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REVIEW

HLA Alleles Associate with Insulin Autoimmune Syndrome

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Abstract: In recent years, there have been hundreds of reports on insulin autoimmune syndrome (IAS) globally; however, fewer than a hundred patients have undergone genetic testing. Our objective is to examine the background of IAS and the variations in drugs that trigger it among patients who have been genetically tested, aiming to deepen our understanding of this condition. HLA Analysis of 68 cases showed that DR4 is predominant, especially in individuals of East Asian descent, notably in DRB1 *0406. Methimazole was the primary drug associated with IAS in these populations, while in Caucasian individuals, the emphasis was on DRB1 *0403, with lipoic acid being the common inducer. The key factor determining disease risk is the combination of chromosomal allele variations, with HLA class II allele DR4 positive patients showing a strong association with DQA1 *0301/DQB1 *0302.

Keywords: insulin autoimmune syndrome, HLA, methimazole, α-lipoic acid

Introduction

Insulin autoimmune syndrome (IAS) is characterized by spontaneous hypoglycemia, elevated endogenous insulin, and positive insulin autoantibodies (IAA). It is often triggered by thiol-containing drugs (including non-thiol drugs like gold thioglucose and albumin) or viral infections, with some cases being idiopathic. IAS was first reported in 1970 by Yukimasa Hirata and colleagues.[1] The pathogenesis of IAS is closely linked to specific HLA typing susceptibility gene loci.[2]

The major histocompatibility complex (MHC) is a genetic locus containing encompassing genes that encode class I and II MHC molecules. In humans, this complex is termed HLA (human leukocyte antigen), and is governed by genes on the short arm of chromosome 6. Class I MHC molecules typically load and present CD8 T cell peptides produced within cells, rather than presenting exogenous peptides, with the second chain remaining unchanged. Class II genes exhibit extensive polymorphism, which influences immune system recognition. Each unique human sequence assigned a four-digit number plus the gene name, such as DRB1 *0401, with an optional fifth number for nucleotide variations that do not affect amino acids. Class II DQ MHC molecules consist of two polymorphic chains (A and B), thus requiring definition, eg, DQA1 *0301/DQB1 *0302. Conversely, DR molecules are mainly polymorphic in the DRB chain, with less variability in the DRA chain, often denoting only the DRB chain, eg, DRB1 *0301[2] (Figure 1).

Previous literature on IAS has mainly focused on Japan, with pathogenic factors including thiol containing drugs and viruses.[3] Our aim is to explore whether there is a correlation between different regional distributions and the pathogenicity of different drugs and HLA typing.

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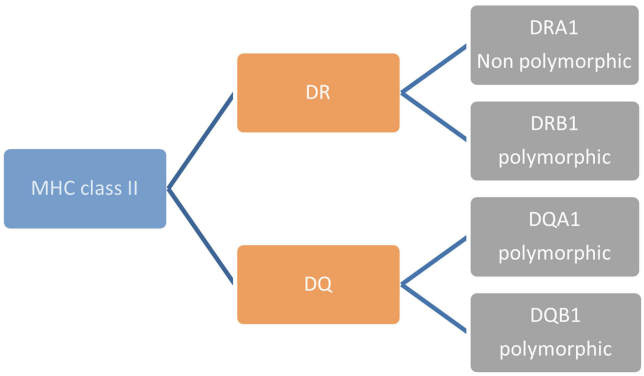

Figure 1 MHC class II gene composition.

Methods

We searched the English literature published in PubMed from 1970 to December 2023 using IAS as the keyword, excluding duplicate cases, literature with incomplete data, and articles with only abstracts or lacking full texts. We extracted, summarized, and analyzed factors such as country of origin, pathogenic drug, gender, age, etc. from the HLA typing test patients reported in the IAS literature. We aimed to explore different HLA subtypes and differences in countries and regions; the association between HLA typing and different pathogenic drugs; and differences in HLA subtypes and gender.

Results

Search Results

We included a total of 168 articles and 501 cases, with 68 cases having completed HLA sequencing (Figure 2 and Table 1). China reported the highest number of cases, followed by Japan; Japan had the highest number of HLA sequencing cases (Figure 3).

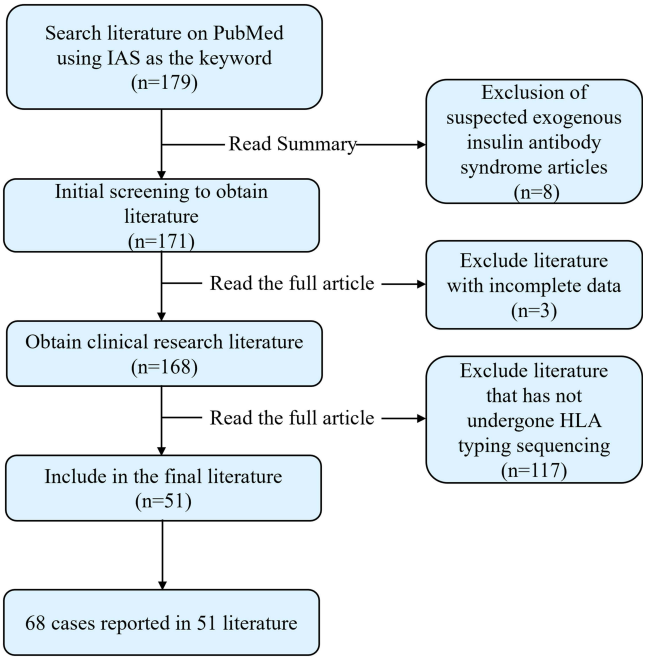

Figure 2 Literature search flowchart.

Table 1 Basic Information of 68 IAS Patients

DRB1	DRB1'	DQB1	DQB1'	DQA1	DQA1'	HLA class I	Country	Inducing Drugs	M/F	Age	Year	References
0405	1302	0402	0604	NA	NA	A23(9)/68, B44/55, Cw2/9(3.1)	Japan	Insulin	M	75	2006	[4]
0406	1502	0302	0601	NA	NA	NA	China	α-lipoic acid	M	48	2017	[5]
0403	0701	0202	0202	NA	NA	NA	China	Clopidogrel	M	66	2021	[6]
04	07	0401	0402	0301	0201	NA	Caucasian	Piritinol	F	3.5	2015	[7]
0403	NA	NA	NA	NA	NA	NA	Japan	NA	M	84	2015	[8]
0401	1201	NA	NA	NA	NA	A24/11, B35/62, Cw3/4	Korea	α-lipoic acid	F	71	2009	[9]
1104	NA	NA	NA	NA	NA	NA	America	Ceftriaxone+ oxacillin	F	7	2013	[10]
0301	0401	NA	NA	NA	NA	NA	America	NA	M	67	2009	[11]
0403	1147	0301	0302	NA	NA	NA	China	Clopidogrel	M	82	2023	[12]
0404	NA	NA	NA	NA	NA	NA	America	Clopidogrel	M	79	2017	[13]
0301	0901	0302	0501	NA	NA	NA	Korea	NA	F	31	2012	[14]
0406	NA	0301	NA	NA	NA	NA	China	NA	NA	NA	1992	[15]
0406	NA	0302	NA	NA	NA	NA	Korea	NA	NA	NA	1992	[15]
0406	NA	0302	NA	NA	NA	NA	Korea	NA	NA	NA	1992	[15]
0406	NA	0302	NA	NA	NA	NA	Japan	NA	NA	NA	1992	[15]
0406	NA	NA	NA	NA	NA	NA	Japan	Albumin	F	80	2016	[16]
0406	NA	NA	NA	NA	NA	NA	Portugal	Penicillin G	F	24	2001	[17]
0403	NA	NA	NA	NA	NA	A23/66, B49/51, Cw2/7	Portugal	NA	F	19	2001	[17]
0406	0901	NA	NA	NA	NA	NA	China	Methimazole	F	17	2014	[18]
0403	15	0302	05	0301	0103	NA	Italy	NA	M	25	2012	[19]
0404	NA	NA	NA	NA	NA	NA	Japan	NA	F	53	2006	[20]
0406	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0403	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0403	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0403	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0403	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0403	NA	NA	NA	NA	NA	NA	America	α-lipoic acid	NA	NA	2014	[21]
0406	1601	0302	0502	0102	0301	NA	China	Methimazole	F	44	2005	[22]
0405	0407	NA	NA	NA	NA	NA	China	Methimazole	M	23	2011	[23]
03	14	NA	NA	NA	NA	NA	America	Omeprazole	F	65	2016	[24]
0406	090102	030201	030302	030101	0302	NA	Japan	Loxoprofen-sodium	F	62	2013	[25]
0701	0901	0202	0303	NA	NA	NA	Brazilian	Captopril	F	63	2018	[26]
0406	NA	NA	NA	NA	NA	NA	Japan	Health supplements	F	70	2013	[27]
0403	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	66	2018	[28]
0406	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	70	2011	[29]
0406	NA	NA	NA	NA	NA	NA	Korea	methimazole	F	15	2013	[30]

(*Continued*)

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Table 1 (Continued).

DRB1	DRB1'	DQB1	DQB1'	DQA1	DQA1'	HLA class I	Country	Inducing Drugs	M/F	Age	Year	References
0403	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	71	2021	[31]
04	15	NA	NA	NA	NA	NA	Japan	Coenzyme Q10	F	52	2019	[32]
0406	1502	NA	NA	NA	NA	NA	Japan	α-lipoic acid	M	55	2007	[33]
0406	NA	0302	NA	0301	NA	NA	Japan	Gold thioglucose	F	56	1994	[34]
0406	NA	NA	NA	NA	NA	NA	Japan	NA	M	84	2011	[35]
0406	090102	NA	NA	NA	NA	NA	China	Methimazole	F	44	2023	[36]
0406	NA	NA	NA	NA	NA	NA	China	Methimazole	F	39	2023	[36]
0406	NA	NA	NA	NA	NA	NA	China	Methimazole	F	50	2023	[36]
0401	0803	0301	0601	0103	0303	NA	Japan	NA	F	88	2000	[37]
1301	0802	NA	NA	NA	NA	NA	Brazilian	NA	M	6	2019	[38]
0406	NA	NA	NA	NA	NA	NA	China	Methimazole	M	31	2022	[39]
0403	NA	NA	NA	NA	NA	NA	Japan	α-lipoic acid	F	45	2007	[40]
0403	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	66	2019	[41]
0403	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	82	2019	[41]
0407	NA	NA	NA	NA	NA	NA	Italy	NA	F	78	2015	[42]
0406	NA	NA	NA	NA	NA	NA	Poland	Methimazole+ captopril	F	39	2012	[43]
0404	0301	0302	0201	03	0501	NA	Netherlands	NA	F	45	1996	[44]
0406	NA	NA	NA	NA	NA	NA	Korea	α-lipoic acid	F	67	2013	[45]
0403	NA	NA	NA	NA	NA	NA	Italy	α-lipoic acid	NA	NA	2021	[46]
0403	NA	0302	NA	NA	NA	NA	Germany	Quinapril+α-lipoic acid	F	69	2001	[47]
0403	09	NA	NA	NA	NA	NA	France	Clopidogrel	M	88	2006	[48]
04	15	NA	NA	NA	NA	NA	Italy	α-lipoic acid	F	35	2018	[49]
0406	1501	NA	NA	NA	NA	NA	Korea	Methimazole	F	53	2013	[50]
0406	0405	NA	NA	NA	NA	NA	Japan	Methimazole	F	26	2016	[51]
0406	090102	NA	NA	NA	NA	NA	Japan	Methimazole	F	29	2016	[51]
0410	140,501	0402	050301	0104	0303	NA	Japan	NA	F	80	2011	[52]
0405	0803	0401	0601	0301	0103	NA	Japan	NA	M	62	1995	[53]
0401	NA	0301	NA	0301	NA	NA	Norwegian	NA	M	42	1995	[53]
0101	1601	0501	0502	0101	0102	NA	Swiss	NA	F	55	1995	[53]
1501	1502	0601	0602	0102	0103	NA	Italy	NA	F	57	1995	[53]
0701	1501	0201	0602	0201	0102	NA	Italy	NA	M	5	1995	[53]
0402	1101	0301	0302	0301	0501	NA	Italy	NA	M	79	1995	[53]

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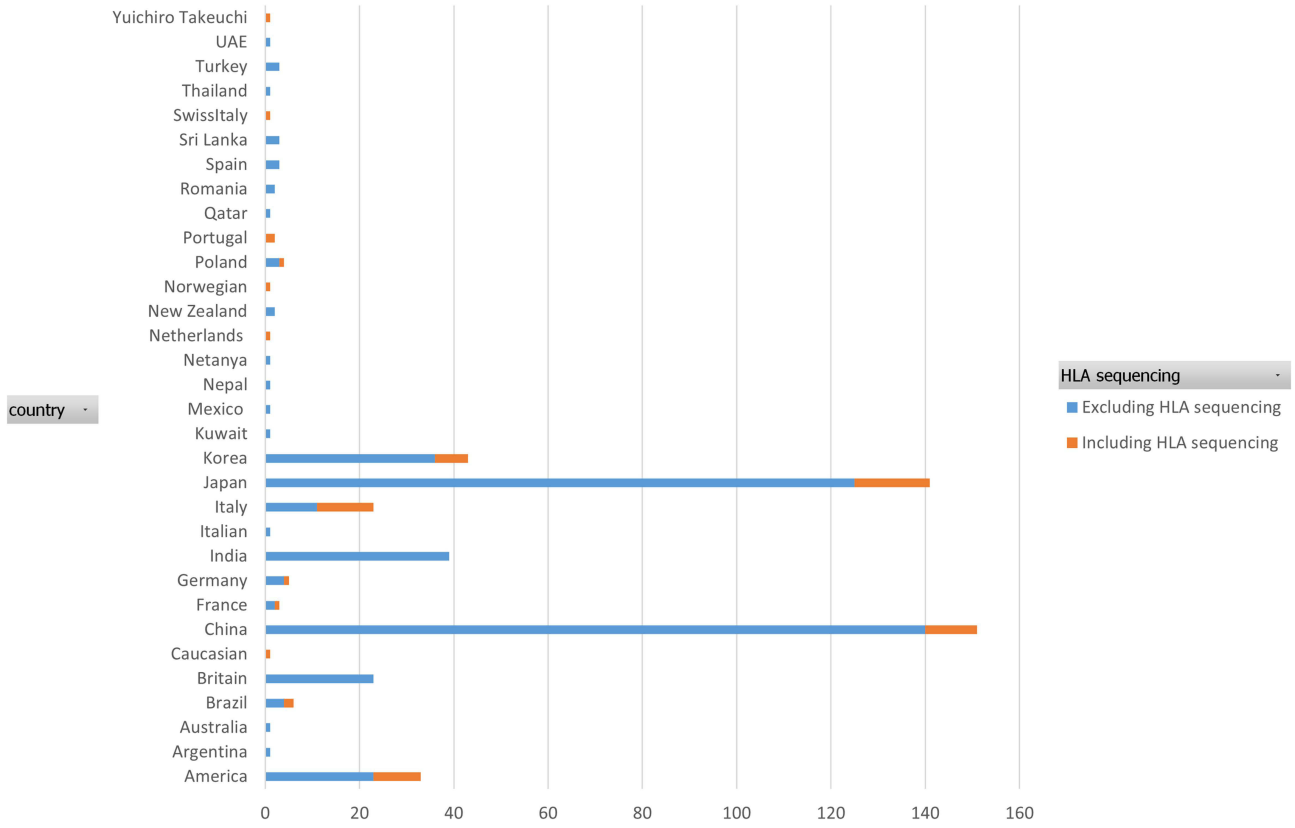

Figure 3 Excluding HLA sequencing and including HLA sequencing in various countries.

Regional Distribution and Linkage of Different HLA Subtypes

Among the 68 patients (Table 1), the HLA-DRB1 sequence revealed that 59 cases were DRB1 *04 (DR40, and 2 cases were DRB1 *03 (DR3), with DR4 being predominant. All cases reported in Japan and China had DRB1 as DR4; Out of the 12 reported cases in Italy, 10 were DR4; Out of the 10 reported cases in the America, 7 were DR4; and out of the 7 reported cases in Korea, 6 were DR4 (Figure 4). Although there are 14 subtypes of DR4,[54] only 8 subtypes were observed in 68 patients. DRB1 *0406 (26 cases, mainly in East Asian countries) (Figure 5) and DRB1 *0403 (18 cases, mainly in non-East Asian countries) (Figure 6) were the most reported, followed by DRB1 *0404 (3 cases) and DRB1 *0405 (3 cases).

Out of 68 patients, 25 underwent HLA-DQB1 sequencing, with the dominant subtypes being DQB1 *0302 (10 cases) and DQB1 *0301 (5 cases), mainly distributed in Japan, China, and Korea (Figure 7). There were 6 cases of association between DRB1 *0406 and DQB1 *0302, accounting for 6/13, and 4 cases of association between DRB1 *0406 and DQB1 *0901, accounting for 4/13, all found in China, Korea, and Japan. Among the 14 patients sequenced for HLA-DQA1, DQA1 *0301 was mainly identified in Japan and Italy (Figure 8).

Drug Correlation Induced by Different HLA- DRB1 Subtypes

In a cohort of 26 DRB1 *0406 patients, 11 were induced by methimazole, 5 by α-lipoic acid, 4 by clopidogrel, and 5 cases had unspecified inducing drugs. Other inducers included 1 case each of penicillin G, albumin, gold thioglucose granulomas, health supplements, and lipoprotein sodium, each with 1 case. Among 18 DRB1 *0403 patients, 12 were induced by α-lipoic acid, 3 by clopidogrel, and 3 had no clear inducing drug. In the DRB1 *0405 group, three patients had different triggers: one by exogenous insulin, one by methimazole, and one unspecified. Of the 3 DRB1 *0401 patients, 2 had unclear inducing drugs, and 1 was induced by α-lipoic acid.

The HLA-DRB1 alleles related to methimazole induction include DRB1 *0406 (11 cases) and DRB1 *0405 (1 case), mainly in China, Japan, and Korea (Table 2). α-lipoic acid-related HLA-DRB1 alleles are DRB1 *0403 (12 cases),

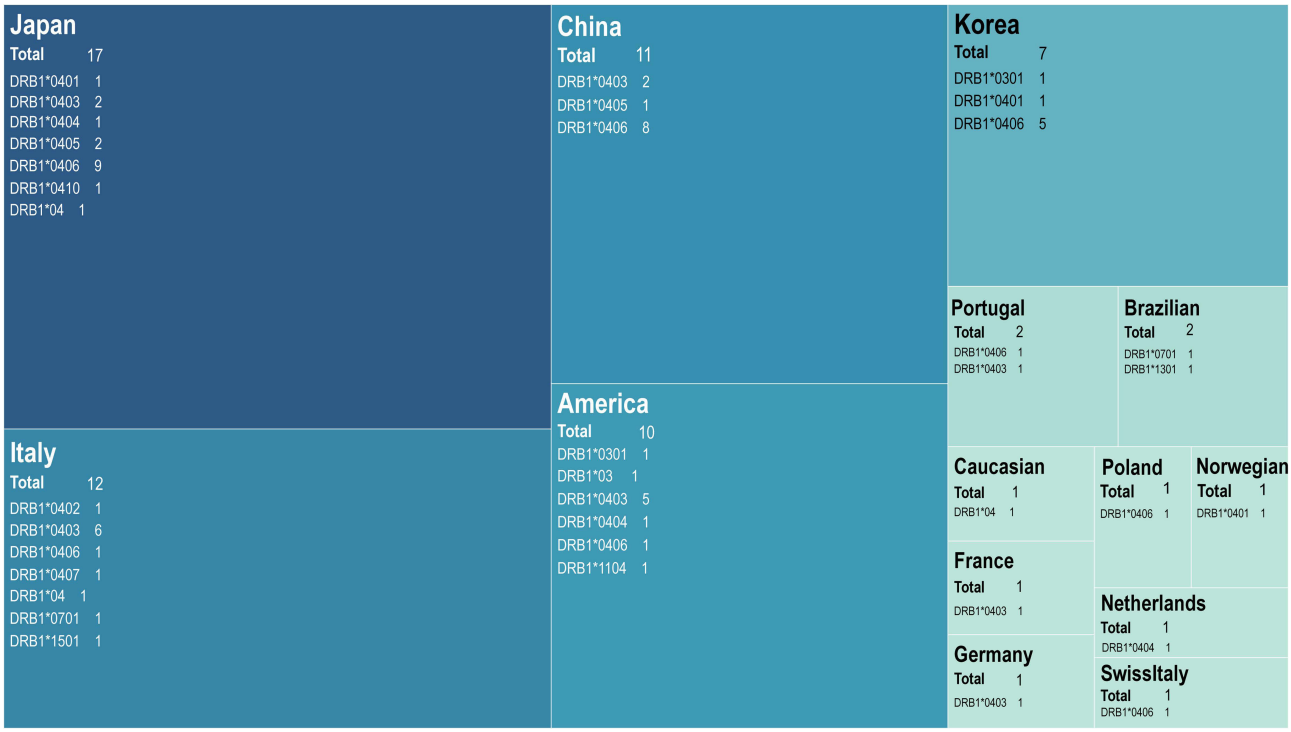

Figure 4 Distribution of DRB1 in different countries.

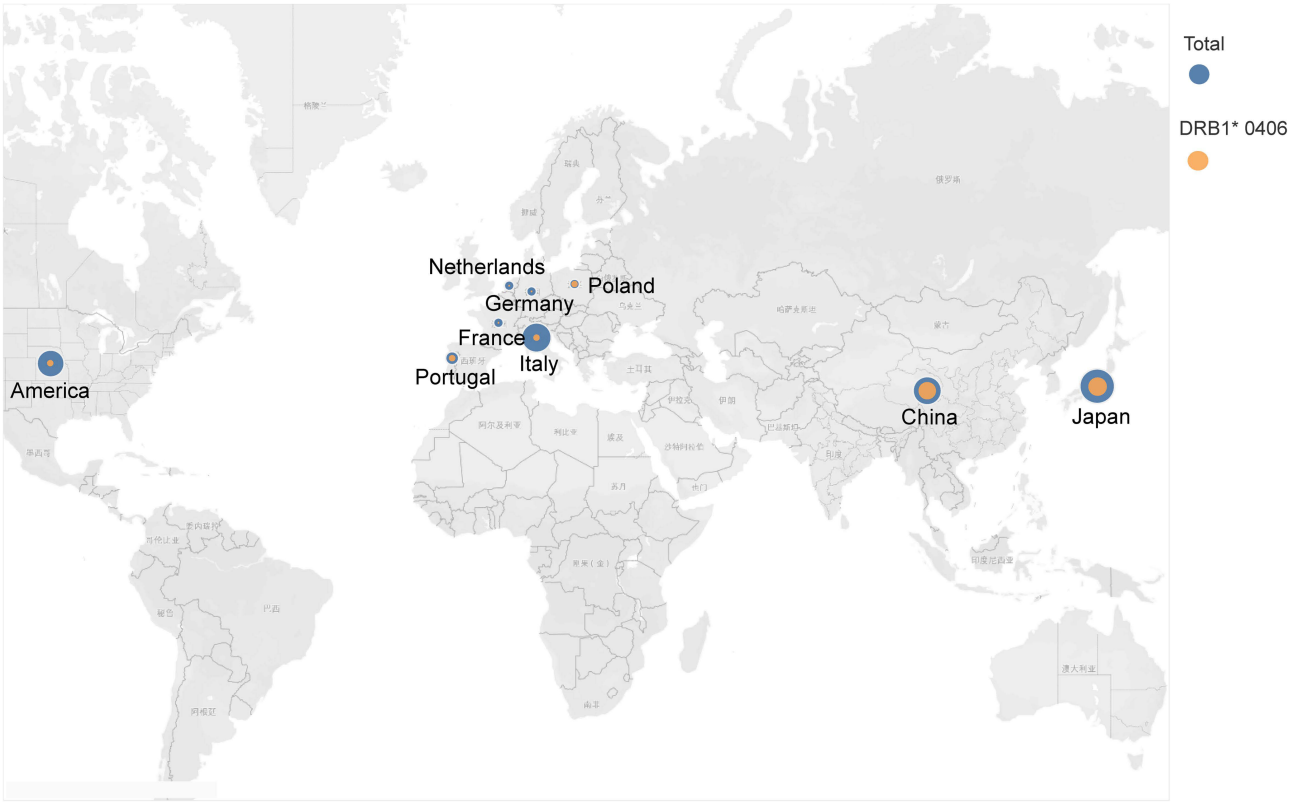

Figure 5 Distribution of IAS patients in different countries and the proportion of DRB1 *0406.

Figure 6 Distribution of IAS patients in different countries and the proportion of DRB1 *0403.

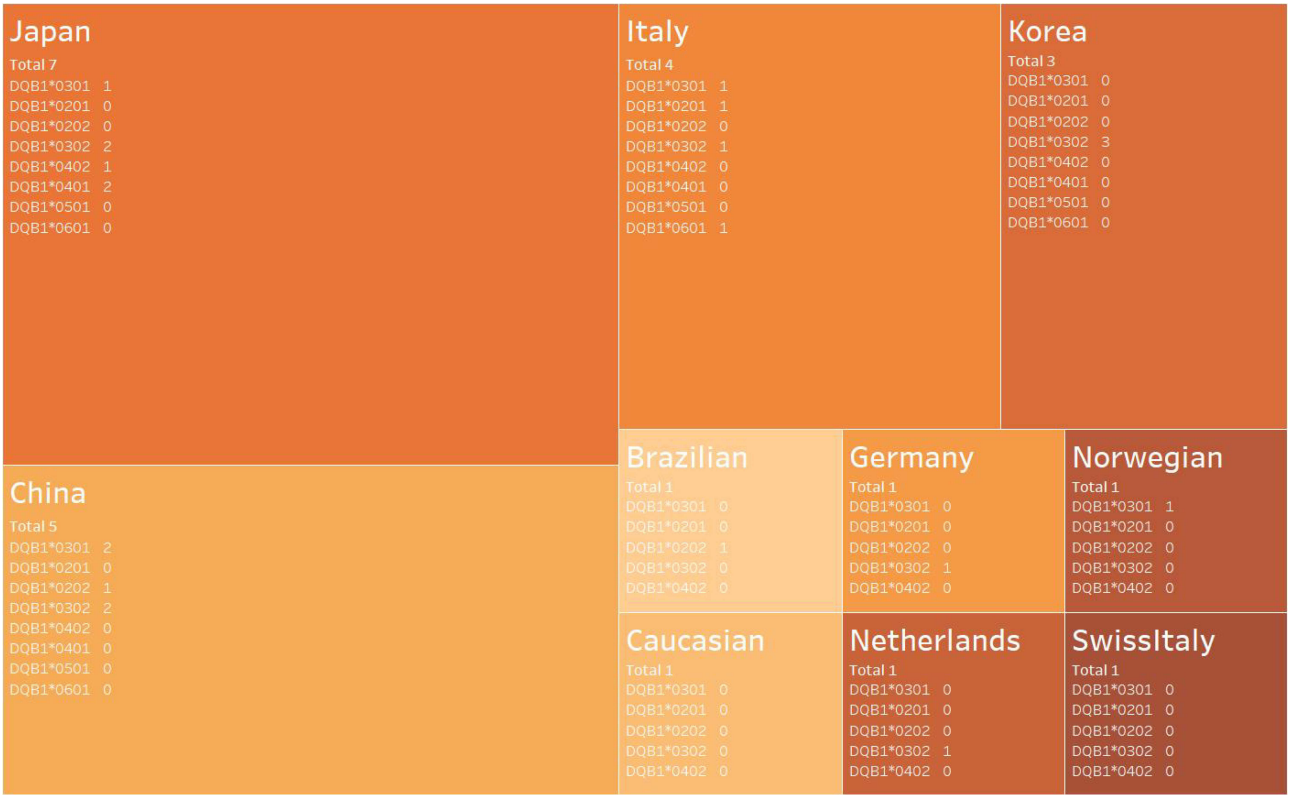

Figure 7 Distribution of DQB1 in different countries.

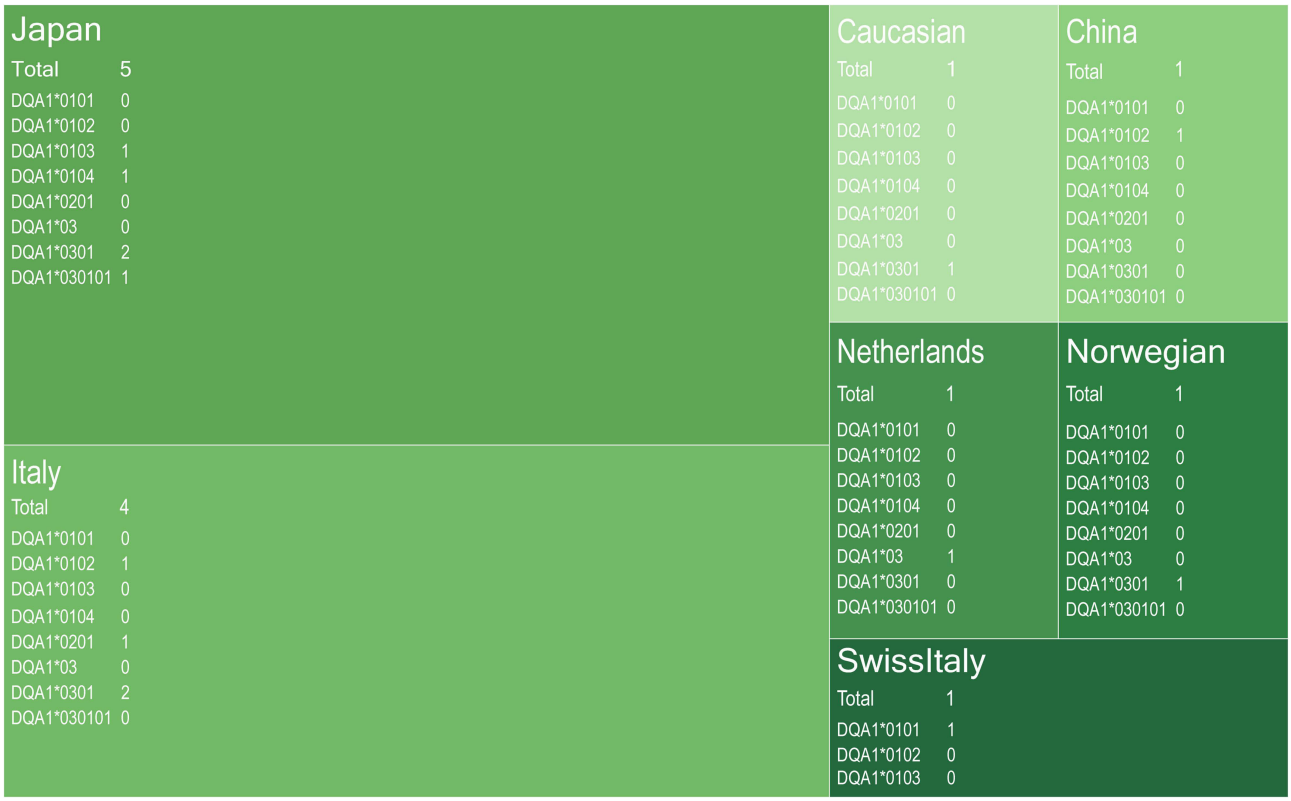

Figure 8 Distribution of DQA1 in different countries.

predominantly in the America and Italy; DRB1 *0406 (5 cases), sporadically; and DRB1 *0401 (1 case) in Korea (Table 3). The HLA-DRB1 alleles linked to clopidogrel induction are DRB1 *0403 (3 cases) in China and France, and DRB1 *0404 (1 case) in the America (Table 4). Other drugs have been associated with sporadic reports.

The Association Between Different HLA Subtypes and Gender

Among the 26 DRB1 *0406 patients, gender was not reported in 5 cases. Of the remaining cases, 17 were female, and 4 were male. All 3 cases with DRB1 *0405 were male. For the three DRB1 *0401 patients, one did not report gender, and two were female. Although there is a higher prevalence of females in DRB1 *0406 patients and all DRB1 *0405 patients are male, suggesting some gender bias, the small sample size limits the accuracy of these observations. Further research with larger sample sizes is necessary to better understand the relationship between genetic differences and gender.

Table 2 Methimazole and HLA Typing

	Methimazole	Methimazole & Captopril	Total
DRB1 * 0405	1	0	**1**
China	1	0	–
DRB1 * 0406	10	1	**11**
China	6	0	–
Japan	2	0	–
Korea	2	0	–
Poland	0	1	–
Total	**11**	**1**	**12**

Table 3 α-Lipoic Acid and HLA Typing

	Quinapril+α-Lipoic Acid	α-Lipoic Acid	Total
DRB1 * 04	0	1	**1**
Italy	0	1	–
DRB1 * 0401	0	1	**1**
Korea	0	1	–
DRB1 * 0403	1	11	**12**
America	0	5	–
Germany	1	0	–
Italy	0	5	–
Japan	0	1	–
DRB1 * 0406	0	5	**5**
America	0	1	–
China	0	1	–
Italy	0	1	–
Korea	0	1	–
Japan	0	1	–
Total	**1**	**18**	**19**

Table 4 Clopidogrel and HLA Typing

	Clopidogrel
DRB1 * 0403	–
China	2
France	1
DRB1 * 0404	–
America	1
Total	**4**

Discussion

IAA is detected in individuals or animals who have not been given exogenous insulin. The presence of both IAA positivity and hypoglycemia characterizes IAS. However, IAA is also found in type 1 diabetes patients treated with exogenous insulin. Scatchard analysis indicates that the IA detected in patients differs from the IA associated with exogenous insulin injection in diabetes patients, but matches the insulin autoantibodies found in IAS patients.[4] This syndrome can occur spontaneously or after exposure to drugs such as methimazole, penicillamine, and α-mercaptopropionyl ester, all of which contains thiol group. However, cases of IAS induced by drugs without thiol groups, such as albumin, have also been reported (albumin).[16]

A survey on DR4 allele prevalence revealed that DRB1 *0406 is more prevalent common among the Han and Manchu populations in Japan, Korea, and northern China, while DRB1 *0403 is more prevalent in Europe, America, the Pacific islands, and other regions, with a lower occurrence of DRB1 *0406. This partially explains the regional differences in IAS incidence.[55] The influence of HLA-II genes is highly polymorphic and related to immune system recognition. The high polymorphism of DRB1, which encodes the DR β chain, accounts for the variations in immune responses of different individuals to different antigens.[54] The combination of allele variations ultimately determines the risk of disease.[2] Among the 14 patients tested by DQA1 in this study, 8 were DQA1 *0301, all of whom were linked to DR4; 5 cases showed a DQA1 *0301/DQB1 *0302 linkage, indicating a strong correlation between DRB1 *04/DQA1

*0301/DQB1 *0302 and IAS. However, DQA1 *0301 may not be essential, as it is also associated with the DRB1 *0405 and DQB1 *0401 combination. Despite its high prevalence among Japanese DR4 positive individuals, no IAS cases with this haplotype have been reported. Therefore, DQB1 *0302 remains a potential factor influencing IAS development.[3]

The microenvironment can also impact the imbalanced expression of HLA-DQA1 alleles.[56] IAS can be induced by exposure to viruses and drugs, with the proposed mechanism suggesting that viral infection acts as a superantigen, triggering the production of IAA, which leads to IAS. Theoretically, drugs with thiol groups can interact with insulin's disulfide bonds, potentially forming cysteine or causing structural changes in insulin molecules, making them immunogenic.[57] In this study of 68 patients, 22 did not report any specific triggering drugs. The spontaneous occurrence of IAS is mainly observed in Japan and appears to be rare in Western countries. It is suggested that cases labeled as spontaneous may actually result from unrecognized triggering factors.[3]

We observed distinct differences in IAS induction by various drugs. Reports indicate that all Japanese IAS patients exposed to methimazole carry DRB1 *0406.[58] In our study, among 12 methimazole-induced IAS cases, 11 were DRB1 *0406 and 1 was DRB1 *0405, showing a significant genetic bias. Although there are instances of alleles other than DRB1 *0406, when Graves disease patients with the Bw62/Cw4/DR4 haplotype carry DRB1 *0406, there is a high likelihood of developing IAS following methimazole treatment.[58] Only 3 out of these 12 patients underwent HLA class I classification testing, showing no notable link with the inducing drug. The HLA-DRB1 alleles linked to α-lipoic acid induction are predominantly DRB1 *0403 and DRB1 *0406. Therefore, individuals with DRB1 *0403 who consume α-lipoic acid may face higher risk of IAS compared to those not exposed to α-lipoic acid,[59] Most DRB1 *0403 carriers are found in non-Asian countries. HLA-DRB1 alleles related to clopidogrel induction are mainly DRB1 *0403*0. Despite clopidogrel-induced HLA-DRB1 alleles being the same as those induced by lipoic acid, there is no apparent clustering in their national distribution. It can be inferred that methimazole, associated with the DRB1 *0406 gene, is the predominant IAS-inducing drug in Asian countries. In non-Asian countries, α-lipoic acid is the main IAS-inducing drug, related to DRB1 *0403.

Among the 68 IAS patients, one case, induced by exogenous insulin necessitates careful distinction: anti-insulin antibodies are classified into two types those associated with exogenous insulin (insulin antibodies, IA) and those linked with the autoimmune system (insulin autoantibodies, IAA). The latter can sometimes be observed in type 1 diabetes patients before and/or shortly after onset and in IAS patients. Differentiating between IAA and IA subtypes using phage display technology[60] remains limited in clinical application and cannot be reliably used for distinction. Clinically, inferences are primarily made based on medical history and clinical manifestations. Patients with Exogenous Insulin-Induced Endogenous Insulin Antibody Syndrome (EIAS) have a history of insulin exposure, characterized mainly by hyperinsulinemia, significant blood sugar fluctuations, and less hypoglycemia due to affinity antibodies. The genetic background common to both EIAS and IAS cases, and the mechanism differentiating endogenously induced IAA from exogenously induced IA, remains unclear. Alleles such as DR7, DR4, and/or B15 predispose individuals to produce IA in response to exogenous insulin, while B8 and/or DR3 exhibit a protective effect.[61,62] The case under discussion presents one of the IAA formation and IAS susceptibility phenotypes, HLA-DR4. However, its molecular type is not DRB1 *0406 but DRB1 *0405, with molecular alleles DRB1 *0405/1302 and DQB1 *0401/*0604. DRB1 *0405 is typically seen in type 1 diabetes patients and appears to confer some protection against IAS.[54] Further research is necessary to verify the regulation mechanisms of IA or IAA, including the DRB1 molecule and other HLA-related factors.[4] The assertion that exogenous insulin induces IAS is subject to investigation.

The article also notes a gender disparity: female patients dominate in the DRB1 *0406 group, while all DRB1 *0405 patients are male. Whether this gender bias holds significant meaning requires further investigation.

Conclusion

In IAS patients, HLA typing indicates that the majority are DRB1 *04 (59/68), with DRB1 *0406 and DRB1 *0403 being the most common. DRB1 *0406 is prevalent in the East Asian population, where methimazole is the main inducing drug, while DRB1 *0403 is found in the Caucasian population, with α-lipoic acid and clopidogrel being the primary inducing drugs. The combination of these allele variants ultimately determines the disease risk, with DRB1 *04/DQA1

*0301/DQB1 *0302 showing the strongest correlation with IAS occurrence. It is essential to differentiate the diagnosis of IAS patients who have undergone insulin therapy from exogenous insulin antibody syndrome.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Medical Health Group of Xiangshan County Traditional Chinese Medicine Hospital (No. P2024-SL-603).

Disclosure

The authors report no conflicts of interest in this work.

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