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# Genetics of IgA Vasculitis: What We Know and Where We Are Going

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**Abstract**
Immunoglobulin A (IgA) vasculitis (IgAV) is the most prevalent systemic vasculitis in children. Although the condition is typically self-limiting with spontaneous recovery within a few weeks, both acute and long-term complications can arise, with renal involvement being the most significant. In recent years, considerable attention has been directed toward unraveling the genetic basis of IgAV. Studies have identified associations between disease susceptibility and specific human leukocyte antigen (HLA) polymorphisms. In addition, variants in genes encoding cytokines, chemokines, and other biologically important proteins – particularly those involved in the abnormal glycosylation of IgA1 – have been linked to both increased risk of developing IgAV and more severe disease manifestations. Notably, polymorphisms in the interleukin-1 receptor antagonist (*IL1RN*) and *IL8* genes have been correlated with an increased risk of glomerular injury. Other gene polymorphisms have also been associated with specific clinical phenotypes, such as *HMGB1* and *RAGE*, whereas polymorphisms in genes involved in mucosal immune defense have not demonstrated any significant correlations to date. Ongoing research is essential to clarify these findings further and determine their implications for clinical practice.

**Key Words:** IgA Vasculitis ▪ Genetics ▪ Human Leukocyte Antigen.

## Introduction

Immunoglobulin A (IgA) vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is the most common systemic vasculitis in children. It typically presents with non-thrombocytopenic palpable purpura, primarily involving the lower extremities and gluteal region, often accompanied by arthritis, nephritis, and/or gastrointestinal symptoms. It is a non-granulomatous systemic vasculitis characterized histologically by leukocytoclastic infiltration of small vessel walls (arterioles, capillaries, and venules) by neutrophils, along with the deposition of immune complexes containing predominantly IgA in the vessel endothelium. These deposits are commonly found in the skin, synovial membrane, and gastrointestinal and urinary tracts (1).

Although IgAV is usually self-limiting and resolves within approximately four weeks, acute complications such as intussusception, gastrointestinal hemorrhage, and bowel perforation may occur. Renal involvement is the most significant long-term complication and primary determinant of morbidity and mortality. Therefore, clinical guidelines recommend follow-up of all IgAV patients for at least 6 to 12 months, even when initial urinalysis and blood pressure are within normal limits (2).

This paper highlights the most significant recent advances in understanding the genetic basis of IgAV and explores their implications for its diagnosis, treatment, and prognosis.

## Genetics of IgAV

The genetic basis of IgAV remains incompletely understood, although recent research is increasingly

revealing its underlying mechanisms. Findings from the first genome-wide association studies (GWAS) conducted in IgAV patients of European ancestry suggest that IgAV is strongly associated with polymorphisms in the human leukocyte antigen (HLA) class II region. Notably, significant associations were identified in the intergenic region between *HLA-DQA1* and *HLA-DQB1*, as well as the *HLA-DRB1 11* and *HLA-DRB1 13* loci. The haplotype *DQA101:01/DQB105:01/DRB101:01* was found to confer increased susceptibility to IgAV, with no apparent overlap with the genetic profiles of other autoimmune or autoinflammatory diseases (3, 4).

In addition to HLA-related genes, several non-HLA loci have been implicated in IgAV susceptibility, including genes encoding cytokines (*IL1RN2*, *IL18*, and *TGFB1*), chemokines (*MCP1*), and other functionally relevant proteins (*C1GALT1*, *NOS2A*, *eNOS*, *PON1*, and *MEFV*) (5). Genes involved in the aberrant glycosylation of IgA1, modulation of vascular homeostasis and neoangiogenesis, T-cell function, proinflammatory cytokine activity, and homocysteine metabolism may influence both susceptibility to IgAV and the severity of its clinical course. A shared pathogenic feature of both IgAV and IgA nephropathy (IgAN) is the aberrant O-glycosylation of IgA1, particularly the overproduction of galactose-deficient IgA1 (Gd-IgA1), which promotes immune complex formation and tissue deposition. Polymorphisms in the *C1GALT1* gene may contribute to increased Gd-IgA1 levels, while variants in *C1GALT1C1* can indirectly affect glycosylation. Additionally, genes such as *ST6GALNAC2* and members of the *GALNT* family play critical roles in determining the structure of O-glycans in the IgA1 hinge region (5).

Genetic variants in the interleukin-1 receptor antagonist (*IL1RN*) and *IL8* genes have been associated with an increased risk of renal involvement and glomerular damage in IgAV (6, 7). Conversely, studies examining polymorphisms in the *IL6* gene and genes encoding protein tyrosine phosphatases have not demonstrated significant associations with either disease susceptibility or the risk of renal complications (8, 9).

Sestan et al. conducted whole exome sequencing (WES) in a cohort of patients with IgAV and did not identify any pathogenic variants definitively associated with disease pathogenesis. However, two rare variants of uncertain significance (VUS) were identified: one in exon 3 of the *BAD* gene (c.462G>C, p.Trp154Cys) and the other in exon 5 of the *DHX58* gene (c.560A>G, p.Gln187Arg). These genes are involved in key immune processes – specifically, apoptosis regulation and type I interferon (IFN-I) signaling, respectively. Although the clinical significance of these variants remains unclear, the authors suggest they may warrant further investigation due to their potential role in autoimmune dysregulation (10).

Polymorphisms in genes involved in mucosal immune defense, including *ITGAM–ITGAX* (rs11150612, rs11574637), *VAV3* (rs17019602), *CARD9* (rs4077515), *DEFA* (rs2738048, rs10086 568), and *HORMAD2* (rs2412971), have been implicated in the regulation of IgA production and have been previously identified as risk loci in IgAN. Given their potential relevance, these variants were investigated for their possible roles in IgAV pathogenesis. However, a study involving both adult and pediatric IgAV cohorts found no statistically significant differences in genotype or allele frequencies for these seven polymorphisms, indicating that they may not play a significant role in IgAV susceptibility (11). In a large pediatric cohort of patients with IgAV, at least one *MEFV* gene alteration was detected in 36.5% of cases, with p.E148Q and p.M694V being the most frequently observed variants. *MEFV* variants, known to cause the autoinflammatory disorder familial Mediterranean fever (FMF), may be associated with increased susceptibility to IgAV. Moreover, these variants appear to influence the clinical course of IgAV, as evidenced by their association with hematuria and disease recurrence (12). This potential link is further supported by a case report of an adult patient heterozygous for p.M694I and p.E148Q who manifested a moderate-to-severe form of IgAV (13).

Batnožić Varga et al. performed genotyping using real-time polymerase chain reaction (RT-PCR) and identified several *HMGB1*

polymorphisms associated with specific clinical phenotypes. Homozygous carriers of the rs1412125 polymorphism had a 3.45-fold increased risk of developing IgA vasculitis nephritis (IgAVN). This polymorphism was also linked to multisystem involvement in IgAV, with patients exhibiting purpura, arthritis, nephritis, and gastrointestinal symptoms more frequently carrying the homozygous C/C genotype under a recessive genetic model. Other *HMGB1* polymorphisms showed no significant association with IgAVN or multisystem involvement. However, individuals with the recessive genotypes of rs1045411, rs2249825, and rs1412125 were more likely to develop generalized rash. Conversely, the delT allele of rs41369348 appeared to confer protection against widespread rash. Carriers of either the homozygous T/delT or heterozygous T/delT genotypes of rs41369348 (under dominant and overdominant models) were less likely to develop generalized purpura. Moreover, patients with the heterozygous T/delT genotype were less likely to present initially with palpable purpura. In the same study, the *RAGE* polymorphism rs1800625 was associated with infections preceding IgAV onset, with the heterozygous A/G genotype linked to the highest risk. Additionally, the A/T genotype of rs1800624 was associated with a lower likelihood of initial skin manifestations (14).

## Conclusion

IgAV is a relatively common disease in children compared to adults. While its genetic architecture remains only partially defined, pathogenesis appears to involve both HLA class II region variants and non-HLA genes related to immune and vascular regulation, suggesting a complex genetic predisposition (3-5). Genetic polymorphisms in *IL-1* and *IL-8* may influence renal involvement, while variants in *IL-6* and protein tyrosine phosphatase genes appear unrelated to disease susceptibility or severity (8, 9). WES in patients with IgAV revealed no definitive pathogenic variants, although rare variants in the *BAD* and *DHX58* genes warrant further study for their potential role in immune dysregulation (10). Moreover, mucosal immune defense polymorphisms do not represent novel genetic risk factors for IgAV pathogenesis (11). Alterations in the *MEFV* gene, along with *HMGB1* and *RAGE* polymorphisms, also play a potential role in the development and clinical course of IgAV (12-14). Further research is needed to clarify these associations and their clinical relevance.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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