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Concise report

Identification of a shared genetic risk locus for Kawasaki disease and immunoglobulin A vasculitis by a cross-phenotype meta-analysis

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Abstract

Objectives. Combining of genomic data of different pathologies as a single phenotype has emerged as a useful strategy to identify genetic risk loci shared among immune-mediated diseases. Our study aimed to increase our knowledge of the genetic contribution to Kawasaki disease (KD) and IgA vasculitis (IgAV) by performing the first comprehensive large-scale analysis on the genetic overlap between them.

Methods. A total of 1190 vasculitis patients and 11 302 healthy controls were analysed. First, in the discovery phase, genome-wide data of 405 KD patients and 6252 controls and 215 IgAV patients and 1324 controls, all of European origin, were combined using an inverse variance meta-analysis. Second, the top associated polymorphisms were selected for replication in additional independent cohorts (570 cases and 3726 controls). Polymorphisms with *P*-values $\leq 5 \times 10^{-8}$ in the global IgAV–KD meta-analysis were considered as shared genetic risk loci.

Results. A genetic variant, rs3743841, located in an intron of the *NAGPA* gene, reached genome-wide significance in the cross-disease meta-analysis ($P = 8.06 \times 10^{-10}$). Additionally, when IgAV was individually analysed, a strong association between rs3743841 and this vasculitis was also evident [$P = 1.25 \times 10^{-7}$; odds ratio = 1.47 (95% CI 1.27, 1.69)]. *In silico* functional annotation showed that this polymorphism acts as a regulatory variant modulating the expression levels of the *NAGPA* and *SEC14L5* genes.

Conclusion. We identified a new risk locus with pleiotropic effects on the two childhood vasculitides analysed. This locus represents the strongest non-HLA signal described for IgAV to date.

Key words: IgA vasculitis, Kawasaki disease, genome-wide association study, single-nucleotide polymorphism

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Rheumatology key messages

- The rs3743841 genetic variant has a pleiotropic effect on IgA vasculitis and Kawasaki disease.
- This locus represents the strongest non-HLA signal described for IgA vasculitis to date.
- The rs3743841 polymorphism affects expression levels of the *NAGPA* and *SEC14L5* genes.

Introduction

Systemic vasculitis comprises a heterogeneous group of chronic diseases characterized by arterial wall inflammation. Vasculitis can be classified pathologically into three main categories by vessel size: large (LVV), medium (MVV) and small vessel vasculitis (SVV) [1]. However, clinical phenotypes of the different forms of vasculitis seem to be independent of the diameter of the vessels and, indeed, some of these diseases can affect vessels of variable types and sizes.

Kawasaki disease (KD), an MVV, and IgA vasculitis (IgAV), an SVV, are the first and second most common paediatric vasculitides in European countries, respectively [2, 3]. KD predominantly affects children <5 years of age, with an increased incidence in Asian countries. It is characterized by fever, rash, redness and edema of the hands and feet, mucosal changes, conjunctival injection, lymphadenopathy and, in some cases, arthritis [2]. IgAV largely affects children, but it also occurs in adults. The main features include palpable purpura, gastrointestinal pain and bleeding, arthritis and glomerulonephritis [3].

In both diseases, the aetiology is unknown and the heightened inflammatory pathogenesis is driven by environmental and genetic factors. In the last decade, genome-wide association studies (GWASs) have revolutionized the study of the genetics of systemic vasculitis, including IgAV and KD [4]. In this regard, several genetic risk loci related to immune responses and regulation have shown robust associations with KD, such as *ITPKC*, *FCGR2A*, *CASP3*, *BLK* and *CD40* [5], whereas only the HLA region has been consistently associated with IgAV to date [6].

However, the low prevalence of systemic vasculitis and the moderate effect conferred by disease-associated variants mean GWASs require large sample sizes for adequate power to meet the accepted standards for genome-wide significance [7]. In this regard, the combined analysis of genomic data from rare phenotypes of similar pathophysiology allows a significant increase in sample size and may identify common genetic determinants indicative of shared pathogenesis. This approach, called cross-phenotype meta-analysis, has been successfully applied to the study of the genetic component shared across different vasculitides, including giant cell arteritis, Takayasu's arteritis, ANCA-associated vasculitis and IgAV [8, 9], suggesting that common molecular mechanisms can be implicated in these diseases.

Interestingly, coexistence of both IgAV and KD has been described in several patients [10–12]. Moreover, additional evidence points to the existence of shared pathogenic mechanisms between both disorders. In this regard, following the identification of a murine model of KD showing deposition of IgA–C3 immune complexes in cardiovascular lesions and kidneys, it has been proposed that KD may be a form of IgAV [13].

Considering this, the aim of this study was to investigate, for the first time, the common genetic components of two forms of paediatric vasculitis by performing a cross-disease meta-analysis of KD and IgAV GWAS data.

Materials and methods

Study design

This study was conducted in two stages: a discovery stage, in which IgAV and KD GWAS data from previously published studies [14, 15] were combined as a single phenotype, with the aim of identifying potential new susceptibility variants for both vasculitides, and a validation stage, in which the most associated single nucleotide polymorphisms (SNPs) in the cross-phenotype meta-analysis were tested in additional independent cohorts. A summarized workflow of the study can be found in Supplementary Fig. S1, available at *Rheumatology* online.

Approval from the local ethical committees of the different participating centres and informed written consent from all participants were obtained in accordance with the tenets of the Declaration of Helsinki.

Discovery stage

Study population

Genomic data from a total of 620 paediatric cases and 7576 healthy controls of European descent, including 215 IgAV patients and 1324 controls from Spain and 405 KD patients and 6252 controls from Australia, The Netherlands, the UK and the USA, were included in the cross-disease meta-analysis. A table summarizing the analysed cohorts is available in Supplementary Table S1, available at *Rheumatology* online.

Quality control and imputation

GWAS data were filtered prior to imputation using PLINK version 1.9 software [16]. SNPs were removed based on a low genotyping rate (<95%), low allele

frequency (minor allele frequency <1%) and deviation from Hardy–Weinberg equilibrium ($P < 0.001$). In addition, individuals with successful call rates <95% were discarded, as well as duplicates and first-degree relatives.

SNP genotype imputation was performed using the Michigan Imputation Server (https://imputationserver.sph.umich.edu), with phase 3 of the 1000 Genomes Project as the reference panel and a probability threshold for merging genotypes of 0.9. Imputed data were subsequently filtered as described above. Additionally, principal component analysis was performed with PLINK version 1.9 and GCTA (Genome-wide Complex Trait Analysis) software [17], using the first 10 principal components to detect possible biased associations by ancestry. Individuals who surpassed 4 standard deviations from the centroid were excluded by considering them as outliers. Principal component plots are shown in Supplementary Fig. S2, available at *Rheumatology* online.

Statistical analysis

PLINK version 1.9 was used to perform logistic regression analysis on each individual disease, including the first 10 principal components and sex as covariates. Quantile–quantile plots are shown in Supplementary Fig. S3, available at *Rheumatology* online. Summary statistics of each disease were then meta-analysed by applying the inverse variance method, to identify shared genetic variants with the same effect in both diseases. In addition, to identify genetic variants with opposite allelic effects, the direction of association was flipped, that is, 1/OR instead of OR, in the IgAV dataset before the KD–IgAV meta-analysis.

SNPs that met our criteria ($P < 0.01$ in each individual disease and $P < 5 \times 10^{-5}$ in the cross-disease meta-analysis) were selected for the validation stage.

Validation stage

Study population and data sources

A total of 570 cases and 3726 healthy controls, including 186 KD patients and 600 controls from Korea and 384 IgAV patients and 3126 controls from four independent cohorts (Spain, Turkey, Slovenia and the USA) were analysed (Supplementary Table S1, available at *Rheumatology* online).

For the KD validation cohort, summary statistics of the selected SNPs were obtained from a previously published GWAS [18]. In the case of the IgAV validation cohorts, genotyping data from part of the samples (cases and controls from the USA and controls from Slovenia) were obtained using SNP genotyping arrays, while data from the remaining samples (cases from Slovenia and cases and controls from Spain and Turkey) were genotyped for the selected SNPs by allelic discrimination assay using TaqMan probes (Applied Biosystems, Waltham, MA, USA) (Supplementary Table S1, available at *Rheumatology* online).

Statistical analysis

Each independent cohort was individually analysed by logistic regression analysis. Subsequently, KD and IgAV cohorts were combined using the inverse variance method. A fixed effects model was used in the absence of heterogeneity across studies. Instead, when heterogeneity was detected, a random effects approach (RE2), implemented in METASOFT (http://genetics.cs.ucla.edu/meta/), was applied. After meta-analysis, those SNPs reaching a genome-wide significance level ($P \leq 5 \times 10^{-8}$) in the cross-disease meta-analysis, including both discovery and validation cohorts, and showing disease-specific *P*-values ≤0.05 in the validation stage were considered as common susceptibility loci for IgAV and KD.

In silico functional characterization

To evaluate the potential functional role of the most strongly associated polymorphism of each shared locus, and their proxies ($r^2 > 0.8$), publicly available functional annotation data were assessed. Specifically, data from Haploreg version 4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) and the GTEx (https://gtexportal.org) and ENCODE (https://www.encodeproject.org/) projects were explored in order to determine whether associated SNPs overlapped with published expression quantitative trait loci (eQTLs), regulatory chromatin marks, DNase I hypersensitive sites (DHSs) and/or transcription factor binding sites (TFBSs) in immune cell lines and/or whole blood.

Results

Meta-analysis

Discovery stage

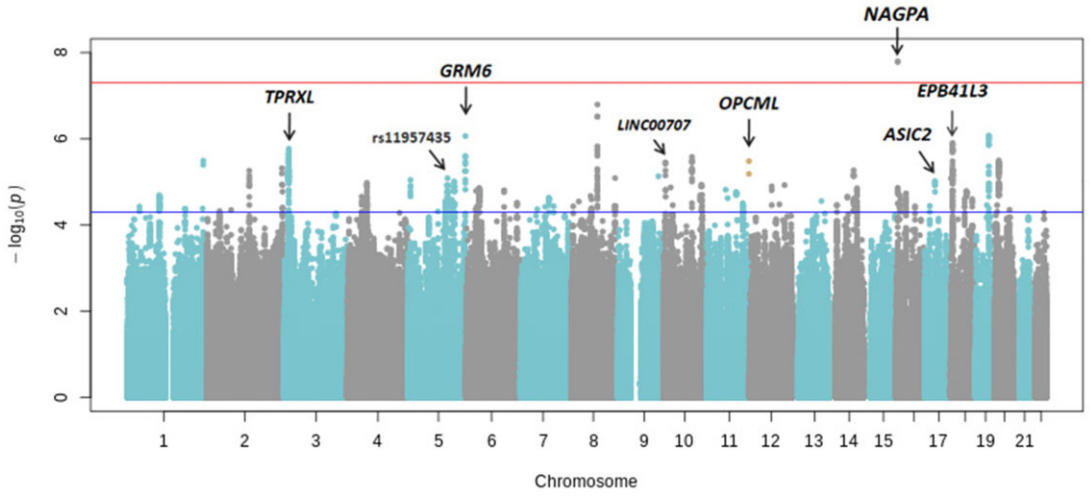
After quality control, 617 cases (215 IgAV cases and 402 KD cases) and 7538 controls were available for analysis. A total of 5 690 841 SNPs that overlapped between the discovery datasets were included in the cross-disease meta-analysis (Fig. 1).

After combined analysis of IgAV and KD GWAS data, assuming same allelic effects in both diseases, genetic variants at seven loci satisfied the established criteria for the discovery phase ($P < 5 \times 10^{-5}$ in the combined analysis; $P < 0.01$ in each independent disease analysis) (Table 1 and Fig. 1). Additionally, when taking into consideration potential opposite allele effects in both diseases, an additional SNP (rs2659608) fulfilled the established criteria (Table 1 and Fig. 1).

Validation stage

Subsequently the top signals within each locus were analysed in independent additional cohorts (Supplementary Table 1, available at *Rheumatology* online). As shown in Table 1, rs3743841, located in an intron of the *NAGPA* (N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase) gene, reached genome-wide significance in the IgAV–KD meta-analysis, including both

FIG. 1 Manhattan plot representing the results of the cross-disease meta-analysis for the discovery phase



The −log10 of the *P*-values are plotted against their physical chromosomal position. The red line represents the genome-wide level of significance ($P < 5 \times 10^{-8}$). The established significance threshold for the discovery stage ($P < 5 \times 10^{-5}$) is highlighted in blue. Loci have been annotated only for those polymorphisms reaching the established criteria for the discovery phase ($P < 5 \times 10^{-5}$ in the combined analysis; $P < 0.01$ in each independent disease analysis). Ochre dots represent those signals showing opposite allelic effect in both vasculitides.

discovery and replication datasets ($P = 8.06 \times 10^{-10}$) (Supplementary Fig. S4, available at *Rheumatology* online). Furthermore, this polymorphism showed statistical significance in the IgAV replication analysis [$P = 5.48 \times 10^{-4}$; OR = 1.39 (95% CI 1.15, 1.68)], although no association was observed in the KD replication cohort [$P = 0.76$; OR = 1.04 (95% CI 0.82, 1.31)] (Table 1).

It should be noted that the rs3743841 variant was near genome-wide significant in the IgAV-only meta-analysis [$P = 1.25 \times 10^{-7}$; OR = 1.47 (95% CI 1.27, 1.69)], including both discovery and replication cohorts. The minor allele frequency of rs3743841 in each of the study cohorts is shown in Supplementary Table S2, available at *Rheumatology* online.

Functional annotation

In order to provide biological context to our findings, we evaluated putative regulatory effects of the rs3743841 polymorphism, using different functional annotation databases. The rs3743841 genetic variant, and its only proxy ($r^2 = 0.99$), appeared to act as eQTLs, affecting expression levels of the *NAGPA* (3.89×10^{-23}) and *SEC14L5* (5.21×10^{-8}) genes in whole blood [19] and in whole blood and monocytes [20], respectively.

Discussion

In the present study, we report the first large-scale cross-disease meta-analysis of IgAV and KD, identifying a potential novel risk locus shared between both paediatric diseases. Specifically, the rs3743841 variant, located in an intron of the *NAGPA* gene, reached genome-wide significance in the overall cross-disease meta-analysis. This suggests a possible shared genetic component and, presumably, common molecular mechanisms involved in the development of both forms of vasculitis. In addition, the *NAGPA* variant showed a strong association with IgAV ($P = 1.25 \times 10^{-7}$; OR = 1.47), thus representing the strongest non-HLA signal described for this disease to date.

Interestingly, *in silico* functional analysis showed that this polymorphism, and its only proxy, acts as an eQTL, altering *NAGPA* and *SEC14L5* gene expression levels in whole blood and monocytes. *SEC14L5* encodes a member of the SEC14 family of proteins, which drives interactions between proteins and phospholipids that are essential for protein targeting, signal transduction, lipid metabolism and transport and compartment maintenance [21]. The *NAGPA* gene is involved in mannose 6-phosphate formation and encodes the uncovering enzyme that catalyzes the second step in the formation of mannose 6-phosphate, a recognition marker on lysosomal hydrolases. It has been reported that inactivation of the *NAGPA* gene in mice results in elevated levels of several acid hydrolases in plasma, which showed a decreased affinity for the cation-independent mannose 6-phosphate receptor and failed to bind to the cation-dependent mannose 6-phosphate receptor [22]. Interestingly, a central role of the lysosomal compartment in regulating different processes of the immune response, such as secretion of inflammatory cytokines or antigen presentation, has been described [23]. Furthermore, lysosomal enzyme activity may be involved in autoantigen generation and, indeed, changes in lysosomal hydrolases have been implicated in different autoimmune diseases [23]. Finally, lysosomes have also been implicated in other vasculitides, specifically in

TABLE 1 Association results obtained in the discovery and validation stages for each individual disease and in the IgAV–KD meta-analysis 16p13.3

Region	Gene	SNP	Test allele	Discovery						Validation				Discovery + validation	
				IgAV		KD		IgAV–KD		IgAV		KD		IgAV–KD	
				P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value		*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	
16p13.3	*NAGPA*	rs3743841	T	**4.32E-05**	**1.58 (1.27, 1.97)**	**6.08E-05**	**1.39 (1.18, 1.63)**	**1.61E-08**		**5.48E-04**	**1.39 (1.15, 1.68)**	**0.76**	**1.04 (0.82, 1.31)**	**8.06E-10***	
5q35.3	*GRM6*	rs67428898	T	2.70E-05	1.61 (1.29, 2.01)	2.30E-03	1.28 (1.09, 1.50)	8.64E-07		7.63E-01	0.96 (0.71, 1.28)	0.37	1.12 (0.88, 1.42)	1.61E-05*	
18p11.31	*EPB41L3*	rs73379591	C	4.52E-03	0.66 (0.49, 0.88)	8.27E-05	0.63 (0.50, 0.79)	1.25E-06		3.95E-03	0.69 (0.53, 0.89)	0.86	0.96 (0.61, 1.50)	6.90E-08	
3p25.1	*TPRXL*	rs2733560	G	1.00E-04	1.52 (1.23, 1.87)	2.00E-03	1.27 (1.09, 1.48)	1.70E-06		2.77E-02	0.82 (0.69, 0.98)	0.71	1.04 (0.82, 1.33)	1.48E-04*	
11q25	*OPCML*	rs2659608	C	1.91E-05	1.6 (1.29, 1.99)	7.22E-03	0.8 (0.69, 0.94)	3.30E-06		6.18E-01	0.95 (0.79, 1.15)	0.69	1.62 (0.15, 17.86)	1.83E-05*	
10p14	*LINC00707*	rs10508313	C	3.64E-03	1.45 (1.13, 1.87)	2.98E-04	1.43 (1.18, 1.73)	3.53E-06		2.02E-02	1.35 (1.05, 1.75)	0.70	0.95 (0.74, 1.22)	1.17E-07*	
5q23.2	–	rs11957435	C	1.30E-03	1.5 (1.17, 1.91)	1.52E-03	1.34 (1.12, 1.60)	8.16E-06		6.42E-01	0.95 (0.76, 1.19)	0.82	0.97 (0.75, 1.25)	1.18E-04*	
17q11.2	*ASIC2*	rs4426392	G	1.76E-03	0.7 (0.56, 0.87)	1.31E-03	0.77 (0.66, 0.90)	9.57E-06		6.71E-03	0.77 (0.63, 0.93)	0.32	1.13 (0.89, 1.43)	1.65E-05	

The polymorphism associated at the genome-wide significance level in the IgAV–KD meta-analysis is marked in bold. *P-values obtained using a random effects model (RE2).

ANCA-associated vasculitis, which are characterized by the presence of autoantibodies targeted against lysosomal enzymes of monocytes and neutrophils [24].

Our study has some strengths. First, this work represents a great international collaborative effort that has made possible the analysis of a large cohort of paediatric vasculitis patients using common case definitions. Second, this is the first study comprehensively examining the genetic overlap between IgAV and KD. However, we acknowledge some limitations. Although the rs3743841 variant reached the genome-wide significance level in the cross-disease meta-analysis, it was not statistically significant in the KD validation cohort. One possible explanation could be that this polymorphism is a genetic marker in linkage disequilibrium (LD) with the real causal variant. In this situation, differences in the LD pattern between Europeans and Asians might be responsible for the observed results. Considering this possibility, the associated polymorphism could be targeting the causal variant in European but not in the Asian population. Alternatively, the absence of association observed in the Korean cohort could be due to a lack of statistical power. Nevertheless, the statistical power for this analysis was almost 80%, considering the minor allele frequency reported in East Asian populations in phase 3 of the 1000 Genomes Project (49%) and the effect of the allele risk observed in the discovery phase (OR = 1.39). Therefore it is unlikely that the absence of association observed in the KD replication cohort was due to limited statistical power, although we cannot discard this hypothesis (Supplementary Table S3, available at *Rheumatology* online). Finally, as shown in Supplementary Table S3, available at *Rheumatology* online, for all the selected SNPs, the statistical power of the IgAV replication analysis was >80% to detect the effect size observed in the discovery IgAV cohort; however, the KD validation analysis did not reach enough statistical power, except for rs3743841 and rs10508313, and therefore, for the remaining six polymorphisms, the lack of replication in KD could be due to the low statistical power of the analysis.

In summary, in the first combined analysis of IgAV and KD GWAS data, we identified a putative susceptibility risk factor shared between both diseases as well as the strongest non-HLA signal described for IgAV to date. Our results point to a potential role of the lysosomal pathway in the IgAV pathogenesis and suggest that this process could represent a common pathogenic mechanism for these two most common types of paediatric vasculitides.

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Data availability statement

Results of the KD–IgAV cross-phenotype meta-analysis are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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