patients, giving a total frequency of 1:67 in Caucasians and 1:121 in Chinese (see Table 2). Interestingly, the prevalence of IgAD among the Chinese SLE patients was >30-fold higher than in the general Chinese population (1:4,146) (73), indicating a strong association between these two diseases regardless of ethnic origin ($P < 2 \times 10^{-16}$).

Available samples of SLE patients with IgAD were genotyped at the HLA-B, -DR and -DQ loci using a sequence-specific primed polymerase chain reaction (PCR-SSP) (Olerup SSP, Saltjöbaden, Sweden). All Swedish SLE patients with IgAD (n = 6) carried the HLA-B8, DR3, DQ2 haplotype in a heterozygous form. Of the five English SLE patients, one patient was homozygous for the HLA-B8, DR3, DQ2 haplotype and one was homozygous for the DR3 allele. However, the HLA alleles of Chinese SLE patients did not conform to the known Caucasian risk alleles either for IgAD or SLE.

Table 3. Prevalence of IgAD among T1D patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1978	96	USA	Adults	421	0 (0)	<0.1
			3–16	366	9 (1:41)	<0.1
1982	216	Canada	8–51	129	2 (1:65)	Undetectable
1983	217	Germany	NM	483	14 (1:35)	NM
1988	94	Italy	2–16	191	7 (1:27)	<0.1
1992	95	USA	15–48	261	1 (1:261)	<0.05
1994	218	UK	Adults	1785	8 (1:223)	NM
1998	219	UK	2–22	167	3 (1:56)	NM
1998	97	Canada	1–18	236	0 (0)	NM
2000	220	Austria	1–22	403	2 (1:202)	NM
2005	98	Italy	18–70	94	0 (0)	<0.9
2005	221	Tunisia	16–60	261	5 (1:52)	<0.8
2010	222	Iran	6–19	300	2 (1:150)	<0.1
Total				5,097	53 (1:96)	
			Present study			
		Sweden	Children, adults	1,252	11 (1:114)	<0.07
		Italy	NM	245	2 (1:122)	<0.07
Total				1,497	13 (1:115)	

NM, not mentioned.

IgAD and Type 1 Diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by destruction of insulin-producing β cells in the pancreas, leading to reduced/absent insulin production. The damage is primarily due to a cell-mediated response, effectuated by activated cytotoxic T cells ($CD8^+$). T1D affects approximately 0.4% of people of European origin (74), but the incidence rate varies greatly between different parts of the world, ranging from 0.6 cases per 100,000 per year in Korea (75) to 40.2 cases per 100,000 per year in selected regions in Finland (76). Furthermore, the incidence of T1D is rising at a rate of 3–5% per year (77,78). Both genetic and environmental factors, including infections, socioeconomic status and nutrition (79–81), influence the development of the disorder. The concordance rate for T1D in MZ twins is approximately 50% (82–85), and in a recently published, prospective, long-term follow-up study of MZ twins, a cumulative incidence of 65% was reported (86). Furthermore, the prevalence of T1D in first-degree relatives is markedly higher than in the general population (87,88). Taken together, these studies suggest that the genetic predisposition may be even more important than previously recognized for the development of T1D.

It is commonly accepted that the MHC class II locus is the most important determinant for T1D (89). The predisposing MHC class II haplotypes, DRB1*0301-DQB1*0201 (DR3, DQ2) and DRB1*0401-DQB1*0302 (DR4, DQ8), are present in at least 90% of cases (90). Other susceptibility genes/regions within the MHC region have also been suggested, including the class I HLA-A and -B regions (91), the class II HLA-DRA and -DPB1 regions (91) and *notch 4* (*NOTCH4*) and *MSH5* in the class III region (92). Furthermore, a variety of non-MHC region genes have been previously shown to be associated with T1D, including *insulin* (*INS*); (*CTLA4*); (*PTPN22*); *interleukin 2 receptor alpha* (*IL2RA*); *SH2B adaptor protein 3* (*SH2B3*); *CLEC16A*; *IFIH1* and *protein tyrosine phosphatase, non-receptor type 2* (*PTPN2*) (reviewed in [93]).

The prevalence of IgAD in T1D has been reported to range from 1:27 (94) to 1:261 (95) in several reports, although no cases were observed in three studies (96–98) (Table 3), indicating an increased frequency compared to the general population. We measured IgA serum levels in three separate cohorts of T1D patients (children and adults) in Italy and Swe-

Table 2. Prevalence of IgAD among SLE patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1969	53	USA	NM	87	4 (1:22)	Undetectable
1972	54	Mexico	NM	106	1 (1:106)	Traces
1976	55	USA	NM	114	3 (1:38)	<0.10
1983	56	UK	NM	138	4 (1:35)	<0.05
1985	57	Turkey	9–66	96	3 (1:32)	<0.05
1988	58	France	NM	72	3 (1:24)	<0.10
1990	59	Spain	NM	130	1 (1:130)	<0.05
1991	60	USA	NM	75	3 (1:25)	NM
1997	61	UK	NM	96	5 (1:19)	<0.5
2007	62	USA	Children	77	4 (1:19)	<0.01
			Adults	152	8 (1:19)	Absent
2010	63	Brazil	Adults	189	11 (1:17)	<0.05
Total				1,332	50 (1:27)	
			Present study			
		Sweden	Adults	706	11 (1:64)	<0.07
		UK	Adults	844	5 (1:111)	<0.07
		USA	Adults	874	20 (1:41)	<0.07
		China	Adults	964	8 (1:121)	<0.07
Total				3,388	44 (1:77)	

NM, not mentioned.

den. Our own data show a prevalence of IgAD of 1:114 in Sweden and 1:122 in Italy (see Table 3), giving an overall prevalence of 1:100 in Caucasians (a roughly fivefold increase compared to the general population). Of the 11 Swedish T1D patients with concomitant IgAD, 3 were homozygous for the HLA-B8, DR3, DQ2 haplotype; 7 carried a copy of the B8, DR3, DQ2 haplotype; and 1 patient carried a copy of the B18, DR3, DQ2 haplotype. None of the two Italian T1D patients with IgAD carried the DR3, DQ2 haplotype.

IgAD and Celiac Disease

Celiac disease (CD) is a chronic inflammatory disorder of the intestinal tract, characterized by villous atrophy, crypt hyperplasia and inflammation in the small bowel. The disease is due to an immune reaction against gluten and related proteins found in wheat, rye and barley. The damage is mainly caused by intestinal intraepithelial lymphocyte-mediated cytotoxicity, and, already in 1975, Ferguson *et al.* reported that a local cell-mediated immunity reaction to gluten causes villous atrophy (99). The prevalence of CD among adults and children is approximately 1% (100–104). The disease is recognized in almost the entire world. The Saharawi population in Algeria has the highest prevalence (5.6%) (105), and CD appears to be rare in individuals of Japanese and Chinese ancestry (106). In Europe, the highest prevalence was reported in Finland (2.4%) and the lowest in Germany (0.3%) (107). These differences might be explained by genetic, environmental and social factors. Genetic factors play a key role in the development of CD, as shown by familial aggregation (5–15%) and a high concordance rate in MZ twins (83–86%) compared to DZ twins (17–20%) (108,109).

CD is strongly associated with genes within the MHC class II region, as almost all patients carry HLA-DQ2 and/or -DQ8. The HLA-DQ2 allele, which shows the strongest association with CD, is often encoded together with HLA-B8 and HLA-DR3 on the ancestral 8.1 haplotype. HLA-DQ2 is present in 20–30% of the general population but only 1–3% of all individuals carrying HLA-DQ2 develop CD (110). HLA-DQ8 is present in approximately 18.7% of the general population; however, only 0.1–0.3% of individuals carrying this allele develop CD. Thus, presence of HLA-DQ2 or HLA-DQ8 is a necessary, but not sufficient, prerequisite for developing the disease (111). Non-HLA genes, including *regulator of G-protein signaling 1* (*RGS1*); *toll-like receptor 7/8* (*TLR7/TLR8*); *chemokine (C-C motif) receptor 4* (*CCR4*); *parkinson protein 7* (*PARK7*); *runt-related transcription factor 3* (*RUNX3*); *nuclear factor I/A* (*NFIA*); *T-cell activation*

Table 4. Prevalence of IgAD among CD patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1992	113	Sweden	20–68	24	4 (1:6)	NM
1997	117	Italy	0–15	688	12 (1:58)	<0.05
1997	114	Ireland	NM	604	14 (1:43)	<0.05
1998	115	Italy	0–15	1,776	46 (1:39)	<0.05
			18–65	322	8 (1:40)	<0.05
2000	116	Turkey	0–16	104	3 (1:35)	NM
2000	223	Spain	NM	47	5 (1:10)	<0.07
Total				3,565	92 (1:39)	
2006	124	UK	NM	4,698[a]	35 (1:131)	<0.06
2008	118	Canada	NM	608[a]	4 (1:152)	<0.05
Present study		Sweden	Children, adults	422,225[a]	2,309 (1:192)	<0.07
Total				427,531	2,348 (1:182)	

NM, not mentioned.
[a]Patients with suspected CD.

RhoGTPase activating protein (*TAGAP*) and *CD80*, were also reported to be specifically involved in CD (112), whereas genetic loci shared with other autoimmune diseases include *SH2B3*; *IRF4*; *v-rel reticuloendotheliosis viral oncogene homolog* (*REL*); *PTPN2*; *zinc finger, MIZ-type containing 1 (ZMIZ1*) and *CTLA4* (reviewed in [112]).

IgAD was previously shown to be associated with CD (113–118), with a reported overall prevalence of 1:39 (Table 4), indicating a 5- to 15-fold increase in the prevalence of IgAD among both children and adults with CD. Conversely, several studies have also shown an increased prevalence of CD among IgAD patients (119–123). Furthermore, two studies demonstrated a higher prevalence of IgAD among patients with suspected CD (118,124).

We recently investigated the association between IgAD and CD in 442,225 individuals in Sweden, referred to immunology centers between 1998 and 2010 because of suspected CD. The patients were screened for anti-endomysium and/or anti-gliadin and anti-transglutaminase (TTG) antibodies, and total serum IgA levels were measured at the time of the investigation.

The frequency of positive anti-TTG samples among the IgA-sufficient patients tested in our own clinic (IgA anti-TTG) during the period 2006–2011 was 1.9% (351 out of 18,811 samples from unique patients). However, the diagnostic accuracy varies during the time period, with 3.6% of positive samples in 2011 (120 out of 3,321 samples from unique patients). Because there is a high degree of concordance between IgA and IgG anti-TTG levels (125–127), the positive samples observed above would also be expected to be positive for IgG anti-TTG antibodies. In IgAD patients, IgG anti-TTG, rather than IgA anti-TTG, serves as a marker for CD with a high sensitivity and specificity (128). The prevalence of IgG anti-TTG among IgAD blood donors ranges from 8.7% to 9.8% (123,128), with the prevalence of 9.3% in our own IgAD blood donor cohort (n = 43). However, among patients with IgAD, referred for anti-TTG screening due to gastrointestinal symptoms, the frequency of positive samples was markedly higher (16.6 %) (61 out of 367 samples from unique patients).

Altogether, 971 children and 1,338 adults with IgAD were identified, giving a frequency of 1:192. Of the hitherto resampled 394 individuals, 92% were shown to have IgAD, and the remaining cases were found to have additional antibody defects (common variable immunodeficiency). CD was confirmed in 58 of the 86 IgAD cases that were biopsied, whereas 28 were negative. A total of 46 of the former patients were HLA typed and 40 of them carried one copy of the DQ2 allele (87%), whereas the remaining carried one copy of DQ3 (a broad specificity including DQ8), suggesting that CD patients with IgAD have a similar HLA-DQ distribution as IgA-sufficient CD patients.

Table 5. Prevalence of IgA deficiency among MG patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1972	224	UK	9–46	54	1 (1:54)	2.5 IU/mL
1976	225	USA	Adults	51	0	NM
1976	226	USA	NM	107	0	NM
1976	227	UK	NM	50	1 (1:50)	Undetectable
1992	228	France	Adults	333	1 (1:333)	0.05
2011	229	Sweden	Adults	512	2 (1:256)	<0.07
Total				1,107	5 (1:221)	

NM, not mentioned.

IgAD and Myasthenia Gravis

Myasthenia gravis (MG) is an antibody-mediated disorder where autoantibodies against the acetylcholine receptor (anti-AChR antibodies) disrupt normal signal transduction across the neuromuscular junction in the vast majority of cases (129). Anti-MuSK (muscle-specific kinase) antibodies may also be detected in patients without anti-AChR (130). The loss of muscle receptors and the resulting reduction of signal transduction from nerve cells to muscle cells cause muscle weakness. Several autoimmune disorders, such as SLE (131–133), RA (134), and GD (134–137), have previously been shown to be overrepresented among patients with MG. The prevalence of MG is approximately 10 per 100,000 in European populations (14.1/100,000 in Sweden [138]) and an incidence of 0.3–3 cases per 100,000 per year (139). The rate of concordance is approximately 35% in MZ and 4–5% in DZ twins (140), indicating a strong genetic component.

The MHC region is reported to be associated with MG (17,141,142). Early-onset MG and patients exhibiting thymic hyperplasia are most strongly associated with the HLA-B8, DR3 haplotype, and late-onset MG is associated with B7 and DR2 alleles (143,144). Non-MHC genes are also known to be associated with MG, including *interleukin* (*IL*)*-1*; *CTLA4*; *IL-10, tumor necrosis factor* (*TNF*)*-α*; *cholinergic receptor, nicotinic, alpha 1* (*CHRNA-1*) and *PTPN22* (reviewed in [145]).

Studies on the frequency of IgAD in cohorts of patients with MG are presented in Table 5. The prevalence of IgAD is slightly elevated from the background rate, although two separate UK reports with 1 IgAD patient in 50 and 54 individuals, respectively, account for a large proportion of the increase. In another study (n = 333), the frequency of IgAD was not significantly increased, with only one patient being IgAD.

We recently investigated the prevalence of IgAD in 512 Swedish MG patients by measuring serum IgA levels using nephelometry. Two IgAD individuals were identified ($P = 0.19$) (14). Combined with previous studies, 5 of 1,107

MG patients screened were classified as IgAD (1:221). Despite a strong overlap of the HLA-B8, DR3, DQ2 haplotype, the prevalence of IgAD is thus not markedly increased in MG patients.

IgAD and RA

RA is a chronic inflammation, mainly of the synovial joints. Diagnosis is made for patients exhibiting 6 of 10 criteria of the ACR/EULAR Rheumatoid Arthritis Classification Criterion (146). Many patients exhibit increased levels of rheumatoid factor and antibodies against cyclic citrullinated protein. Juvenile rheumatoid arthritis (JRA), also termed juvenile idiopathic arthritis, typically appears from 6 months to 16 years of age (147). The condition in children appears to differ from that in adults, although definitive causes for each, and possible common mechanisms, are poorly understood. The prevalence of RA is approximately 1% worldwide (148), whereas JRA has a lower prevalence among European populations, reportedly between 0.04% in Spain (149) and 0.1% in Finland (150) and other European/North American populations (151). Concordance rates have been reported to be 15.4% in MZ twins and 3.6% in DZ twins (152), reflecting a genetic component that appears to require strong environmental factors for disease development, where the strongest single risk factor is smoking (153).

The HLA-DR4 allele has been shown to be the strongest genetic risk factor for RA (154). The B27 (155,156) and DR1 (154) alleles also appear to constitute risk alleles for RA development. Furthermore, there are suggestions that genes within the B8, DR3 haplotype also contribute to susceptibility to RA (18,155, 57–159), including JRA (156). Other risk alleles for JRA include the DR5 (160), DR8 (161) and B35 (161) alleles, whereas the DR15 and DR4 alleles have been shown to be protective (161,162). In addition to the HLA locus, over 30 genetic loci have been associated with risk for RA, many of which have been identified in recent years. RA was initially reported to be associated with *PTPN22* in Caucasians (163) and *peptidyl arginine deiminase, type IV* (*PADI4*) in Asian patients (164). Other genes found to be associated with RA by GWAS include *tumor necrosis factor receptor–associated factor 1 and encoding complement component 5* (*TRAF1-C5*); *STAT4*; *TNFAIP3*; *IL2-IL21*; *CD40*; *IL2RA*; *protein tyrosine phosphatase, receptor type, C* (*PTPRC*) and *IRF5* (reviewed in [165]), where *CTLA4* was associated with both RA and JRA (166). Other genes associated with JRA include *TNFα, macrophage migration inhibitory factor* (*MIF*) and *IL-6* (reviewed in [167]).

Studies on RA and JRA contain a total of 5,724 individuals, of whom 74 were IgAD (1:77). In JRA, 55 of 2,030 patients were IgAD (1:37), whereas in RA, 19 of 3,694 patients were IgAD (1:194) (Table 6). It is therefore likely that the increase in IgAD in rheumatic diseases is accountable to large increases in its frequency in JRA, with only a trend for a higher prevalence in RA patients.

Table 6. Prevalence of IgA deficiency among JRA and RA patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1970	229	USA	2.5–25	200	2 (1:100)	Undetectable
1972	230	USA	Children	176	3 (1:59)	0.2
1973	231	Finland	2–16	115	5 (1:23)	Undetectable
1973	232	USA	1–21	200	8 (1:25)	0.005
1977	233	USA	Children	324	14 (1:23)	0.01
1979	234	UK	Children	582	12 (1:49)	0.1
1983	235	Finland	Children	350	10 (1:35)	0.02
2011	236	Iran	Children	83	1 (1:83)	NM
Total for JRA				2,030	55 (1:37)	
1969	53	USA	NM	61	1 (1:61)	Undetectable
1971	237	Norway	NM	3187	8 (1:398)	Undetectable
1985	57	Turkey	NM	25	1 (1:25)	NM
1997	238	India	1–70	69	1 (1:69)	Undetectable
2003	239	UK	18–75	352	8 (1:44)	<50 IU/mL
Total for RA				3,694	19 (1:194)	
Total				5,724	74 (1:77)	

NM, not mentioned.

DISCUSSION

A common genetic background for selected autoimmune disorders, such as GD, SLE, T1D, CD and potentially MG and RA, involving both MHC and non-MHC encoded genes, has previously been suggested (14,168). There is also a considerable overlap in concomitant diseases; for example, T1D is prevalent in patients with GD, SLE, CD and RA. Furthermore, CD is overrepresented in patients with GD (168), and patients with

Table 7. Overlap between immune-mediated diseases.

	IgAD	GD	SLE	T1D	CD
IgAD in patients with	—	1.6%	1.3–3.8%	0.9–1.1%	2.6%
GD in patients with	11.8%	—	0.5%	0–24%	5%
SLE in patients with	ND	0.5–2.9%	—	0.6%	2.4%
T1D in patients with	2.8%	1.1–15%	11.6%	—	5%
CD in patients with	7.7–8.7%	0.9–5.4%	2.4%	4–9%	—

ND, not determined.

SLE also show a higher prevalence of thyroid disorders (169,170). In this report, we have added IgAD to this group of diseases, since it shows a markedly increased prevalence in GD, SLE, T1D and CD (Table 7).

IgAD is thought to be present from birth in most cases. Theoretically, the increased frequency of infections associated with IgAD could therefore precipitate autoimmune disorders such as GD and SLE. However, in CD, IgAD has occasionally been reported to occur after the onset of the gastrointestinal symptoms. Thus, the common genetic background is likely to be the main contributor to the different autoimmune disorders where environmental factors determine if, and when, the primary and subsequent diseases will appear.

The gene(s) involved are primarily located within the MHC region, where the population-attributable risk is strong in T1D, CD and RA and moderate in GD and SLE (168). Our recent preliminary work in IgAD, based on 100 multicase families, suggests a similarly strong MHC-associated risk in these patients. However, owing to strong linkage disequilibrium within the MHC region, the gene(s) involved in disease pathogenesis, with the possible exception of HLA-DQ in CD, have not yet been identified.

It is well documented that IgAD is strongly associated with the MHC region, in particular, the HLA-B8, DR3, DQ2 haplotype (9). This haplotype is also associated with GD, SLE, T1D and CD (reviewed in [16,171]). Although single loci within the MHC region were initially thought to confer susceptibility or resistance to different autoimmune diseases, the current picture is markedly more complex, since multiple loci/genes have been shown to confer independent risk both in SLE (12,51,172) and T1D (91,92,173,174) (Figure 1). This also appears to be true for IgAD where genes both within the class II (9,175) and class III region (176–178) have been shown to be associated with the defect (Figure 1). Multiple loci have also been suggested to be involved in MG (17), another 8.1 haplotype–associated disease, as well as immune-mediated diseases associated with other HLA haplotypes, including multiple sclerosis (MS) (179) and RA (18,159,175,180).

Case-control studies in European SLE patients have shown a consistent association with the HLA-DRB1*1501 allele and its linked haplotypes (45,46). An association with the DRB1*1501 allele (rs3135391 serving as a tagging SNP) has also been observed in patients with MS (12). Although a few case reports on IgAD in MS patients have been published, no large-scale screening studies have been performed to date. In view of the almost complete protection against IgAD by the DRB1*1501 allele (12), its frequency among MS patients would be expected to be quite low. Similarly, the DRB1*1501-DQB1*0602 haplotype confers protection from T1D (181). Thus, the same allele confers risk or protection in different immune-mediated diseases, suggesting its involvement at a crucial step in pathogenesis.

The association between a given disease and the MHC could either be due to coding mutations/variations in a given gene, directly influencing its function, or, alternatively, mutations/variations in regulatory sequences, affecting the expression of the gene. Examples of the former include copy number variation of functional C4 alleles in SLE (46) and potentially IgAD (182) and promoter polymorphisms in *nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1* (*NFKBIL1*, also known as *IKBL*) (183), *DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B* (*DDX39B*, also known as *BAT1*) (184) and HLA-DQA1 (185) in the latter.

We previously suggested that an IgAD predisposing (mutated/variant) haplotype (B8, DR3, DQ2) is present at a frequency of 0.46% in the general Swedish population (10). Preliminary experiments have indeed shown multiple sequence differences between patients and controls homozygous for the 8.1 haplotype. Similar findings have previously been reported by Yan *et al.* (186) in Alaskan natives with RA, where multiple mutations/variations were identified in the disease-associated haplotype. The presence of such a predisposing haplotype may explain the overlap in HLA between IgAD and autoimmunity, since the affected variant of the 8.1 haplotype might constitute a risk factor for developing additional disorders, including GD, SLE, T1D, CD and potentially MG and RA. However, additional studies in cohorts of patients with different autoimmune diseases will be necessary to substantiate this notion, and full sequencing of the MHC region of the 8.1 haplotype may ultimately be required to identify the potential mutations/variants involved.

The mechanism underlying the induction of IgAD still remains elusive. It is however likely that the pathophysiological process involves a break of tolerance against IgA itself (since 30% of IgAD patients have demonstrable titers of IgG antibodies against IgA) or one of the factors involved in the switching process (such as a *proliferation-inducing ligand* [*APRIL*] or *B-cell activating factor* [*BAFF*]).

A number of non-MHC genes have also been shown to be associated with GD, SLE, T1D and CD. These genes generally cluster into pathways involved in T-cell differentiation, cell activation/signaling and innate immunity and have been shown to be associated with single or several diseases (Table 8). It is however noteworthy that there is also a lack of association of given "autoimmune" genes such as *PTPN22*, which shows association with a large number of diseases, including some of the above disorders, suggesting differences in the pathophysiological pathways.

IFIH1 is located on chromosome 2q24 and encodes the interferon induced with helicase C domain 1 protein. Together with *retinoic acid-inducible gene I* (*RIG-1*), it functions as a sensor for viral infections. *IFIH1* expression is highly upregulated in activated immune cells in response to type 1 interferon induced by viral infections, suggesting that it could

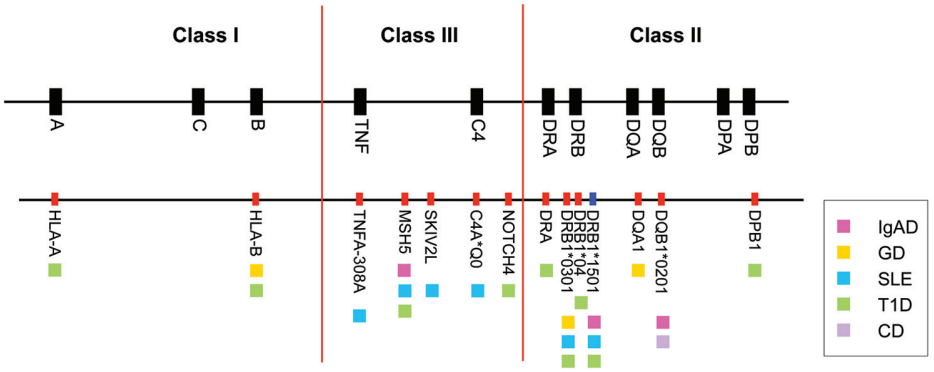

Figure 1. Markers across the HLA region associated with risk and protection to IgAD and selected autoimmune disorders. The HLA-DRB1*1501 allele constitutes a risk factor for SLE, but is a protective factor for IgAD and T1D.

potentially be involved in the pathogenesis of autoimmune diseases including T1D (187). Several SNPs within the *IFIH1* gene and its 3′ untranslated region show an association with T1D (rs2111485, rs13422767, rs1990760 and rs3747517) (188), where the rs1990760 marker (Ala946Thr) is the most strongly associated (reviewed in [189]). Most of these rare *IFIH1* alleles are protective against disease (190).

A recent large-scale study also showed a highly significant association of rs1990760 to SLE in Caucasian (191)

Table 8. SNPs reported to be associated with IgAD and selected autoimmune disorders.[a]

			IgAD		GD		SLE		T1D		CD	
Locus	Gene	SNP	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1p13	*PTPN22*	rs2476601					1.35 (1.24-1.47)	3.40E-12	2.04 (1.81-2.29)	2.71E -63		
1q25.3	*NMNAT2*	rs2022013					0.85 (0.79-0.90)	1.08E-07				
1q31.2	*RGS1*	rs2816316							0.89 (0.84-0.95)	1.23E-04	0.80 (0.76-0.84)	2.20E-17
2q12.1	*IL18RAP*	rs917997									1.19 (1.14-1.25)	1.11E-15
2q24	*IFIH1*	rs1990760	0.67 (0.59-0.76)	7.30E-10			1.17 (---)	3.20E-05	0.85 (0.81-0.90)	3.27E-09		
2q32.2	*STAT4*	rs7574865					1.57 (1.49-1.69)	1.40E-41				
2q33.2	*CTLA4*	3 SNPs			1.49 (1.34-1.66)	6.00E-14			0.85 (0.78-0.92)	8.89E-05	1.14 (1.09-1.19)	5.79E-09
3p14.3	*PXK*	rs6445975					1.25 (1.16-1.35)	7.10E-09				
3p21	*CCR1/CCR3*	2 SNPs									1.30 (1.23-1.39)	3.26E-17
3q25.33	*IL21A*	rs17810546							1.09 (1.04-1.14)	3.40E-04	1.36 (1.29-1.44)	3.98E-28
3q28	*LPP*	rs1464510									1.29 (1.25-1.34)	2.98E-40
4q27	*IL2-IL21*	2 SNPs			0.87 (0.79-0.95)	1.81E-03			1.27 (1.15-1.39)	6.35E-07	0.74 (0.70-0.78)	2.18E-27
5p13	*IL7R*	rs6897932							0.89 (0.84-0.94)	8.07E-05		
6p21.32	*HLA*	Multi-SNPs	2.53 (2.17-2.95)	2.20E-33	4.6 (---)	2.30E-08	2.36 (2.11-2.64)	1.71E-51	6.85 (---)	1.71E-52	6.23 (5.95-6.52)	1.00E-50
6q21	*ATG5*	rs573775					1.19 (1.12-1.27)	1.36E-07				
6q23.3	*TNFAIP3*	3 SNPs					1.17 (1.10-1.25)	4.00E-07	0.90 (0.86-0.95)	3.20E-05	1.23 (1.17-1.28)	4.46E-19
6q25.3	*TAGAP*	rs1738074							0.92 (0.88-0.96)	7.90E-05	1.16 (1.12-1.21)	2.94E-15
7p21.3	*ICA1*	rs10156091					1.32 (1.19-1.47)	1.90E-07				
7q32	*IRF5*	rs2070197					1.88 (1.78-1.95)	5.80E-24				
8p23.1	*BLK*	rs2736340					1.35 (1.27-1.43)	7.90E-17				
8q12	*LYN*	2 SNPs					0.77 (0.70-0.84)	5.40E-09				
10p11	*NRP1*	rs2666236							1.21 (1.11-1.31)	1.05E-05		
11p15.5	*KIAA1542*	rs4963128					0.78 (0.71-0.85)	1.30E-07				
11p15.5	*INS*	rs7111341							1.25 (1.15-1.35)	2.28E-07		
12q13.2	*ERBB3*	rs2292239							1.28 (1.21-1.35)	6.46E-19		
12q24	*SH2B3*	rs653178							1.28 (1.22-1.35)	2.72E-24	1.20 (1.15-1.24)	7.15E-21
16p11.2	*ITGAM*	3 SNPs					1.62 (1.47-1.78)	1.61E-23				
16p13.13	*CLEC16A*	3 SNPs	0.64 (0.54-0.77)	1.80E-07			1.16 (---)	1.60E-04	0.81 (0.77-0.86)	7.43E-14	0.86 (0.82-0.91)	3.12E-08
18p11.21	*PTPN2*	2 SNPs							1.30 (1.22-1.40)	1.49E-14	1.17 (1.12-1.23)	2.52E-10
18q22.2	*CD226*	rs763361							1.16 (1.10-1.22)	2.82E-08		
22q11.21	*UBE2L3*	2 SNPs					1.22 (1.14-1.32)	7.53E-08			1.13 (1.08-1.19)	1.84E-07
22q13.2	*SCUBE1*	rs2071725					0.78 (0.72-0.86)	1.21E-07				

[a]Color-code from dark red to green represents the strong and weak association, respectively:
5E-32~lower 5E-26~5E-32 5E-20~5E-26 5E-14~5E-20 5E-08~5E-14 5E-08~higher.

but not in Japanese patients (192). Moreover, GD has also been shown to be associated with rs1990760 (193), although this point remains controversial (194–196). CD, on the other hand, does not appear to be associated with rs1990760 (74).

In 2010, we performed a GWAS on a large cohort of patients with IgAD (13) and identified an association with rs1990760 in the *IFIH1* gene. Taken together, there is thus ample evidence for the implication of *IFIH1* both in IgAD and in several autoimmune disorders, although the mechanism involved remains elusive.

CLEC16A, located on chromosome 16p13, is widely expressed on B lymphocytes, natural killer and dendritic cells (197). Several SNPs (rs2903692, rs17673553, rs725613 and rs12708716) within the *CLEC16A* gene have been shown to be associated with T1D in different populations (196,198–203). Dubois *et al.* (204) recently also identified an association between the *class II, major histocompatibility complex, transactivator* (*CIITA*)*–suppressor of cytokine signaling 1* (*SOCS1*)-*CLEC16A* region and CD, although it just reached borderline genome-wide significance. Another study, however, suggested that *CLEC16A* (rs2903692) is not involved in susceptibility to CD development (205). rs12708716 was also suggested to be associated with SLE (191) where the A allele confers susceptibility. Awata *et al.*, on the other hand, showed that rs2903692 was not associated with GD in Japanese patients (206). In IgAD, we recently showed suggestive evidence for association with *CLEC16A* (rs6498142 and rs7201845) (13), again suggesting a common genetic link.

One remaining question is whether the MHC- and non-MHC–associated susceptibility genes are acting independently or synergistically in the pathophysiological processes underlying autoimmune diseases. A number of studies have addressed this question, and Hodge *et al.* (207) and Jacobson *et al.* (25) showed that interaction between HLA-DRB1*03 and different *thyroglobulin* variants conferred an increased risk for GD. A subsequent study in Japanese subjects (208) suggested that there was also an interaction between selected HLA-A and DP alleles and *CTLA4* in a subgroup of GD patients, although Kula *et al.* (209) suggested that the interaction with *CTLA4* was due to HLA-DR encoding genes.

In T1D, a study in Belgian patients showed no interaction between HLA-DQ and the *IFIH1* rs1990760 SNP (210). However, *PTPN22* Trp620 (rs2476601) has a higher relative risk in T1D patients carrying low-risk MHC class II genotypes (non-DR3/DR4) than in those carrying the high-risk ones, suggesting a potential interaction (211–213). Moreover, a Norwegian study indicated a weak synergistic effect between *FOXP3* and the HLA-DR3, DQ2, haplotype both in T1D and CD patients (214). A recent case-control collection study also showed a significant interaction between HLA-DR3 and *IRF5* in patients with SLE (215). Similar interaction studies in IgAD have not yet been performed.

In summary, IgAD is markedly more prevalent in patients with a variety, albeit not all (such as MG [14]), of 8.1 haplotype–associated autoimmune diseases. Similarities in the genetic susceptibility suggest involvement of common pathophysiological pathways, implicating that IgAD, as recently suggested by Ferreira *et al.* (13), may in fact be an autoimmune disease. However, additional dense SNPing and sequencing of the implicated genes may be required to fully understand the mechanisms involved.

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DISCLOSURE

TW Behrens is a full-time employee of Genentech.

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