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Received: 19 June 2021 | Revised: 08 September 2021 | Accepted: 26 September 2021

DOI: 10.1111/coa.13870

SYSTEMATIC REVIEW

WILEY

Single-nucleotide polymorphism in chronic rhinosinusitis: A systematic review

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Funding information
This research received no external funding

Abstract

Objectives: We performed a systematic review on single-nucleotide polymorphisms and risk-related chronic rhinosinusitis.

Design and Setting: A comprehensive review of the last 20 years' English language literature regarding chronic rhinosinusitis and single-nucleotide polymorphisms was performed. We included in the synthesis all the papers reporting gene variation implicated in the pathogenesis of chronic inflammation and polyps.

Results: We found 12 papers with 9127 patients, of which 2739 CRS cases and 6388 controls. The major comorbidities reported related to chronic rhinosinusitis were atopy in 4555 (49.9%), asthma in 4594 (50.33%), Samter Triad in 448 (4.9%) and eosinophilia in 391 subjects (4.28%).

Conclusion: Our systematic review revealed the major SNPs significantly associated with chronic rhinosinusitis and the specific pathways involved. Given the presence of different extraction methods and samples sequencing, further studies with larger courts are necessary to identify significative single-nucleotide polymorphisms.

KEYWORDS
chronic rhinosinusitis, metagenomics, polymorphism, sequencing, SNP

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1 | INTRODUCTION

Chronic rhinosinusitis represents a multifactorial disease involving multiple environmental, immunological and genetic factors. Although several potential aetiological agents have been recognised as allergic comorbidities, specific microbes, mucociliary disorders and impaired epithelial barriers, the aetiology remains unclear.[1–3]

Various authors have attempted to demonstrate the mechanisms and genetic correlations underlying the inflammatory process based on strong evidence for the implication of CRS pathophysiology with nasal polyps (CRSwNP).[4–6]

The germline substitution of a single nucleotide at a specific genome position defined as single-nucleotide polymorphism (SNP) was proposed as playing a key role in CRS genetic predisposition.[7–9] Among the SNPs predominantly indicated in CRS are ion channels, tissue remodelling, innate immunity, generic or type 2 inflammation, and arachidonic acid metabolism.[10–12]

Purkey et al. in 2014 evaluated channels regulating ion transport and mucociliary clearance in 5911 patients (828 with nasal polyps vs. 5083 healthy subjects), identifying KCNMA1 and KCNQ5 genetic variants associated with chronic rhinosinusitis (CRS).[13]

Later, Purnell et al. demonstrated the importance of SNP taste receptor signalling in CRS, correlating the GNB3 rs5443 variation with the pathogenesis of chronic inflammation and polyps.[14]

In the present study, we carried out a systematic review of the different genetic variants associated with the pathophysiology of CRSwNP.

Key points

- CRS represents a pathology of complex interpretation conditioned by a great phenotypic variability.
- Genetic analysis of single-nucleotide polymorphisms present in CRS patients provides a better understanding of the pathophysiology of the disease.
- Each gene alteration triggers an alteration of signal transmission downstream, with specific altered pathways.
- Among the main mechanisms of genesis and perpetuation of chronic inflammation are barrier deficits, alteration of ion channels or genes involved in the TH2 inflammatory response.
- SNPs may carry an increased risk of both polyposis-associated and non-polyposis CRS compared to the general population.

2 | MATERIALS AND METHODS

2.1 | Protocol data extraction and outcomes

Three authors analysed the data from the literature. The study team solved any disagreements through discussion. Thus, included studies were analysed to gather all available data and guarantee eligibility among enrolled subjects. In addition, the patient's features, symptoms, diagnostic procedures, treatment modalities, genes analysed and main polymorphisms identified were collected. The following information was also collected: author data, year, sample size (CRSwNP group and control), study design, statistical analysis, findings and conclusions. We contacted the authors of the included studies if the required data were not complete using the corresponding author's email or Research Gate (http://www.researchgate.net/).

2.2 | Electronic database search

We performed a systematic review of the current literature according to the PRISMA checklist for review and meta-analysis[15] and through the PICOS search approach.[16]

We searched PubMed, Scopus and Web of Science electronic databases for studies on single-nucleotide polymorphisms in chronic rhinosinusitis patients over 20 years (from 1 January 2001 to 1 May 2021) by three different authors, using MeSH, Entry Terms and related keywords. The related search keywords used were as follows: "single nucleotide polymorphisms," "chronic rhinosinusitis," "nasal polyp polymorphisms," "nasal polymorphism gene," and "single nucleotide polymorphisms CRSwNP."

We also considered the 'Related articles' option on the PubMed homepage. Reference manager software (EndNote X7®, Thomson Reuters) was used to collect references and remove duplicates. Consequently, titles and abstracts of papers available in the English language were examined by the investigators.

Subsequently, the identified full texts were screened for original data, and the related references were retrieved and checked manually to identify other relevant studies.

2.3 | Eligibility criteria

We used the PICOS approach, including Medical Subject Headings (MeSH), Entry Terms or keywords found in articles in this field. We considered Participants (CRS patients); Intervention (SNP sequencing); Control (applied); Outcome (association between SNP with CRS and nasal polyps) and Study type (observational study). Language, publication date and publication status were imposed as restrictions. In particular, we considered a higher prevalence of CRS significantly associated performance with specific SNPs as the primary outcome. Instead, other parameters assessed in the studies were considered secondary outcomes.

All studies that met the following criteria were included:

1. Original articles;
2. The article was published in English;
3. The studies included clinically confirmed SNP polymorphisms in cases of chronic rhinosinusitis with polyps;

4. The studies reported detailed information on SNP polymorphisms, minor allele frequency (MAF), different treatment modalities and patient's comorbidities;

5. We excluded from the study case reports, editorials, letters to the editor or reviews;

6. Studies including animal models were also excluded from the analysis.

2.4 | Synthesis of results

Because of different laboratory procedures, tissue samples and the various genetic polymorphisms identified, the outcomes could influence the results of quantitative analysis. Therefore, a narrative synthesis was employed following the guidelines of the synthesis without meta-analysis reporting items.[17]

2.5 | Statistical analysis

We performed the research protocol according to the approved reporting items' quality requirements for systematic review and meta-analysis protocol (PRISMA) declaration.[15] We adopted the studies' quality assessment (QUADAS-2) instrument to estimate the included studies' design features, and the results of the risk of bias were presented descriptively.[18] Moreover, the probable risk of bias in observational studies was assessed using the Joanna Briggs Institute Critical Assessment Checklist for Observational Studies.[19]

Statistical analysis was performed using statistical software (IBM SPSS Statistics for Windows, IBM Corp. Released 2017, Version 25.0.: IBM Corp).

3 | RESULTS

3.1 | Retrieving studies

The systematic review of the literature identified 732 potentially relevant studies (Figure 1). After removing duplicates and applying the criteria listed above, 532 records were potentially relevant to the topic. Through the records analysis and subsequent articles' full-text screening, we excluded all the studies that did not match inclusion criteria (*n* = 519). The remaining 13 papers were included in a qualitative synthesis for data extraction. Moreover, because of the meta-analysis established criteria, we did not perform a quantitative analysis. A graphical display of bias analysis outcomes is shown in Figure 2, summarising the possible risk of bias.

3.2 | Study features

Thirteen studies were included.[7–14,19–23] According to the study design analysis, 12 papers were prospective controlled studies, while one study was an uncontrolled retrospective study.[22]

The studies' sample sizes ranged from 74 [14] to 5,911[13] participants. A total of 9,127 participants were assessed. The relevant data

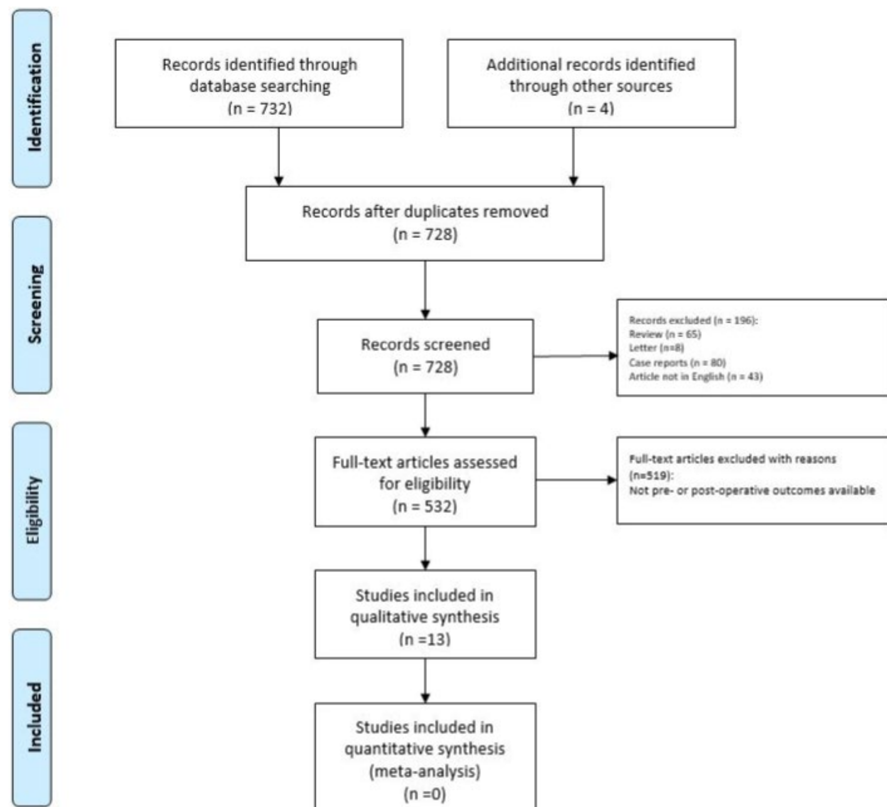

FIGURE 1 PRISMA flow diagram

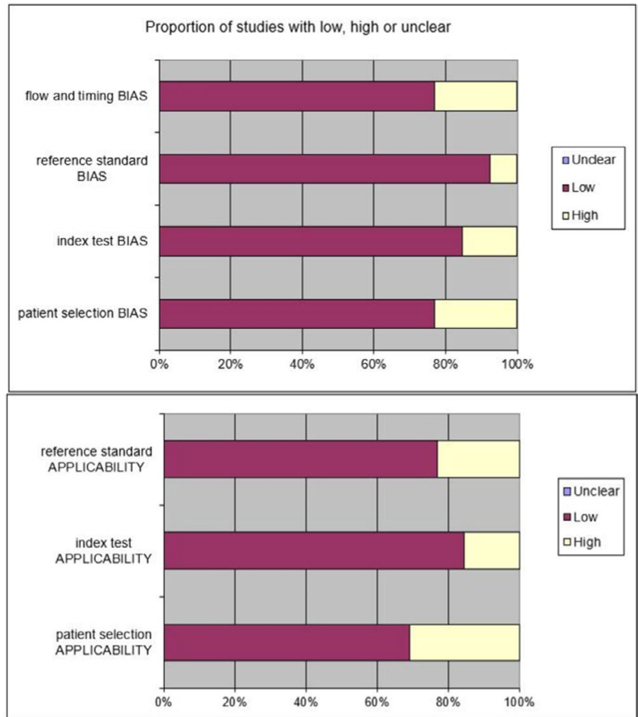

FIGURE 2 QUADAS2

retrieved from the included original studies are described in Table 1. The quality of evidence evaluation conducted by the GRADE assessment was considered low. It was mainly because of study design (observational studies), heterogeneous methodology and risk of bias in the included studies. The evidence appraisals are summarised in Figure 3.

3.3 | Patients' features, comorbidities and treatment

The patients' average age was 45.3 ± 10.87 years, ranging from 12 to 55 years old. Among the 9127 (74.1% male vs. 25.9% female) patients enrolled, 2739 were CRS subjects and 6388 were controls. The major comorbidities associated with chronic rhinosinusitis were atopy in 4,555 (49.9%) patients, asthma in 4594 (50.33%) and ASA in 448 (4.9%) cases. In addition, eosinophilia was reported in 391 (4.28%) cases.

All papers enrolled CRS patients treated with endoscopic nasal surgery, one paper associated adenoidectomy in paediatric patients[13] while Fruth et al. performed combined turbinoplasty.[12]

3.4 | DNA extraction method and SNP genotyping

All the authors isolated DNA from peripheral blood leukocytes collected in citrate-treated tubes. Instead, DNA was extracted from saliva in 3 papers.[7,9,11]

One paper analysed nasal samples.[12] While the mucosal biopsies of CRS patients were performed from ethmoid sinus surgery, control biopsies were provided from the inferior turbinate and used immediately for DNA and mRNA isolation.

PCR-RFLP (Restriction Fragment Length Polymorphism) was used in one paper, performing the genotyping for the TNFA locus −308 G>A (rs1800629) SNP in both patients and controls.[8]

3.4.1 | Real-time PCR System

Fruth et al. used a long range-PCR system for SNP Genotyping, amplification, and analysing gene polymorphisms.[12] The primary PCR was performed using the KAPA Taq Extra HS PCR Kit. Instead, Purnell et al. performed genotyping using TaqMan primer-probe sets and Type-it Fast SNP Probe PCR Kits (Qiagen).[14] Moreover, Wang et al. in 2008 carried out genotyping using TaqMan technology (Real-Time PCR System; Applied Biosystems), and reactions were performed in 96-well microplates with ABI 9700 thermal cyclers (Applied Biosystems).[22] Later, the authors confirmed the procedure on 203 patients (64 CRSwNP vs. 139 healthy subjects).[23]

3.4.2 | Mass spectrometry-based sequencing

Zhang et al. genotyped the selected SNPs through the Mass Array system (Sequenom) with primers and probes, while one SNP (rs12302873) was evaluated by preliminary direct sequencing of PCR products of genomic DNA.[24] Instead, 3 papers genotyped SNPs using Sequenom matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF) (Sequenom).[7,11,21] Primers were usually designed using available software (SNP Assay Design, version 3.0 for iPLEX reactions; Sequenom).

3.4.3 | 1st generation sequencing

Dar et al. extracted genomic DNA for PCR amplification using intronic forward and reverse primers of the promoter, and exonic regions of the FcεR1α gene, thus using 1st generation Sequencing (Fluorescent Dye Terminator Sequencing).[10]

Another paper applied the Big Dye Terminator Sanger sequencing in both directions using a 3130XL Genetic Analyzer (Life Technologies).[20]

3.4.4 | Next-generation Sequencing

Two authors genotyped CRS patients' samples through the Illumina Human 1 M Genotyping BeadChip, which shares 535 752 common SNP markers and interrogates 1 million SNPs (Illumina Corporation).[11,13]

TABLE 1 Studies included in the analysis and main features retrieved

Reference	Study Design	Patients	Age	Gender	DNA Extraction
Purkey et al. 2014	Prospective controlled	5911 (828 Np vs 5083 CG)	12	NA	Peripheral blood leucocytes
Purnell et al. 2019	Prospective controlled	74 (45 Np vs 19 CG)	55	38 male 36 female	Peripheral blood leucocytes
Al Shemari et al. 2008	Prospective controlled	200 (150 Np vs 50 CG)	48.8 ± 15.0	6 male 8 female	Peripheral blood leucocytes, Salivary
Wang et. al 2010	retrospective controlled	203 (64 Np vs 139 CG)	43.8	137 male 66 female	Peripheral blood leucocytes
Endam et al. 2013	Prospective controlled	614 (408 Np vs 190CG)	52.3 ± 13.0	347 male 267 female	Peripheral blood leucocytes, Salivary
Szabó et al. 2012	Prospective controlled	375 (326 Np vs 49 CG)	48.8	55 male 46 female	Peripheral blood leucocytes
Fruth et al. 2012	Prospective controlled	104 (15 Np vs 59 CG)	43 ± 17.2	67 male 37 female	Peripheral blood leucocytes, Nasal
rs2303063 G = 0.494282					
Endam et al. 2010	Prospective controlled	206 (154 Np vs 52 CG)	48.8	86 male 110 female	Peripheral blood leucocytes, Salivary
IL1B (Interleukin 1 beta) TNF (Tumour necrosis factor A)	FESS	Asthma, Atopy, Eosinophilia, Aspirin Intolerance	rs1800587: A = 0.295463/28443 rs2048874: T = 0.11864/16382 rs2856838: A = 0.393081/3761 rs17561: A = 0.289758/51920		
Zhang et al. 2012	Retrospective controlled	638(306 Np vs 332CG)	43 ± 16	370 male 268 female	Peripheral blood leucocytes
Dar et al. 2017	Prospective controlled	150 (100 Np vs 50 CG)	29 ± 9 Vs 24 ± 4	63 male 37 female	Peripheral blood leucocytes
Kilty et al. 2010	Prospective controlled	206 (154 Np vs 27 CG)	52.4 ± 13.2	88 male 108 female	Peripheral blood leucocytes
Henmyr et al. 2016	Prospective controlled	310 (138 Np vs 172CG)	46	195 male 115 female	Peripheral blood leucocytes
Wang et al. 2008	Prospective controlled	136 (70 Np vs 66 CG)	42.5	96 male 40 female	Peripheral blood leucocytes

Note: All SNP reported were significantly associated with nasal polyps.

Abbreviations: CG, Control group; NA, Not available; Np, Nasal polyps.

Genes	Treatment	Comorbidities	Frequency MAF
KCNMA1 (potassium calcium- channel) KCNQ5 (potassium channel)	FESS Adenoidectomy	Asthma, allergy	rs2917454: G = 0.164991/361 rs7900261: A = 0.403312/18191 rs6907229: T = 0.311213/15143 rs9343015: T = 0.268304/11536
GNB3 (G-protein subunit beta 3) TAS2R19 (taste 2 receptor member 19) TAS2R38 (taste 2 receptor member 38)	FESS	Asthma, Allergy, Migraine	rs5443: 0.367 rs10772420: 0.505 rs713598: 0.423 rs7528947: 0.516
ALOX5AP (arachidonate 5-lipoxygenase-activating protein) CYSTLR1 (Cysteinyl leukotriene receptor 1) CYSTLR2 (Cysteinyl leukotriene receptor 2) LTC4S (Leukotriene C4 synthase)	FESS	Asthma, Atopy, Eosinophilia	rs3780894: G = 0.164991/361 rs17612127: T = 0.083029/364
MMP 9 (matrix metallopeptidase 9)	FESS	NA	rs3918242: T = 0.180169/427 rs3787268: A = 0.191044/1186 rs2274756: A = 0.141643/14800 rs17577: A = 0.141643/14800
TAS2R13 (taste 2 receptor member 13) TAS2R49 (taste 2 receptor member 49)	FESS	Asthma, Atopy Eosinophilia, Aspirin Intolerance	rs10246939: C = 0.461616/67708 rs10772420: A = 0.486656/58024 rs1726866: G = 0.468433/66643
308 G>A (Tumour necrosis factor A)	FESS	Asthma, Aspirin Intolerance	rs1800629: A = 0.155316/16999
SPINK5 (Serine peptidase inhibitor Kazal type 5)	FESS, Turbinoplasty	Asthma, Atopy, Aspirin Intolerance	rs750103232 G = 0.000008
IL1A (Interleukin 1 alpha)			
RYBP (RING1 and YY1 binding protein) AOAH (acyloxyacyl hydrolase)	FESS	Atopy, Eosinophilia	rs4532099: T = 0.232538/35909 rs4504543: C = 0.361366/50245
FcεR1α (Fc fragment of IgE receptor Ia)	FESS	Atopy, Eosinophilia	rs2427827: T = 0.418812/1594
SERPINA1 (Serpin family A member 1)	FESS	Atopy, Asthma, Aspirin Intolerance	rs12884390: C = 0.486649/46730 rs1243168: A = 0.203327/8606 rs4900229: T = 0.17481/5427
PARS2 (prolyl-tRNA synthetase 2 mitochondrial)	FESS	NA	rs2873551: C = 0.368515/32405
MMP2 (matrix metallopeptidase 9)	FESS	NA	rs857403: T = 0.190585/417 rs243865: T = 0.199446/4322

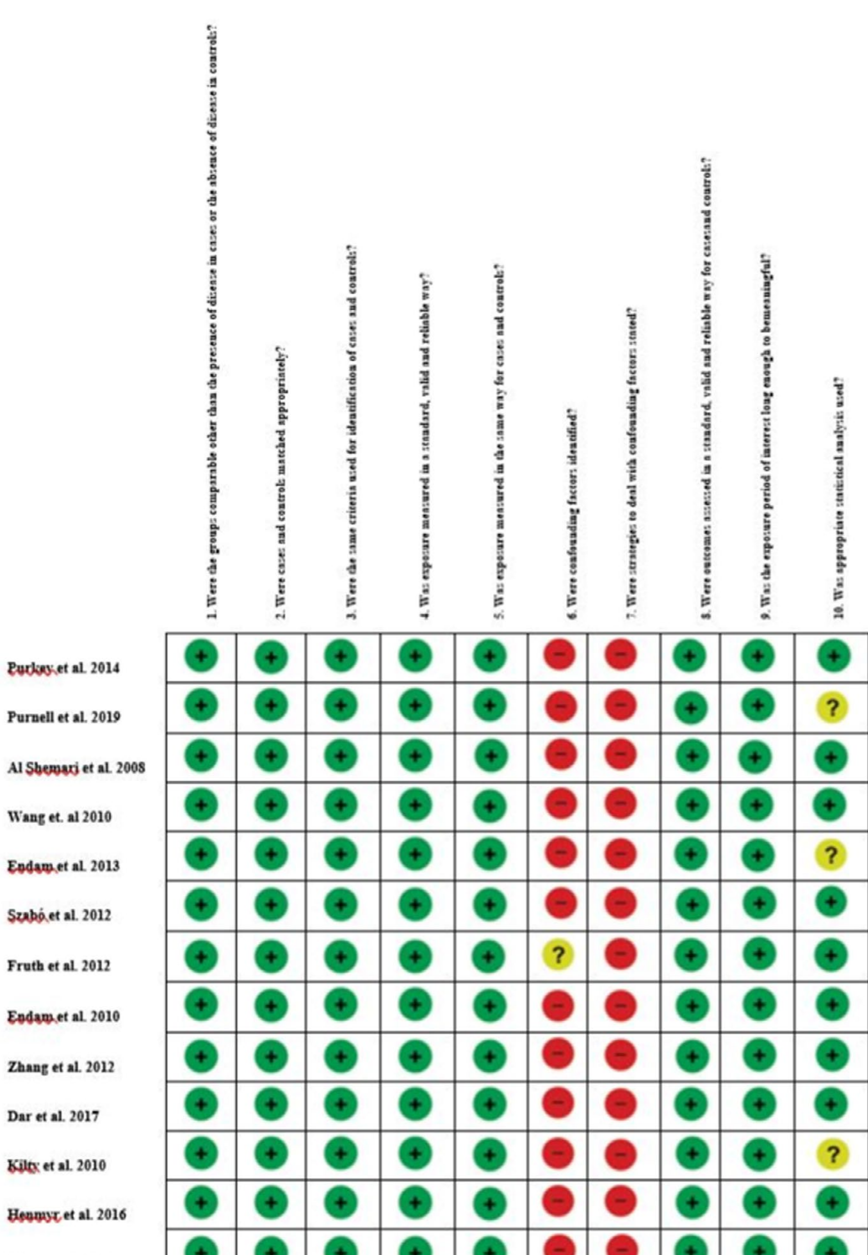

FIGURE 3 Risk of bias summary, authors' judgement for each included study, assessed by the Joanna Briggs Institute (JBI). Critical appraisal checklist for case-control studies

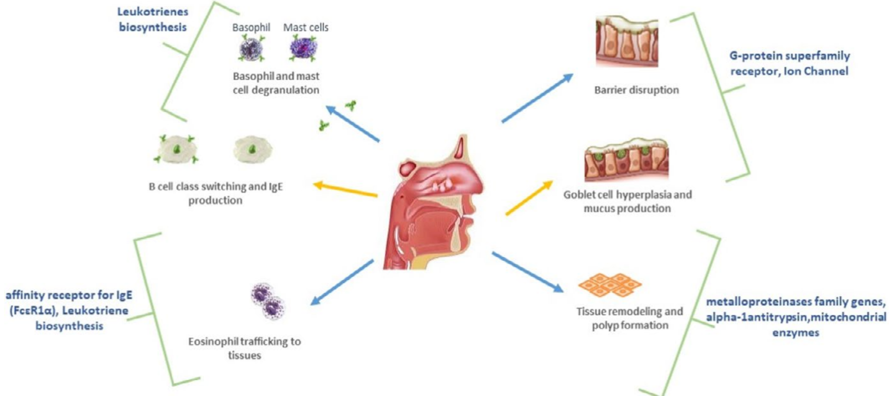

FIGURE 4 CRS physiopathogenetic pathways and SNPs involved

Moreover, through the pGWAS approach, an equal amount of DNA pool from each patient was genotyped using a high-throughput SNP array.

3.5 | Gene family polymorphisms

Purkey et al. analysed the potassium channel gene's role in the predisposition of chronic rhinosinusitis, reporting a strong association for polymorphisms of KCNMA1 (calcium-potassium channel) and KCNQ5 (voltage-dependent potassium channel) ($p = 0.022$; $p = 0.027$ respectively).[13] Moreover, two papers demonstrated correlations between gene products belonging to the family of taste receptors and CRS (G-protein-coupled receptor superfamily), with higher MAF in patients expressing TAS2R19, TAS2R38, TAS2R13 and TAS2R49 polymorphisms.[11,14] Another paper confirmed the relevance of the G-protein component downstream in nasal polyps, with an increased MAF of 0.493 ($p = 0.014$) for GNB3 SNP (rs = 5443).[14]

Al-Shemari et al. reported the lipid mediator's role, including lipoxygenase-activating arachidonate 5-lipoxygenase (ALOX5AP or FLAP), two G-protein-coupled receptors, cysteinyl leukotriene receptor 1 and 2 (CYSLTR1 and CYSLTR2) and Leukotriene C4 synthase (LTC4S) reaching the nominal *p*-value threshold ($p < 0.05$ for all).[9]

Moreover, zinc-metalloproteinases family genes MMP 9 (rs3918242) and MMP 2 (rs857403), involved in the degradation of the extracellular matrix, were found significantly associated with CRSwNP in two in two subsequent studies performed in 2008 and 2010 by Wang et al. ($p = 0.023$; $p = 0.03$ respectively).[22,23]

Three papers established the gene variation in regulation of transcription RING1 and YY1 binding protein (RYBP), inflammatory response Acyloxyacyl hydrolase (AOAH) and TNFA locus, presenting single-nucleotide polymorphisms (SNPs) responsible for certain chronic inflammatory sinusitis and Nasal polyps.[7,8,24]

Moreover, SNP polymorphisms coding for mitochondrial enzymes (PARS2 locus), implicated in protein biosynthesis, expressed a significant correlation with the CRS phenotype. However, no significance was detected when subdividing the CRS population into CRS with and without nasal polyps.[20]

Finally, two articles demonstrated the correlation between the high-affinity receptor for IgE (FcεR1α) and the gene of the Serpinic family A member 1 (SERPINA1), involved in chronic inflammation tissue remodelling and polyposis.[10,21]

4 | DISCUSSION

The potential correlations with CRS described in the literature are innumerable, ranging from epithelial barrier deficiency, nasal pathogenic microbacteria to dysregulation of innate immune responses.[25–27] Different stimulants for the chronic immune response have been identified in CRS, including allergens, bacteria such as Staphylococcus Aureus, fungi and various environmental factors.

Furthermore, growing evidence suggests a crucial genetic role in CRS (Figure 4).[28–30]

Purkey et al. examined the association between selected potassium channels and CRS status in a study comparing 828 children with CRS against 5083 controls and found that two epithelial potassium channels *KCNMA1* and *KCNQ5* were associated with CRS status in Caucasian and African American children respectively.[13] This line of research, together with the *TAS2R38* findings and known associations with *CFTR*, suggests that genes regulating ion flux in epithelial cells may confer a significant genetic predisposition to CRS.

Chronic rhinosinusitis with nasal polyposis and asthma shares characteristic evidence of airway remodelling, the main agent of which is often matrix metalloproteinases (MMP).

The regulation of MMPs is complex, preventing different proteins involved in both chronic inflammation and remodelling with the formation of polyposis.[22,23]

Moreover, patients with CRSwNP could also develop asthma and aspirin sensitivity, an association known as aspirin-exacerbated respiratory disease (AERD).

This correlation has its genetic basis in the cytokine imbalance characteristic of CRS and in the altered metabolism of arachidonic acid.[9]

The role of barrier dysfunction is known among the pathophysiological hypotheses of the genesis of nasal polyps, among which desmogleins and other proteins involved in barrier formation are important. In this regard, Fruth et al. demonstrated that SPINK5 gene polymorphisms are significantly associated with CRSwNP, especially in aspirin-intolerant patients compared to controls.[12]

Among the alternative factors for PNS and chronic inflammatory diseases, smoking is considered crucial for upper respiratory tract disorders, particularly in CRS.[9,14,22,23] However, in the literature, only a few authors have analysed a correlation between smoking and CRS polymorphisms. In 2008, Shemari et al. reported a high smoking rate in patients with severe CRS, reaching 11.2%.[9] Subsequently, Endam et al. confirmed the significant prevalence of smoking history in CRS patients presenting with SNP while the control group reported no smoking activity.[7]

The genetic evidence is, however, much discussed because of some intrinsic limitations of the studies carried out in this regard.

The lack of scientific evidence on adequate animal models of the various genetic profiles is relevant. Patients with chronic rhinosinusitis often fall into different phenotype and endotype groups; however, genetic analysis is not currently considered a key factor in profiling patients with CRS. Evidence in this regard is scarce, and often studies have a weak study design. For this reason, randomised controlled trials with large samples would be needed, but genetic methods are difficult both for data collection and analysis as they are often very expensive. However, as discussed in the literature, CRS remains a pathology to be discovered and analysed in many ways, and for this reason, it is necessary to shift our attention to the physiopathogenetic moments that characterise it.

In this regard, further elaboration on the distinction between eosinophilic and non-eosinophilic subjects could be useful in the stratification of patients with CRS.[7,9–11,24] Dar et al. in 2007 found a highly significant (461.22 IU/ml vs. 83.62 IU/ml; $p < 0.0001$) association of high IgE levels in CRSwNP cases compared to controls. Moreover, the authors found a high FcεR1α antibody level (292.38 ± 115.27) in CRSwNP cases as compared to controls (160.56 ± 105.9; $p < 0.0001$).[10]

Moreover, Zhang et al. analysing the RYBP and AOAH gene polymorphisms, associated with chronic rhinosinusitis in a Chinese population, found increased IgE in the CRS group vs. controls (112.16 kU/l vs. 57.46 kU/l; $p = 0.0183$).[24]

Papers included in the systematic reviews were performed different procedures, from PCR to NGS for the sequencing of SNPs. PCR is a more accessible method because of cost, ease of use and speed, as well as requiring less qualified laboratory personnel. However, inherent limitations of the technique are the impossibility of sequencing stretches longer than 1000bp and a representation that is only homozygous or heterozygous; in this sense, less represented mutations could escape analysis. On the contrary, next-generation sequencing (NGS) has been shown to be capable of detecting even mutations represented not in heterozygosity or homozygosity.

Although the sample price analysed is progressively reduced for NGS, the latter requires more processing time and more qualified personnel than other sequencing methods.

The main limitation of the present study is the heterogeneity between included studies regarding patient populations, inclusion criteria and methods of assessment of DNA sequencing. All of these points may limit arriving at a clear conclusion. However, this study is the first systematic review investigating such associations and, therefore, provides an overview of the literature, which may be useful for future studies.

5 | CONCLUSION

CRS represents a pathology of complex interpretation conditioned by a great phenotypic variability.

Genetic analysis of CRSwNP single-nucleotide polymorphisms is a promising prospect for understanding the pathophysiology of the disease. Further cohort studies with large samples are needed to evaluate all the variables associated with the disease and the use of state-of-the-art laboratory resources supported by adequate financial resources.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

A.M. and N.M. conceptualised the study. S.S and S.S. designed the methodology. A.M., F.M. and S.C. designed the software. M.S. validated the study. JR. L and A.M. involved in formal analysis. C.V. and C.CH. involved in investigation. A.M. collected resources. I.LM. and C.S. involved in data curation. A.M. involved in writing—original draft preparation. I.L.M. involved in writing—review and editing; S.S. visualised the study. N.M., S.S involved in supervision, S.F. A.B and S.C. involved in project administration. All authors have read and agreed to the published version of the manuscript.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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How to cite this article: Antonino M, Nicolò M, Jerome Renee L, et al. Single-nucleotide polymorphism in chronic rhinosinusitis: A systematic review. *Clin Otolaryngol*. 2021;47:14–23. https://doi.org/10.1111/coa.13870