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Review

Genetics of immunoglobulin-A vasculitis (Henoch-Schönlein purpura): An updated review

Raquel López-Mejías [a,*], Santos Castañeda [b], Fernanda Genre [a], Sara Remuzgo-Martínez [a], F. David Carmona [c,d], Javier Llorca [e], Ricardo Blanco [a], Javier Martín [c], Miguel A. González-Gay [a,f,g,*]

[a] Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain
[b] Division of Rheumatology, Hospital Universitario de la Princesa, IIS-IPrincesa, Madrid, Spain
[c] Instituto de Parasitología y Biomedicina 'López-Neyra', CSIC, PTS Granada, Granada, Spain
[d] Departamento de Genética e Instituto de Biotecnología, Universidad de Granada, Granada, Spain
[e] Division of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain
[f] School of Medicine, University of Cantabria, Santander, Spain
[g] Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

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ABSTRACT

Immunoglobulin-A vasculitis (IgAV) is classically a childhood small-sized blood vessel vasculitis with predominant involvement of the skin. Gastrointestinal and joint manifestations are common in patients diagnosed with this condition. Nephritis, which is more severe in adults, constitutes the most feared complication of this vasculitis. The molecular bases underlying the origin of IgAV have not been completely elucidated. Nevertheless, several pieces of evidence support the claim that genes play a crucial role in the pathogenesis of this disease. The human leukocyte antigen (HLA) region is, until now, the main genetic factor associated with IgAV pathogenesis. Besides a strong association with HLA class II alleles, specifically *HLA-DRB1* alleles, HLA class I alleles also seem to influence on the predisposition of this disease. Other gene polymorphisms located outside the HLA region, including those coding cytokines, chemokines, adhesion molecules as well as those related to T-cells, aberrant glycosylation of IgA1, nitric oxide production, neoangiogenesis, renin-angiotensin system and lipid, Pyrin and homocysteine metabolism, may be implicated not only in the predisposition to IgAV but also in its severity. An update of the current knowledge of the genetic component associated with the pathogenesis of IgAV is detailed in this review.

Abbreviations: AAV, antineutrophil cytoplasmic antibody associated vasculitis; ACE, angiotensin-converting enzyme; Agt, angiotensin; ANCA, antineutrophil cytoplasmic antibody; AT1R, angiotensin II receptor type 1; AT2R, angiotensin II receptor type 2; CCL2, chemokine C-C motif ligand 2; CCL5, chemokine C-C motif ligand 5; CD, cluster of differentiation; CD152, cluster of differentiation 152; CD282, cluster of differentiation 282; CD284, cluster of differentiation 284; CSK, SH3 of c-src tyrosine kinase; CTLA-4, cytotoxic T lymphocyte-associated protein 4; CXCL5, the C-X-C motif chemokine 5; C1GALT1, core 1 synthase glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase 1; C4, complement component 4; ELAM-1, endothelial leukocyte adhesion molecule-1; ENA-78, epithelial-derived neutrophil-activating peptide 78; eNOS, endothelial nitric oxide; FVL, factor V Leiden; GCA, giant cell arteritis; GI, gastrointestinal; GWAS, genome-wide association studies; HDL, high density lipoprotein; HLA, human leukocyte antigen; Hsp70s, 70 kDa heat shock proteins; HSPA2, 70 kDa heat shock protein member 2; ICAM1, intercellular adhesion molecule 1; IFN, interferon; IFNG, interferon gamma; IgA1, immunoglobulin A1; IgAN, immunoglobulin nephropathy; IgAV, immunoglobulin A vasculitis; IL, interleukin; IL-1, interleukin 1; IL-1β, interleukin 1 beta; IL-1ra, interleukin 1 receptor antagonist; IL-6, interleukin 6; IL-6R, IL-6 receptor subunit; IL-6ST, interleukin 6 signal transducer; IL-8, interleukin 8; IL-18, interleukin 18; iNOS, inducible nitric oxide synthase; Lyp, lymphoid-specific phosphatase; MASP, mannose binding lectin associated serine protease; MBL, mannose binding lectin; MCP-1, chemokine monocyte chemoattractant protein-1; MEFV, mediterranean fever; MIF, migration inhibitory factor; MTHFR, methylenetetrahydrofolate reductase; nNOS, neuronal nitric oxide; NO, nitric oxide; NOS, nitric oxide synthases; NOS1, nitric oxide synthase 1; NOS2, nitric oxide synthase 2; NOS2A, nitric oxide synthase 2A; NOS3, nitric oxide synthase 3; NPHS2, nephrosis 2, idiopathic, steroid-resistant (Podocin); PAX2, paired box 2; PON1, paraoxonase1; PTP, protein tyrosine phosphatase; PTPN22, protein tyrosine phosphatase 22; RANTES, regulated upon activation normal T cell expressed and secreted; RAS, Renin-angiotensin; SELE, selectin E; SELP, selectin P; TGF-β, transforming growth factor beta; TGFB1, transforming growth factor beta 1; Th 1, T-helper 1; TLR, toll-like receptor; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TNF, tumor necrosis factor; TNFA, tumor necrosis factor alpha; UG, Uteroglobin; UTR, untranslated region; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial growth factor A; VNTR, variable number tandem repeats.

* Corresponding authors at: Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Avenida Cardenal Herrera Oria, s/n, Lab. 201/202, 39011, Santander, Spain.
E-mail addresses: rlopezmejias78@gmail.com (R. López-Mejías), miguelaggay@hotmail.com (M.A. González-Gay).

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Contents

1. Introduction

Immunoglobulin-A vasculitis (IgAV), formerly called Henoch-Schönlein purpura, is an inflammatory vascular disease that affects small blood vessels, predominantly capillaries, venules, or arterioles, with IgA1-dominant immune deposits [1–12].

IgAV is classically a childhood disease [1–3, 6, 7, 9, 11–13] with an incidence of about 10 cases per 100,000 a year [2, 12, 14–17]. The pediatric form of this pathology is generally considered benign and self-limited [2, 6, 18, 19]. In contrast, IgAV in adults is less common but often associated with worse clinical course and outcome [1, 2, 5, 6, 12, 13, 20].

IgAV typically involves the skin and gastrointestinal (GI) tract and, frequently, affects the joints [1–3, 5–7, 9–13, 18, 21–23]. Skin involvement is considered the main clinical feature of this disease [1, 5, 11–13, 18, 22, 24, 25]. It consists of symmetric erythematous petechiae or papules on the buttocks and lower extremities, which evolve to a typical palpable purpura [11, 24]. Other skin lesions may be observed in patients with this pathology [2, 11]. GI symptoms are common in IgAV [3, 5]. These manifestations encompass colicky abdominal pain that may mimic an acute abdomen associated with nausea and vomiting [2, 3, 5, 26–28], symptoms of bowel angina and GI bleeding [1–3, 12, 28–31] manifested as melena or hematemesis sometimes with in some cases may lead to massive hemorrhage [1, 3, 5, 28]. Joint involvement includes arthralgias [1, 3, 13] or arthritis [1, 2, 28, 32] that often affect knees and ankles [1, 3, 20, 28] and may precede the development of palpable purpura in many cases [1, 2, 16, 28, 33].

Besides the classic clinical triad mentioned above, IgAV frequently affects kidneys [1–3, 5–7, 9–13, 18, 21–23]. Nephropathy is generally characterized by hematuria with or without proteinuria [1, 18]. Some cases may present severe renal involvement characterized by the presence of nephrotic or nephritic syndrome [1, 18]. Several reports have confirmed that nephritis and especially severe renal involvement occurs most commonly in adults [1–3, 5, 7, 9–11, 13, 18, 34]. In this regard, nephritis constitutes the most serious feature of IgAV that may lead in some cases to end-stage kidney disease [1–3, 5–7, 9–13, 18, 35, 36]. Because of that, the long-term morbidity and mortality of this pathology are almost completely due to renal complications [1, 9, 13, 18, 34, 37].

Since the last decade of the past century, several authors have tried to determine the mechanisms implicated in the pathogenesis of IgAV. However, the etiology of this vasculitis has not been completely elucidated [1, 3, 18, 38]. Numerous pieces of evidence support the claim that genetics is crucial in the pathogenesis of IgAV [1, 6, 18, 38–40]. In addition, precipitating events, such as upper respiratory tract infections [1, 3, 5, 13, 16, 41–48] and drug intake [1–3, 5, 20, 41, 42], may modulate the incidence and severity of this vasculitis in those individuals genetically predisposed.

An overview of the main studies addressing the genetic background of IgAV susceptibility and/or severity is detailed throughout this review. In addition, a concise summary of these studies is shown in Tables 1 and 2, respectively.

2. Genetics in the pathogenesis of IgAV

2.1. Overview aspects of genetics in IgAV

Genes play a key role in IgAV [5, 6, 38, 39, 40]. Significant geographic and ethnic differences in the prevalence of this disease speak in favor of this fact [49, 50]. Asians show a relatively higher incidence of IgAV than Caucasian individuals [50] while black population exhibits the lowest incidence rate of this pathology [49, 50]. In addition, the increased IgAV risk described among first degree relatives of affected patients [6] as well as familial aggregation strengthen the hypothesis that genetic factors are essential in the pathogenesis of this disorder [6, 51, 52].

According to these considerations, much effort has been carried out to identify the genetic background of IgAV. Until recently, most genetic studies performed in this field were designed as candidate gene studies in which a specific polymorphism or a set of genetic variants within certain loci was genotyped. These polymorphisms were selected according to their potential biological function or their location in a region previously reported as associated with the disease. Alternatively to candidate gene studies, large-scale studies using high-throughput genotyping techniques have become the priority approach to unravel the genetic component of IgAV during the last years.

Overall, the results derived from these studies evidence that the genetic component implicated in the pathogenesis of IgAV is complex, probably as a result of gene–gene interactions in which the specific role of a single gene is small.

2.2. Human leukocyte antigen (HLA) genes in IgAV

HLA region includes a group of genes located in chromosome 6 (6p21) that encode the most polymorphic human proteins, class I and class II antigen-presenting molecules [53]. Accordingly, HLA is the main genetic factor implicated in inflammatory immune-mediated pathologies, being associated with more diseases than any other region of the human genome [54].

In relation to the HLA class I region, the influence of *HLA-B* on IgAV pathogenesis has been a matter of debate [55–60]. Whereas a lack of association of this gene with IgAV susceptibility was suggested in small cohorts of Europeans [55, 58], a recent well-powered study revealed a susceptibility effect of *HLA-B* in Caucasian patients, identifying the *HLA-B*4102* as a potential etiological allele [56]. Also, *HLA-B*7, HLA-B*15, HLA-B*35, HLA-B*40* and *B*52* [60] as well as *HLA-B*35, HLA-B*49* and *HLA-B*50* [59] were postulated as alleles involved in IgAV predisposition in Asians and Turks, respectively. Regarding IgAV severity, *HLA-B*35* was proposed as a risk allele for renal damage in small series of

Table 1
Genetic association studies assessing IgAV susceptibility.

Gene	Results
HLA-B	• No association [55, 58]. • *HLA-B*7* ↓ susceptibility [60]. • *HLA-B*15* ↑ susceptibility [60]. • *HLA-B*35* ↑ susceptibility [59, 60]. • HLA-B*40 ↓ susceptibility [60]. • *HLA-B*4102* ↑ susceptibility [56]. • *HLA-B*49* ↓ susceptibility [59]. • *HLA-B*50* ↓ susceptibility [59]. • *HLA-B*52* ↑ susceptibility [60].
HLA-A	• No association [58]. • *HLA-A*1* ↓ susceptibility [59]. • *HLA-A*2* ↑ susceptibility [59]. • *HLA-A*11* ↑ susceptibility [59, 60]. • *HLA-A*26* ↑ susceptibility [60].
HLA-C	• No association [58].
HLA-DRB1	• No association [61, 65]. • *HLA-DRB1*01* ↑ susceptibility [62–64] due to the *HLA–DRB1*0103* allele [64]. • *HLA-DRB1*03* ↓ susceptibility [64]. • *HLA-DRB1*07* ↓ susceptibility [62, 63]. • *HLA-DRB1*11* ↑ susceptibility [63].
HLA-DQA	• No association [63]. • *HLA-DQA1*0301* ↑ susceptibility [66].
HLA-DQB	• No association [63].
C4	• Involved in IgAV susceptibility [66, 68].
TNFA	• rs1800629-308 A allele ↑ susceptibility [73]. • No association of rs1800629 −308 [G/A] [74, 75].
HSPA2	• 1267 GG genotype ↑ susceptibility [73].
IL6	• No association of rs1800795 −174 [G/C] [89, 90]. • No association of rs2069827 [G/T] [90]. • No association of rs2069840 [C/G] [90].
IL6R	• No association of rs2228145 [A/C] [99].
IL6ST	• No association of rs2228044 [C/G] [99].
IL1ß	• No association of rs16944 −511 [C/T] [105, 106].
IL1ra	• No association of *IL1RN*2* [112].
IL18	• rs187238 −137 G allele ↑ susceptibility [114]. • No association of rs1946518 −607 [C/] [114]. • No association of rs360719 −1297 [T/C] [114].
IFNG	• No association of rs2430561 + 874 [A/T] [122].
TGFB1	• rs1800469 −509 TT genotype ↑ susceptibility [75].
MIF	• No association of −173 [G/C] [132, 133].
IL8	• No association of 2767 [G/A] [136, 137].
CXCL5	• No association of rs352046 −156 [G/C] [136].
CCL5	• No association of rs2107538 −403 [G/A] [136, 141]. • No association of rs2280788 −28 [C/G] [141].
MCP1	• −2518 TT genotype and −2518 T allele ↑ susceptibility [141, 147].
SELP	• −2123 GG genotype and −2123 G allele↑ susceptibility [153]. • No association of −825 [152].
SELE	• No association of 561 [A/C] [156].
ICAM1	• No association of 241 R/G [160]. • No association of 469 K/E [160].
Agt	• rs4762 T174M-T allele ↑ susceptibility [165]. • No association of rs699 M235T [C/T] [165, 167]. • rs699 M235T-M allele ↓ susceptibility whereas rs699 M235T-TT genotype ↑ in adults [166]. • rs699 M235T-MT, rs699 M235T-TT and rs699 M235T-T ↑ susceptibility in children [168].
AT1R	• No association of 1166 [A/C] [165, 168].
ACE	• No association of I16D [179]. • I6D-D ↑ susceptibility [165, 181]. • I6D-DD ↑ susceptibility [167, 182]. • I6D-ID/DD ↑ susceptibility [168]. • I6D-ID+DD ↑ susceptibility [181].
TLR2	• No association of Arg753Gln [189].
TLR4	• No association of rs4986790 896 [A/G] [189, 191]. • No association of Thr399Ile [189].
MBL	• No association of rs1800450 [A/B] [195].
PTPN22	• No association of rs2476601 [G/A] (R620W) [204, 205]. • No association of rs33996649 [C/T] (R263Q) [205].
CSK	• No association of rs34933034 [G/A] [205]. • No association of rs1378942 [A/C] [205].
PAX2	• No association of 1410 [C/T] [209]. • No association of 1521 [A/C] [209]. • No association of 1544 [C/T] [209]. • No association of 798 [C/T] [210].
CTLA4	• No association of 909 [A/C] [210]. • No association of 164 [T/A] [210]. • No association of 49 [A/G] [65, 227].
C1GALT1	• rs5882115 −292 DI and II genotypes ↑ susceptibility [235]. • No association of rs9639031 −734 [C/T] [235]. • No association of rs73045773 −465 [A/G] [235]. • No association of rs1008898 −330 [G/T] [235]. • No association of rs1047763 1365 [G/A] [235].
UG	• No association of 38 [A/G] [242].
VEGFA	• No association of rs1570360 −1154 [GA] [249]. • No association of rs2010963 −634 [G/C] [249, 250].
NOS2A	• CCTTT repeat ↑ susceptibility [258].
eNOS	• No association of VNTR in intron 4 [256]. • No association of 5557 [G/T] [256]. • No association of −786 [T/C] [256, 257]. • No association of 894 [G/T] [257]. • 894 T allele and GG genotype ↑ susceptibility [259].
PON1	• 192 QQ genotype ↑ susceptibility [265]. • 55 MM genotype ↓ susceptibility [265].
MEFV	• M694V↑ susceptibility [269, 273, 274]. • M694V↓ susceptibility [268, 270, 271]. • E148Q ↑ susceptibility [272]. • E148Q ↓ susceptibility [269, 274]. • No association of E148Q [268, 270, 271]. • V726A ↑ susceptibility [275]. • No association of V726A [268–271, 273, 274]. • No association of M694I [268, 269, 271, 275]. • No association of K695R [268, 269, 271, 275]. • No association of M680I [268, 274]. • No association of P369S [268, 269, 272, 275]. • No association of A744S [268, 269, 273, 275]. • No association of L110P [270]. • No association of F479L [268, 269, 275]. • No association of R761H [268, 269, 275]. • No association of I692del. [268, 269, 275].
FVL	• No association of 1691 [G/A] [281].
Prothrombin	• No association of 20210 [G/A] [281].
MTHFR	• No association of rs1801133 677 [C/T] [281, 285].

IgAV: Immunoglobulin A vasculitis; HLA: human leukocyte antigen; *C4: complement component 4; TNFA: tumor necrosis factor alpha; HSPA2: 70 kDa heat shock protein member 2*; *IL6: interleukin 6; IL6R: interleukin 6 receptor; IL6ST: interleukin 6 Signal Transducer; IL1ß: interleukin 1 ß; IL1ra: interleukin 1 receptor antagonist; IL18: interleukin 18; IFNG: interferon-gamma*; *TGFB1: transforming growth factor beta 1*; *MIF: macrophage migration inhibitory factor; IL8: interleukin 8; CXCL5: C-X-C motif chemokine 5; CCL5: chemokine (C-C motif) ligand 5; MCP1: chemokine monocyte chemoattractant protein 1; SELP: selectin P; SELE: selectin E; ICAM1: intercellular adhesion molecule 1; Agt: angiotensin; AT1R: angiotensin II receptor, type 1; ACE: angiotensin-converting enzyme; TLR2: toll-like receptor 2; TLR4: toll-like receptor 4; MBL: mannose binding lectin; PTPN22: protein tyrosine phosphatase nonreceptor 22; CSK: c-src tyrosine kinase; PAX2: paired box 2; CTLA4: cytotoxic T lymphocyte-associated protein 4; C1GALT1: glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1; UG: uteroglobin; VEGFA: vascular endothelial growth factor A; NOS2A: nitric oxide synthase 2; eNOS: endothelial nitric oxide synthase;* VNTR: variable-number tandem-repeat polymorphism; *PON1: paraoxonase1; MEFV: mediterranean fever; FVL: factor V Leiden; MTHFR: methylentetrahydrofolate reductase.*

patients from Spain [55] and UK [57] whereas *HLA-B*44, HLA-B*56* and *HLA-B*58* were related to a poor outcome in Turks [59]. By contrast, negative results regarding the severity of the disease were obtained in Germans [58] and in the largest cohort of Caucasian patients ever assessed for genetic studies [56].

Other genes located in the HLA class I region were tested with respect to IgAV [58–60]. In this regard, whereas no implication of *HLA-A* and *HLA-C* in the susceptibility and/or severity of the disease was found in children from Denmark [58], *HLA-A*1, HLA-A*2* and *HLA-A*11* [59] as well as *HLA-A*11* and *HLA-A*26* [60] were described as alleles implicated in the susceptibility of IgAV in Turks and Asians, respectively. In addition, *HLA-A*1* and *HLA-A*3* were associated with worse clinical features in patients from Turkey [59].

With respect to HLA class II region, different results were obtained when *HLA-DRB1* gene was evaluated in patients with IgAV [61–65]. No relationship between this gene and the predisposition to the disease was detected in children from India [61] and Turkey [65]. Interestingly,

Table 2
Genetic association studies assessing IgAV severity.

Gene	Clinical manifestations	Results
HLA-B	• Age at onset, joint, GI, renal	• No association [56].
	• Nephritis	• No association [58].
	• GI and renal symptoms, RS	• *HLA-B*35* ↑ renal manifestations [55].
	• Nephritis	• *HLA-B*35* ↑ nephritis [57].
	• Skin, joint, GI and renal symptoms	• *HLA-B*44* ↑ joint involvement [59].
	• Joint, GI and renal symptoms	• *HLA-B*56* ↑disease severity [59].
	• Joint, GI and renal symptoms	• *HLA-B*58* ↑disease severity [59].
HLA-A	• Nephritis	• No association [58].
	• Joint, GI and renal symptoms	• *HLA-A*01* ↑ disease severity [59].
	• Joint, GI and renal symptoms	• *HLA-A*03* ↑ joint involvement [59].
HLA-C	• Nephritis	• No association [58].
HLA-DRB1	• GI and renal symptoms	• No association [61].
	• Skin, GI and renal symptoms, RS	• No association [62].
	• Renal symptoms	• No association [63].
	• Age at onset, RS and joint, GI, renal symptoms	• No association [64].
	• Joint, GI and renal symptoms	• *HLA-DRB1*13* ↑ nephrotic proteinuria [65].
HLA-DQA	• Renal symptoms	• No association [63].
HLA-DQB	• Renal symptoms	• No association [63].
TNFA	• Nephritis	• No association of rs1800629 −308 [G/A] [73].
	• Nephritis	• rs1800629 −308 GA genotype and A allele ↑ nephritis [74].
HSPA2	• Nephritis	• No association of 1267 [A/G] [73].
IL6	• Nephritis, renal and GI symptoms	• No association of rs1800795 −174 [G/C] [89].
	• Nephritis, GI symptoms, age at onset	• No association of rs1800795 −174 [G/C] [90].
	• Nephritis, GI symptoms, age at onset	• No association of rs2069827 [G/T] [90].
	• Nephritis, GI symptoms, age at onset	• No association of rs2069840 [C/G] [90].
IL6R	• Nephritis, GI symptoms, age at onset	• No association of rs2228145 [A/C] [99].
IL6ST	• Nephritis, GI symptoms, age at onset	• No association of rs2228044 [C/G] [99].
IL1ß	• Joint, GI and renal symptoms, severe nephropathy, RS	• rs16944 −511 T allele ↑ severe nephropathy [105].
	• Age at onset, renal and GI symptoms, severe nephropathy, RS	• rs16944 −511 TT genotype and T allele ↑ severe nephropathy and RS [106].
IL1ra	• GI and renal symptoms, severe nephropathy, RS	• *ILRN*2* allele ↑ severe nephropathy and RS [112].
	• Nephritis	• *ILRN*2* allele ↑ nephritis [113].
IL18	• Nephritis, GI symptoms	• No association of rs187238 −137 [G/C] [114].
	• Nephritis, GI symptoms	• No association of rs1946518 −607 [C/] [114].
	• Nephritis, GI symptoms	• No association of rs360719 −1297 [T/C] [114].
IFNG	• Nephritis	• No association of rs2430561 +874 [A/T] [122].
TGFB1	• Renal symptoms	• rs1800469−509 TT genotype↑ renal complications [75].
MIF	• Nephritis, GI symptoms, RS	• No association of −173 [G/C] [132].
	• Nephritis, GI and joint symptoms	• No association of −173 [G/C] [133].
IL8	• GI and renal symptoms, RS	• 2767 A allele ↑ renal manifestations [136].
	• Renal symptoms, RS	• 2767 A allele ↑ renal manifestations [137].
CXCL5	• GI and renal symptoms, RS	• No association of rs352046 −156 [G/C] [136].
CCL5	• GI and renal symptoms, RS	• No association of rs2107538 −403 [G/A] [136].
	• GI and renal symptoms	• rs2107538 −403 TC and TT genotype ↑ renal manifestations [141].
	• GI and renal symptoms	• No association of rs2280788 −28 [C/G] [141].
MCP1	• GI and renal symptoms	• No association of −2518 [141].
	• Skin, GI and joint symptoms	• -2518TT ↑ skin lesions, GI complications and joint pain [147].
SELP	• Nephritis	• −825 AA genotype and −825 A allele ↑ renal symptoms [152].
	• Nephritis	• No association of −2123 [153].
SELE	• Nephritis	• No association of 561 [A/C] [156].
ICAM1	• GI and renal symptoms, RS	• No association of 241 R/G [160].
	• GI and renal symptoms, RS	• 469 K/E ↑GI manifestations [160].
Agt	• Joint, GI and renal symptoms	• rs4762 T174M-T allele ↑ joint and GI symptoms [165].
	• Joint, GI and renal symptoms	• rs699 M235T-T allele ↓ severe renal damage [165] .
	• Renal symptoms	• rs699 M235T-TT and rs699 M235T-T ↑ nephritis [168].
	• Nephritis	• No association of rs699 M235T [C/T] [166].
	• Joint, GI and renal symptoms	• No association of rs699 M235T [C/T] [167].
AT1R	• Joint, GI and renal symptoms	• No association of 1166 [A/C] [165].
	• Renal symptoms	• No association of 1166 [A/C] [168].
ACE	• Joint, GI and renal symptoms	• No association of I16D [167].
	• Renal symptoms	• No association of I16D [168].
	• Renal symptoms	• No association of I16D [180].
	• Renal symptoms	• I16D-DD ↑ nephritis [182].
	• Renal symptoms	• I16D-DD ↑ persistent proteinuria [183].
	• Renal symptoms	• I16D-DD ↑ nephritis [185].
	• Joint, GI and renal symptoms	• I16D-D ↑ severity of renal complications [165].
	• Renal symptoms	• I16D-D ↑ nephritis [184].
	• Renal symptoms	• I16D-D ↑ nephritis [186].
TLR2	• Nephritis	• No association of Arg753Gln [189].
TLR4	• Nephritis	• No association of rs4986790 896 [A/G] [189].
	• GI and renal symptoms, RS	• No association of rs4986790 896 [A/G] [191].
	• Nephritis	• No association of Thr399Ile [189].
PTPN22	• GI and renal symptoms, RS	• No association of rs2476601 [G/A] (R620W) [204].
	• Age at onset, sex and joint, GI renal symptoms	• No association of rs2476601 [G/A] (R620W) [205].
	• Age at onset, sex and joint, GI renal symptoms	• No association of rs33996649 [C/T] (R263Q) [205].
CSK	• Age at onset, sex and joint, GI renal symptoms	• No association of rs34933034 [G/A] [205].
	• Age at onset, sex and joint, GI renal symptoms	• No association of rs1378942 [A/C] [205].

Table 2 (*continued*)

Gene	Clinical manifestations	Results
PAX2	• Skin, joint, GI and renal symptoms	• 1410 CT/1521 AC genotype ↑ renal damage [209].
	• Skin, joint, GI and renal symptoms	• No association of 1544 [C/T] [209].
	• Age, gender, joint, GI and renal symptoms	• 798 [C/T]/909 [A/C] ↑ renal manifestations [210].
	• Age, gender and joint, GI, renal symptoms	• No association of 164 [T/A] [210].
NPHS2	• Nephritis	• No association of 954 [T/C] [218].
	• Nephritis	• No association of 1038 [A/G] [218].
CTLA4	• Joint, GI and renal symptoms	• 49 AG genotype ↑ nephrotic proteinuria [65].
	• Renal symptoms	• 49 GG genotype and 49 G allele ↑ renal damage [227].
C1GALT1	• Nephritis	• rs1047763 1365 GG genotype and G allele ↑ nephritis [234].
	• Nephritis	• No association of rs9639031 −734 [C/T] [234].
	• Nephritis	• No association of rs73045773 −465 [A/G] [234].
	• Nephritis	• No association of rs1008898 −330 [G/T] [234].
	• Nephritis	• No association of rs5882115 −292 [C/−] [234].
VEGFA	• GI symptoms, nephritis, RS	• −1154 G allele and -1154G/-634C haplotype ↑ nephritis [249].
	• Nephritis	• -634 CC genotype and −634 C allele ↑ nephritis [250].
NOS2A	• GI symptoms, nephritis, RS	• CCTTT repeat ↑ nephritis [258].
eNOS	• Joint and GI symptoms, nephritis	• No association of VNTR in intron 4 [256].
	• Joint and GI symptoms, nephritis	• No association of 5557 [G/T] [256].
	• Nephritis	• 894 [G/T] ↑ nephritis [257].
	• Joint and GI symptoms, nephritis	• No association of −786 [T/C] [256].
	• Nephritis	• −786 [T/C] ↑ nephritis [257].
	• Meta-analysis	• −786 TT genotype ↑ nephritis [259].
MEFV	• Gender, age at onset, edema and joint, GI renal symptoms	• M694V↑ edema, joint and GI damage [268].
	• Subcutaneous edema and GI, renal, articular, urogenital, neurological, cardiac symptoms	• M694V ↑ urogenital manifestations [269].
	• Age at onset, edema, arthritis	• Patients with M694V were younger and had ↑ frequency of edema and arthritis [274].
	• Gender, age at onset, edema and joint, GI, renal symptoms	• E148Q ↑ edema, joint and GI symptoms [268].
	• Joint and GI symptoms, nephritis	• E148Q ↑ joint manifestations [272].
	• Subcutaneous edema and GI, renal, articular, urogenital, neurological, cardiac symptoms	• No association of M680I, E148Q, V726A, M694I, P369S, F479L, A744S, R761H, I692del., K695R [269].
	• Gender, age at onset, subcutaneous edema and joint, GI, renal symptoms	• No association of M694V, E148Q, M680I, V726A, L110P [270].
	• Gender, age at onset, fever, arthritis, hematuria and GI symptoms	• No association of M694V, E148Q, M680I, V726A, M694I, K695R [271].
	• Joint and GI symptoms, nephritis,	• No association of M694V, M680I, P369S [272].
	• Age at onset, edema, arthritis	• No association of E148Q, M680I, V726A [274].
	• Gender, age at onset, joint and GI symptoms, recurrence	• No association of M694V, E148Q, M680I, V726A, M694I, P369S, F479L, R761H, I692del., K695R [275].
FVL	• Fever, gender, age at onset, arthritis, GI symptoms, hematuria	• FVL allele is associated with fever [281].
Prothrombin	• Fever, gender, age at onset, arthritis, GI symptoms, hematuria	• No association of 20,210 [G/A] [281].
MTHFR	• Fever, gender, age at onset, arthritis, GI symptoms, hematuria	• rs1801133 677 TT genotype ↑ hematuria [281].
	• Renal symptoms	• rs1801133 677 CC genotype ↑nephritis [285].

IgAV: Immunoglobulin A vasculitis; HLA: human leukocyte antigen; GI: gastrointestinal; RS: renal sequelae; *TNFA: tumor necrosis factor alpha; HSPA2: 70 kDa heat shock protein member 2; IL6: interleukin 6; IL6R: interleukin 6 receptor; IL6ST: interleukin 6 Signal Transducer; IL1ß: interleukin 1 ß; IL1ra: interleukin 1 receptor antagonist; IL18: interleukin 18; IFNG: interferon-gamma; TGFB1: transforming growth factor beta 1; MIF: macrophage migration inhibitory factor; IL8: interleukin 8; CXCL5: C-X-C motif chemokine 5; CCL5: chemokine (C-C motif) ligand 5; MCP1: chemokine monocyte chemoattractant protein 1; SELP: selectin P; SELE: selectin E; ICAM1: intercellular adhesion molecule 1; Agt: angiotensin; AT1R: angiotensin II receptor, type 1; ACE: angiotensin-converting enzyme; TLR2: toll-like receptor 2; TLR4: toll-like receptor 4; PTPN22: protein tyrosine phosphatase nonreceptor 22; CSK: c-src tyrosine kinase; PAX2: paired box 2; NPHS2: nephrosis 2, idiopathic, steroid-resistant (Podocin); CTLA4: cytotoxic T lymphocyte-associated protein 4; C1GALT1: glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1; VEGFA: vascular endothelial growth factor A; NOS2A: nitric oxide synthase 2; eNOS: endothelial nitric oxide synthase;* VNTR: variable-number tandem-repeat polymorphism; *MEFV: mediterranean fever; FVL: factor V Leiden; MTHFR: methylentetrahydrofolate reductase.*

*HLA-DRB1*01* [62, 63] and *HLA-DRB1*11* [63] were proposed as susceptibility alleles of IgAV, while *HLA-DRB1*07* [62, 63] seemed to confer a protective effect to the disease in small cohorts of Mediterranean patients. A recent well-powered cohort of Spaniards confirmed the susceptibility effect of *HLA-DRB1*01* in this pathology and pointed to *DRB1*0103* as the etiological allele [64]. In addition, a potential protective role of *HLA-DRB1*03* was suggested [64].

With regard to the influence of HLA-class II region in disease severity, including higher risk of nephritis and renal sequelae, no association was seen in Spaniards [61–64]. Nevertheless, *HLA-DRB1*13* was suggested as a potential risk allele for nephrotic proteinuria in Turks [65].

The potential involvement of other HLA class II genes in IgAV was also evaluated [63, 66]. In line with this, a potentially increased frequency of *HLA-DQA1*0301* in patients with IgAV from Korea was published [66]. However, no association between *HLA-DQA* and *HLA-DQB* and the susceptibility and/or severity of IgAV was described in Italians [63].

Besides class I and II, HLA complex also includes the HLA class III region. Genes located in this region encode components of the complement system (like the component complement 4 [C4]), cytokines (such as tumor necrosis factor [TNF]-α) and molecules involved in immune responses (including the 70 kDa heat shock proteins [Hsp70s]).

Complement system consists of a number of small proteins found in blood [67]. These molecules enhance the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation and attack the pathogen's plasma membrane [67]. Among these proteins, C4 serves a number of critical functions in the immune response, tolerance and autoimmunity [67]. Regarding IgAV, variations in the *C4* gene were proposed as genetic risk factors for the disease [66, 68]. Particularly, *C4A*Q0* and *C4B*Q0* genotypes were associated with predisposition to IgAV [68].

TNF-α is a cytokine produced essentially by activated macrophages [69, 70], although it can be produced by many other cell types. This molecule is involved in systemic inflammation, acute phase response and in the pathogenesis of inflammatory diseases [71]. TNF-α seems to be increased during the acute stage of IgAV and may enhance the binding activity of IgA anti-endothelial cell antibodies [72]. The potential implication of *TNFA* rs1800629 −308 [G/A] polymorphism in the pathogenesis of IgAV was assessed [73–75]. Although a lack of association between this genetic variant and the susceptibility of the disease was

described by some authors [74, 75], a susceptibility effect of *TNFA* rs1800629 –308 A allele was proposed by others [73]. Similarly, negative results were obtained when *TNFA* rs1800629 –308 [G/A] was evaluated according to IgAV severity in some studies [73] whereas an increased risk of nephritis in patients carrying *TNFA* rs1800629 –308 GA genotype and *TNFA* rs1800629 –308 A allele was described in some others [74].

Hsp70s are the largest and most highly conserved group of heat shock proteins [73]. These molecules, synthesized under stress conditions, are related to renal cell survival and matrix remodeling of acute and chronic renal diseases [76]. Among these proteins, Hsp70–2 is encoded by *HSPA2* [77]. A polymorphism located in this gene (*HSPA2* 1267 [G/A]) was associated with immune-mediated disorders [78–80]. The potential implication of this genetic variant in the pathogenesis of IgAV was also tested [73]. With respect to this, an increased frequency of *HSPA2* 1267 GG genotype in patients with this pathology was reported [73]. However, no statistically significant differences of *HSPA2* 1267 [G/A] genotype and allele frequencies were observed when patients were stratified according to the presence of nephritis [73].

2.3. Non-HLA genes in IgAV

2.3.1. Cytokines genes in IgAV

Cytokines are a broad category of small proteins, produced by a wide variety of cells, which play an important role in many physiological responses including cell signaling, body growth, adiposity and hematopoiesis [70, 81]. These molecules are crucial in immunological phenomena [82, 83].

One of the most relevant pro-inflammatory cytokine is interleukin (IL)-6. This protein is produced by different cells [84] and is essential in adaptive immunity [85]. Besides, IL-6 acts in the innate immune response contributing to inflammatory effects [85]. A polymorphism located at *IL6* promoter, rs1800795 –174 [G/C], was related to several inflammatory disorders [86–88]. However, no association between this genetic variant and the susceptibility and/or severity of IgAV was first described by Amoli et al. [89]. Afterwards, a large study, in which the major variability of *IL6* was covered by tagging, confirmed the lack of association between *IL6* rs1800795 –174 [G/C] and the pathogenesis of the disease [90]. Additionally, data derived from this study revealed no influence of *IL6* rs2069827 [G/T] and *IL6* rs2069840 [C/G] variants on IgAV [90]. Moreover, no significant results were found when these 3 polymorphisms were combined conforming haplotypes [90].

IL-6 cytokine levels and actions appear to be partially controlled by its receptor [91]. In this sense, IL-6 receptor is a protein complex consisting of an IL-6 receptor subunit (IL-6R) and IL-6 signal transducer Glycoprotein 130 (also called IL-6ST). Genetic studies evaluated the influence of *IL6R* rs2228145 [A/C] (that alters IL-6R levels [92]) and *IL6ST* rs2228044 [C/G] variants on several inflammatory diseases [93–98]. Regarding IgAV, neither *IL6R* rs2228145 [A/C] nor *IL6ST* rs2228044 [C/G] was implicated in the occurrence and/or severity of this pathology [99].

IL-1β is a pro-inflammatory pleiotropic cytokine [100] that stimulates the expression of genes associated with immune responses and increases the expression of endothelial adhesion molecules [101]. High IL-1β expression was observed in the skin biopsy specimens of IgAV patients [102] and in the serum of individuals with nephritis [103]. The role of *IL1ß* rs16944 –511 [C/T] (a polymorphism that influences IL-1ß production [104]) in the pathogenesis of IgAV was studied [105]. Although no significant results were observed when IgAV susceptibility was assessed, this genetic variant was proposed as a potential marker of renal involvement in a small cohort of Caucasian patients [105]. Later, a well-powered study confirmed that *IL1ß* rs16944 –511 TT genotype and *IL1ß* rs16944 –511 T allele were related to the development of severe renal symptoms and persistent renal damage [106].

Interleukin 1 receptor antagonist (IL-1ra), an endogenous agent that binds to IL-1 receptor and thus competitively inhibits the binding of IL-1ß [107], is encoded by *IL1RN*. A variable number tandem repeats (VNTR) polymorphism in intron 2 of this gene was characterized [108]. The *IL1RN*2* allele, that corresponds to 2 tandem repeats, was associated with lower circulating protein levels [109, 110] and the development of autoimmune diseases [109–111]. The implication of this variant in the pathogenesis of IgAV was analyzed [112, 113]. No relationship between *IL1RN*2* and the occurrence of the disease was observed [112]. Interestingly, *ILRN*2* was related to nephritis [113] and also to severe renal involvement and permanent renal damage in patients with IgAV [112].

A member of the IL-1 family cytokine that exerts a relevant pro-inflammatory function is IL-18 [69]. This protein induces Interferon gamma (IFN)-γ and other T-helper (Th)1 cytokines [69]. Genetic variants located at the promoter of *IL18* gene, rs187238 –137 [G/C], rs1946518 –607 [C/A] and rs360719 –1297 [T/C], were tested to determine their potential influence on the pathogenesis of IgAV [114]. The result of this assessment revealed that *IL18* rs187238 –137 G allele frequency was increased in patients compared to healthy individuals [114]. By contrast, a lack of association between rs1946518 –607 [C/A] and rs360719 –1297 [T/C] and the predisposition to IgAV was observed [114]. According to IgAV severity, no influence of these 3 genetic variants on the development of renal damage and GI symptoms was found [114].

IFN-ϒ is a pleiotropic cytokine, member of the type II interferons [70, 115]. This molecule is involved in innate and adaptive responses [116] by upregulating a variety of pro-inflammatory mediators [117]. Variations in the *IFNG* gene, especially the adenine to thymine transition at position +874 (rs2430561), was associated with several rheumatic diseases [118–120], including vasculitis [121]. In accordance with this issue, the implication of *IFNG* rs2430561 +874 [A/T] was analyzed regarding IgAV [122]. However, the results derived from this study did not support a role of this genetic variant in the pathogenesis of the disease [122].

Transforming growth factor beta 1 (TGF-β1), a multifunctional cytokine belonging to the TGF-β superfamily, is implicated in the modulation of both immunity and inflammation [123]. Pathological dysregulation of this molecule was implicated in the development of immune-mediated disorders [124–126]. Some reports proposed that TGF-β may have a role in IgAV since an increased number of TGF-β-secreting T cells in children with acute disease was observed [127]. Because of that, a genetic variant located at *TGFB1* promoter, *TGFB1* rs1800469 –509 [C/T], was genotyped in patients with IgAV [75]. With respect to this, children carrying *TGFB1* rs1800469 –509 TT genotype exhibited an increased IgAV susceptibility and also more severe clinical presentations, in terms of renal involvement, than non-TT [75].

2.3.2. Chemokines genes in IgAV

Chemokines are a family of small secreted proteins [128] that stimulate chemotaxis of cells [129]. In particular, these molecules are involved in the leukocyte movement, regulating the migration of these cells from the blood to sites of infection [128, 129]. Consequently, chemokines are key players in immune-mediated processes [83, 130].

The macrophage migration inhibitory factor (MIF) is a potent activator of macrophages that inhibits the random migration of these cells, concentrating them at the inflammatory site [69]. MIF appears to be crucial in vasculitides since high serum levels of this molecule were detected in patients with Wegener's granulomatosis [131]. Regarding IgAV, a polymorphism located at *MIF* promoter, *MIF* -173 [G/C], was evaluated [132, 133]. However, no association between this genetic variant and the susceptibility of the disease was observed [132, 133]. It was also the case when patients were stratified by the presence of GI complications [132, 133], nephritis [132, 133], renal sequelae [132] and joint damage [133].

IL-8 is a chemotactic cytokine produced by macrophages and other cell types [134]. This molecule induces chemotaxis, primarily in neutrophils [135]. Additionally, IL-8 also induces phagocytosis and it is involved in the up-regulation and activation of integrins [135]. Case–

control studies aimed to investigate the correlation between the polymorphism at position 2767 [A/G] in the 3′-untranslated region (UTR) region of the *IL8* gene and the development of IgAV [136, 137]. However, no association between this genetic variant and the occurrence of IgAV was reported [136, 137]. By contrast, a significantly increased frequency of the *IL8* 2767 A allele was found in patients who developed renal manifestations compared with patients without these complications [136, 137].

Another chemokine that stimulates the chemotaxis and homeostasis of neutrophils is the C-X-C motif chemokine 5 (CXCL5), also known as epithelial-derived neutrophil-activating peptide 78 (ENA-78) [83]. This protein possesses angiogenic properties [129] and is implicated in connective tissue remodeling. A polymorphism located at *CXCL5* promoter, rs352046 –156 [G/C], was related to some inflammatory diseases [138]. Because of that, this genetic variant was tested in patients with IgAV [136]. In keeping with results obtained in giant cell arteritis (GCA) [139] and erythema nodosum [140], no association between *CXCL5* rs352046 –156 [G/C] and the susceptibility of IgAV was observed [136]. This was also the case when IgAV patients with and without renal and/or severe GI manifestations were compared [136].

The regulated upon activation normal T cell expressed and secreted (RANTES), also known as CCL5, is a chemoattractant protein, mainly for T cells [129]. Two polymorphisms at the promoter of *CCL5* gene (*CCL5* rs2107538 –403 [G/A] and *CCL5* rs2280788 –28 [C/G]) were analyzed regarding the pathogenesis of IgAV [136, 141]. A lack of association between both genetic variants and the susceptibility of the disease was disclosed [136, 141]. Nevertheless, contradictory results were obtained when IgAV severity was evaluated [136, 141]. Whereas *CCL5* rs2107538 –403 [G/A] [136] and *CCL5* rs2280788 –28 [C/G] [141] did not seem to be associated with renal and GI manifestations in different studies, *CCL5* rs2107538 –403 TC and TT genotypes were proposed as markers of renal damage in children from China [141].

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a strong chemoattractant for monocytes/macrophages [142, 143] and displays chemotactic activity, also for basophils. MCP-1 is present in urine of patients with glomerular diseases and its levels correlate with the amount of proteinuria and degree of inflammatory cell infiltration [144–146]. The implication of *MCP1* –2518 [T/C] in the pathogenesis of IgAV was assessed [141, 147]. Whereas *MCP1* –2518 TT genotype and *MCP1* –2518 T allele were proposed as susceptibility factors for IgAV [141, 147], the role of *MCP1* –2518 [T/C] in the severity of the disease is a contentious issue [141, 147]. In this context, *MCP1* –2518 TT was associated with skin lesions, GI involvement and joint pain in Iranian Azeri–Turkish children [147]. However, no relationship of this polymorphism with renal and/or GI manifestations in Chinese children was found [141].

2.3.3. Adhesion molecules genes in IgAV

Cell adhesion molecules are transmembrane proteins whose function is to promote adhesive interactions with other cells or the extracellular matrix [148]. These molecules play crucial roles in cell migration and cellular activation in innate and adaptive immune mechanisms [83, 148].

The Selectin family of cell adhesion molecules consists of three members (P-selectin, E-selectin and L-selectin) which mediate rolling of leukocytes along the endothelium [149].

P-selectin is implicated in the recruitment of leukocytes on the vascular surface at inflammatory foci, their extravasation and the adhesion of platelets to the endothelium [150]. Increased levels of soluble P-selectin were detected in patients with IgAV and nephritis [151]. Based on this assumption, genetic variants located at the promoter of P-selectin gene (*SELP* -825 and *SELP* -2123) were evaluated in IgAV [152, 153]. In this sense, whereas *SELP* -2123 GG genotype and *SELP* -2123 G allele were related to an increased disease predisposition [153], no influence of *SELP* -825 on the susceptibility of IgAV was found [152]. Conversely, while *SELP* -2123 was not associated with the severity of IgAV [153], patients carrying *SELP* -825 AA genotype and *SELP* -825 A allele exhibited a greater occurrence of renal involvement [152].

E-selectin (also called ELAM-1 [endothelial leukocyte adhesion molecule-1]) [154] is present exclusively in endothelial cells and its expression is regulated by increased transcription after stimulation by inflammatory cytokines [148]. This protein is encoded by *SELE* and a single nucleotide polymorphism located at this gene (*SELE* 561 [A/C]) was described as risk factor for the development of some inflammatory diseases [155]. However, no influence of this genetic variant on the predisposition to and/or severity of IgAV was disclosed in patients from Northwest Spain [156].

Integrins are cell adhesion molecules expressed constitutively on leukocytes and many other cell types [148]. Among them, intercellular adhesion molecule 1 (ICAM-1) was described as decisive in leukocyte firm arrest on endothelium [157].

ICAM-1 is highly expressed in the adventitial micro-vessels and neovessels within inflammatory infiltrates of patients with GCA [158]; and changes in the concentrations of circulating soluble ICAM-1 were correlated with the disease activity [159]. Two genetic variants affecting *ICAM1* gene (241 R/G and 469 K/E) were genotyped in patients with IgAV [160]. No relationship between both polymorphisms and disease susceptibility was found [160]. Interestingly, although no association of *ICAM1* 241 R/G and IgAV severity was observed, a significantly decreased risk of severe GI complications in those patients not carrying the codon 469 K/E genotype was disclosed [160].

2.3.4. Renin-angiotensin system (RAS) genes in IgAV

RAS is involved in the modulation of vascular tone and possibly vascular structure either directly or via various factors such as endothelin and nitric oxide (NO), among others [161].

Angiotensin (Agt) II is a potent vasoconstrictor implicated in inflammation [162–164]. *Agt* polymorphisms (rs4762 T174M [C/T] and rs699 M235T [C/T]) were evaluated regarding IgAV. As for *Agt* rs4762 T174M [C/T], T174M-T allele was related to a higher IgAV prevalence and to the development of joint and GI manifestations [165]. Regarding *Agt* rs699 M235T [C/T], contradictory results were published [165–168]. Whereas a lack of association between this genetic variant and IgAV predisposition was observed by some authors [165, 167], this polymorphism was described as a susceptibility factor in children [168] and adults [166] by others. Likewise, no relationship between *Agt* rs699 M235 T [C/T] and IgAV severity was observed in some populations [166, 167], while a higher risk of nephritis in children carrying M235 T-TT and M235 T-T [168] and a decreased frequency of severe renal complications in those patients carrying M235T-T [165] was described in some others.

Agt II shows its physiological function by binding to Agt II receptor type 1 (AT1R) and type 2 (AT2R) [163]. The influence of a variant in the gene encoding AT1R, corresponding to an adenine to cytosine (A → C) transversion at nucleotide position 1166 of the mRNA sequence, on the pathogenesis of IgAV was assessed [165, 168]. However, this polymorphism failed to be relevant to this disease [165, 168].

Angiotensin-converting enzyme (ACE) is the key limiting enzyme of RAS which influences the formation of Agt II [165]. *ACE* gene contains an insertion (I)/deletion (D) polymorphism within intron 16 (*ACE* I16D) that involves the presence or absence of a 287 bp repeat sequence [169, 170]. This genetic variant was studied in the context of vasculitis [171–178] and, in particular, in the pathogenesis of IgAV [165, 167, 168, 179–186]. Different results were obtained regarding this issue [165, 167, 168, 179–186]. *ACE* I16D did not seem to be related to the occurrence [179] and/or severity of IgAV [167, 168, 180] in some studies. By contrast, an association of I6D-D [165, 181], I6D-DD [167, 182], I6D-ID/DD [168] and I6D-ID+DD [181] with an increased IgAV susceptibility was proposed by several authors. Also, an increased risk of renal complications in children diagnosed with IgAV was related to I16D-D [165, 184, 186] and I16D-DD [182, 183, 185].

2.3.5. Potential association of other genes in IgAV

Toll-like receptors (TLRs), single membrane-spanning non-catalytic receptors, usually expressed in sentinel cells, recognize structurally conserved molecules derived from microbes [69, 70, 187]. These molecules participate in the innate response and signal the activation of adaptive immunity [83].

TLR2 (also designated as CD282) recognizes endogenous inflammatory mediators in addition to microbial components, like lipoteichoic acid of Gram-positive bacteria [69, 187, 188]. An influence of *TLR2* 753 Arginine/Glutamine polymorphism on chronic inflammatory diseases was postulated [187]. However, no association of this genetic variant in the susceptibility and/or severity of IgAV was reported [189].

Activation of TLR4 (also called CD284), depending on bacterial lipopolysaccharides of Gram-negative bacteria [187, 188], promotes the production and release of pro-inflammatory cytokines [83]. A single nucleotide polymorphism located in *TLR4* gene, rs4986790 896 [A/G], resulting in the amino acid substitution Aspartic acid/Glycine at position 299, was related to decreased susceptibility to some autoimmune disorders [190]. By contrast, this genetic variant did not appear to be a genetic risk factor for the predisposition to and/or severity of IgAV [189, 191]. Similarly, no relationship between the amino acid substitution Threonine/Isoleucine at position 399 of *TLR4* and the pathogenesis of IgAV was observed [189].

Mannose-binding lectin (MBL) is a calcium-dependent lectin that plays an important role in innate immunity by activating the complement [67] through the MBL associated serine protease (MASP) pathway and phagocytosis [67, 192]. The genetic variant *MBL* rs1800450 [A/B] was reported to be associated with a decrease of MBL levels in the circulation, causing predisposition to infectious and autoimmune diseases [193, 194]. Regarding IgAV, a lack of association between this genetic variant and the predisposition to the disease was published [195].

Protein tyrosine phosphatases (PTPs) are critical regulators of T cell signal transduction [196, 197]. Among them, lymphoid-specific phosphatase (Lyp) is encoded by *PTPN22* (*protein tyrosine phosphatase nonreceptor 22*). The influence of the functional *PTPN22* rs2476601 [G/A] (R620W) and *PTPN22* rs33996649 [C/T] (R263Q) polymorphisms (related to inflammatory diseases [196–200] and vasculitis [201–203]) on IgAV was evaluated [204, 205]. In this context, no relationship between *PTPN22* rs2476601 [G/A] (R620W) and the pathogenesis of the disease was first described in a small cohort of patients [204] and, subsequently, confirmed in a well-powered genetic study [205]. In addition, a lack of association between *PTPN22* rs33996649 [C/T] (R263Q) and IgAV was reported [205]. Moreover, negative results were found when *PTPN22* rs2476601 [G/A] (R620W) and *PTPN22* rs33996649 [C/T] (R263Q) variants were tested together conforming haplotypes [205].

Lyp is expressed in lymphocytes where it physically associates to the SH3 of c-src tyrosine kinase (CSK) [196]. Some studies described an association between two well-known genetic variants located in *CSK* gene (*CSK* rs34933034 and *CSK* rs1378942) and several immune-mediated disorders [206, 207]. However, no implication of these two polymorphisms in the predisposition to IgAV and/or severity of the disease was described in the largest series of Caucasian patients ever assessed for genetic studies [205].

Paired box 2 (PAX2) is an essential nuclear transcription factor involved in the development of the human embryonic kidney [208]. *PAX2* gene is expressed in the distal tubules and podocytes of IgAV children with nephritis [209] and its expression appears to correlate with the severity of the renal pathology [209]. Several *PAX2* polymorphisms (1410 [C/T], 1521 [A/C], 1544 [C/T], 798 [C/T], 909 [A/C] and 164 [T/A] [209, 210]) were analyzed regarding IgAV pathogenesis. No influence of these genetic variants on the susceptibility of the disease was found [209, 210]. In addition, a lack of association between *PAX2* 1544 [C/T] [209] and *PAX2* 164 [T/A] [210] and IgAV severity was described. Interestingly, *PAX2* 1410 CT/1521 AC [209] and *PAX2* 798 [C/T]/*PAX2* 909 [A/C] genotypes [210] were involved in the development of renal manifestations in patients with IgAV.

An important molecule localized on the membranes of podocyte pedicels where it oligomerizes in lipid rafts together with nephrin to form the filtration slits, is the Podocin [211]. Mutations in the gene encoding podocin (*NPHS2*) were related to nephrotic syndrome, such as focal segmental glomerulosclerosis or minimal change disease [212]. In addition, the potential implication of *NPHS2* polymorphisms on IgA nephropathy (IgAN) was evaluated and contradictory results were observed [213–217]. Regarding IgAV, no significant association between *NPHS2* 954 [T/C] or *NPHS2* 1038 [A/G] polymorphisms and the presence of renal damage in children diagnosed with this pathology was disclosed [218].

Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (also known as CD152), a protein expressed on activated T cells [219], helps to regulate T cells [220]. *CTLA4* gene polymorphisms were associated with several rheumatic diseases [221–223] and, in particular, with vasculitis [224–226]. With respect to this, *CTLA4* 49 [A/G] was genotyped in patients with IgAV [65, 227]. No implication of this genetic variant in the occurrence of the disease was reported [65, 227]. Nevertheless, a significant association between carriage of the *CTLA4* 49 AG genotype and nephrotic proteinuria was described [65]. Also, *CTLA4* 49 GG genotype and *CTLA4* 49 G allele were related to increased risk of renal damage [227].

Aberrant glycosylation of IgA1 plays a pivotal role in the pathogenesis of IgAV [228–231]. Core 1 synthase glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase 1 (also known as C1GALT1) is an enzyme which activates the attachment of galactose to N-acetylgalactosamine [232, 233]. The reduced activity of this molecule could lead to aberrant glycosylation affecting, thus, the development of IgAV [234]. Accordingly, five tagging *C1GALT1* polymorphisms (rs9639031 −734 [C/T], rs73045773 −465 [A/G], rs1008898 −330 [G/T], rs5882115 −292 [C/−] and rs1047763 1365 [G/A]) were evaluated in Chinese cohorts of patients with IgAV [234, 235]. As a result of these studies, *C1GALT1* rs5882115 −292 [C/−] was proposed as genetic risk factor for developing IgAV [235]. Additionally, an increased frequency of *C1GALT1* rs1047763 1365 GG genotype and *C1GALT1* rs1047763 1365 G allele in patients who exhibited nephritis compared to those without this complication was found [234].

Uteroglobin (UG) is a steroid-inducible pleiotropic protein with immunomodulatory and anti-inflammatory properties [236, 237]. A potential implication of this molecule in human glomerulonephritis was suggested [238]. In fact, a genetic variant, at position +38 in exon 1 of the *UG* gene (38 [A/G]) was related to rapid-progression of IgA nephropathy [239–241]. However, results obtained by Eisenstein et al. did not support a role of this polymorphism in susceptibility to childhood IgAV [242].

Vascular endothelial growth factor (VEGF) is described as a molecule with pro-inflammatory, pro-atherogenic and pro-angiogenic properties [70, 243, 244]. High expression of VEGF was reported in patients with vasculitis [245–247] and, specifically, in children with IgAV in the acute phase of the disease [248]. Polymorphisms within *VEGFA* gene (rs2010963 −634 [G/C] [249, 250] and rs1570360 −1154 [GA] [249]) were tested regarding IgAV pathogenesis. No influence of both genetic variants on IgAV susceptibility was disclosed [249, 250]. Interestingly, *VEGFA* rs2010963 −634 CC and *VEGFA* rs2010963 −634 C were related to renal damage in Chinese children [250] whereas *VEGFA* rs1570360 −1154 G allele and - *VEGFA* rs1570360 −1154 G/*VEGFA* rs2010963 −634 C haplotype were associated with nephritis in Spaniards [249].

The conversion of L-arginine to L-citrulline by endothelial (eNOS or NOS3), neuronal (nNOS or NOS1) or inducible (iNOS or NOS2) synthases leads to NO production [251]. Increased levels of this molecule were detected in individuals with vasculitis [252, 253], especially in children with acute phase IgAV [254, 255]. *NOS2A* and *eNOS* genes were analyzed in the context of IgAV pathogenesis [256–259]. With respect to *NOS2A*, a CCTTT repeat polymorphism was associated with disease predisposition and nephritis presence [258]. Regarding *eNOS*, different results were published [256, 257, 259]. No influence of a VNTR polymorphism in intron 4 and *eNOS* 5557 [G/T] variant on IgAV

susceptibility and/or severity was reported [256]. Although the role of *eNOS* 894 [G/T] in the occurrence of the disease was debatable [257, 259], this polymorphism was described as a marker of renal damage [257]. Finally, *eNOS* -786 [T/C] was not related to IgAV predisposition [256, 257] and its potential involvement in the severity of the disease was controversial [256, 257, 259].

Paraoxonase1 (PON1) is a high density lipoprotein (HDL)-associated enzyme involved in prevention of lipid peroxidation [260–262]. Reduced activity of this molecule was detected in patients diagnosed with vasculitis [263]. In addition, polymorphisms in the gene coding PON1 were related to vascular diseases [264] by influencing on the development and progression of arterial damage. With respect to IgAV, two *PON1* polymorphisms located at coding regions, 192 Q/R and 55 L/M, were analyzed [265]. Data derived from this study exhibited a significantly increased frequency of *PON1* 192 QQ and a significantly decreased frequency of *PON1* 55 MM in children with IgAV from Turkey [265].

Mediterranean fever (*MEFV*) gene encodes a protein involved in the regulation of neutrophil activity, called Pyrin [266, 267]. The potential role of *MEFV* variations in the pathogenesis of IgAV was widely assessed and apparently contradictory results were obtained [268–275]. Whereas a relationship between M694V [268–271, 273, 274], E148Q [269, 272, 274] and V726A [275] variants with IgAV susceptibility was observed by some authors, no influence of both E148Q [268, 270, 271] and V726A [268–271, 273, 274] in the occurrence of the disease was observed by others. Similarly, M694V and E148Q were described as variants involved in IgAV severity in a few studies [268, 269, 272, 274] although no implication of M694V [270–272, 275], E148Q [269–271, 274, 275] and V726A [269–271, 274, 275] in the severity of the disease was found in others. A lack of association between M694I, K695R, M680I, P369S, A744S, L110P, R761H, F479L and I692del variants and predisposition to [268–275] and/or severity of [269–272, 274, 275] IgAV was also disclosed.

Finally, several inflammatory genetic defects are associated with an increased risk for venous thrombosis and arteriosclerosis [276–280]. The common inherited risk factors for thrombosis include *mutant factor V Leiden* (*FVL*), *prothrombin* 20,210 [G/A] polymorphism and the 677 [C/T] variant of *methylenetetrahydrofolate reductase* (*MTHFR*) [277–280].

A common mutation at position 1691 of *FVL* gene, leading to an arginine/glutamine substitution, conveys resistance to the stimulation of activated protein C, resulting thus in an increased risk for thrombosis [280]. When IgAV pathogenesis was analyzed, no association of this genetic variant and the occurrence of the disease was detected [281]. Interestingly, an increased frequency of the *FVL* allele in patients who manifested fever in the acute phase of the disease compared to those patients without fever was disclosed [281]. However, no significant results were found when IgAV patients were stratified according to the age of onset, gender, presence of arthritis, GI and renal manifestations [281].

Prothrombin gene is the precursor of the serine protease thrombin, a key enzyme involved in the processes of hemostasis and thrombosis. *Prothrombin* 20,210 [G/A] polymorphism was associated with high risk for venous thrombosis [277]. However, this genetic variant does not appear to be involved in the pathogenesis of IgAV since no significant results regarding both predisposition to and/or severity of the disease were found [281].

MTHFR is an enzyme that catalyzes the irreversible reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate (the methyl donor for the conversion of homocysteine to methionine) [282]. Genetic variants located in *MTHFR* were related to decreased MTHFR enzyme activity. The common polymorphism at codon 677 of this gene (rs1801133 [C/T]) was related to vasculitis [283, 284]. Regarding IgAV, no influence of this genetic variant on the predisposition of the disease was reported [281, 285]. Remarkably, a potential role of *MTHFR* rs1801133 [C/T] in the severity of IgAV was described [281, 285]. In this sense, an increased *MTHFR* rs1801133 CC genotype frequency in children with IgAV and nephritis was observed [285]. In addition, homozygosity for the *MTHFR* rs1801133 TT genotype was associated with hematuria [281].

2.4. High-throughput genotyping techniques for the assessment of the genetic influence of IgAV: a genome-wide association study (GWAS)

As previously mentioned, large-scale studies using high-throughput genotyping techniques have become the priority approach to unravel the genetic component of IgAV during the last years.

Unlike candidate gene studies, in high-density polymorphism arrays, hundreds of thousands of probes are arrayed on a small chip allowing for many genetic variants to be interrogated simultaneously. Among them, GWAS is a large-scale approach used in the genetic characterization of immune-mediated diseases [286, 287]. This strategy is a free-hypothesis genetic method [288] in which hundreds of thousands of single-nucleotide polymorphisms located across the whole genome can be analyzed [289].

GWAS have proven to be a powerful tool to unravel the genetic component of complex diseases during the last decade, including primary vasculitides [290] such as Takayasu Arteritis [291], Kawasaki [292–294] and Behçet [295, 296] diseases as well as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [297]. In line with this, the first GWAS focused on IgAV has been recently conducted by our group in the largest series of patients of European ancestry ever assessed for a genetic study [298]. Interestingly, a linkage disequilibrium block of polymorphisms that maps to an intergenic region in HLA class II, between *HLA-DQA1* and *HLA-DQB1*, was strongly associated with the susceptibility of the disease [298]. In particular, interesting p-values were observed for the HLA-DRB1 positions 13 and 11 [298]. Moreover, a suggestive association in the HLA class I region and some potential signals outside the HLA were related to IgAV predisposition [298].

3. Current situation and future perspectives

Vasculitides are a heterogeneous group of diseases characterized by a primary process of inflammation and damage of the blood vessel wall [6, 21]. These disorders often have overlapping clinical and pathologic manifestations [21] being difficult to distinguish among them in many cases. Nevertheless, differences between vasculitides in molecular terms have been described [40, 290].

As mentioned above, IgAV is a small-sized blood vessel vasculitis [1–12, 18, 21, 24] with predominant involvement of the skin [1, 5, 11–13, 18, 22, 24, 25]. The present review article reveals the importance of the genetic component in the pathogenesis of this condition.

Particularly relevant is the association of IgAV with the HLA class I and class II region. Data derived from different studies do not seem to be completely conclusive due to the limited statistical power of the many of them or the lack of replication of the results obtained [59, 60, 65, 66]. Nevertheless, consistent conclusions were obtained in patients from Europe in which a robust association of IgAV pathogenesis with the HLA region [56, 62–64, 298], mainly with HLA class II alleles [62–64, 298], was confirmed.

Susceptibility to IgAV was strongly associated with *HLA-DRB1* [62–64, 298] in Europeans, mainly due to *HLA-DR1*0103* [64]. In addition, a relationship with HLA class I alleles was also found in these patients [56, 298]. However, this association was not as strong as that found with the HLA class II region [56, 298].

In keeping with the above mentioned, it is worth noting that susceptibility to most systemic vasculitides is also essentially linked to the HLA region [40, 290, 299, 300]. GCA, the prototype of large vessel vasculitis in elderly people from Western countries, is firmly associated with *HLA-DRB1*04* alleles [40, 290, 299, 300]. Takayasu arteritis, another large vessel vasculitis that, unlike GCA, is more common in young women from Asian and South-American background, is predominantly related to

HLA class I alleles, in particular to *HLA-B52* [40, 290]. Furthermore, AAV, a group of small vessel vasculitides, are linked to HLA genes, specifically with *HLA-DP* [40, 290].

Association with HLA class II alleles was also found in patients with cryoglobulinemic vasculitis [301], a small vessel vasculitis mainly affecting the skin. This condition is rarely idiopathic and in most cases is associated with hepatitis C virus infection [302, 303]. Therefore, at the time of making a differential diagnosis between IgAV and vasculitis involving small blood vessels with predominant skin symptoms, the main challenge is to differentiate it from hypersensitivity vasculitis, also called isolated cutaneous vasculitis limited to skin, according to the new nomenclature [21]. Clinical differences between IgAV and hypersensitivity vasculitis are based on the lower prevalence of the latter in children, the higher association with drug intake before the onset of the pathology and the lesser degree of systemic involvement and disease severity in patients with hypersensitivity vasculitis [20]. Unfortunately, there is little information on genetic susceptibility to hypersensitivity vasculitis. Genetic studies on this vasculitis are scarce [132] and no association of this condition with the HLA region was confirmed, suggesting a heterogeneous etiology in the pathogenesis of this vasculitis that often is restricted and limited to skin.

An issue of potential concern at the time of assessing the genetic role in IgAV is that the association observed with the HLA region in Europeans seems to be restricted to disease susceptibility. In this context, no influence of HLA class I or class II genes on a specific phenotype of the disease, in terms of disease severity or outcome, was observed by most authors [56, 62–64]. Only two studies, performed in small series of patients, postulated a potential association of *HLA-B35* with the development of renal damage [55, 57].

Studies on non-HLA region suggest that gene markers associated with immune and inflammatory pathways (such as cytokines [75, 105, 106, 112–114], chemokines [136, 137, 141], adhesion molecules [141, 147, 152, 153, 160] and T-cells [65, 227]), aberrant glycosylation of IgA1 [234, 235], NO production [257–259], neoangiogenesis [249, 250], RAS [165, 166, 168, 181–186] as well as lipid [265], Pyrin [268–275] and homocysteine [281, 285] metabolism may be related to IgAV pathogenesis in different populations. It is also the case for the nuclear transcription factor *PAX2* [209, 210]. However, these potential associations do not seem to be as strong as the influence of the HLA region and, in most cases, they deserve further replication in larger and independent cohorts.

Among the signals located outside the HLA region, *IL18* [114], *TGFB1* [75], *MCP1* [141, 147] *SELP* [153], *Agt* [165, 166, 168], *ACE* [165, 168, 181, 182], *C1GALT1* [235], *NOS2A* [258], *eNOS* [259], *PON1* [265] and *MEFV* [268–275] may be implicated in the predisposition to IgAV.

Regarding the severity of IgAV, *IL1ß* [105, 106], *IL1ra* [112, 113], *TGFB1* [75], *IL8* [136, 137], *CCL5* [141], *SELP* [152], *Agt* [165, 168], *ACE* [165, 182–186], *PAX2* [209, 210], *CTLA4* [65, 227], *MTHFR* [281, 285], *C1GALT1* [234], *NOS2A* [258], *eNOS* [257, 259], *VEGF* [249, 250] and *MEFV* [269] may be considered as markers of renal damage and/or renal sequelae while *MCP1* [147], *ICAM1* [160], *Agt* [165] and *MEFV* [268] variants may be associated with GI involvement. In addition, *MCP1* [147], *Agt* [165] and *MEFV* [268, 272, 274] may be also related to the presence of joint symptoms.

An issue that needs to be kept in mind at the time of studying IgAV is that most data on IgAV were retrieved from children as this vasculitis is typical in young people. Despite being less common, paradoxically, IgAV is more severe in adults leading in some cases to end stage renal failure [13]. Therefore, future studies including larger number of adults with IgAV are required. It would be useful to determine if there are specific gene polymorphisms influencing the susceptibility to IgAV in adults.

In line with the above, studies performed up to now did not disclose genetic differences between IgAV in children and adults [56, 62, 64, 90, 99, 106, 136, 160, 256]. A possible explanation for that may be the relative small number of adults included in these studies. Therefore, further assessment for potential differences between children and adults in terms of disease susceptibility and, in particular, on disease severity are needed.

Another issue to be addressed in future studies is the search for genetic markers of disease severity in IgAV. So far, data looking for gene variants associated with a more severe disease, in particular with the risk of nephritis and renal sequelae, are promising. However, they are based on small case-series that need replication in independent cohorts.

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