Genetics and Epigenetics of Nasal Polyposis: A Systematic Review

Martin MJ[1,2,3], Garcia-Sanchez A[1,2,4], Estravis M[1,2,4], Gil-Melcón M[5], Isidoro-Garcia M[1,2,6,7], Sanz C[1,2,8], Davila I[1,2,4,9]

[1]IBSAL, Institute of Biomedical Research of Salamanca, Salamanca, Spain
[2]Network for Cooperative Research in Health-RETICS ARADyAL, Salamanca, Spain
[3]Department of Biochemistry and Molecular Biology, University of Salamanca, Salamanca, Spain
[4]Department of Biomedical and Diagnostics Sciences, University of Salamanca, Salamanca, Spain
[5]Department of Otorhinolaryngology/Servicio de Otorrinolaringología, Hospital Universitario de Salamanca, Salamanca, Spain
[6]Department of Clinical Biochemistry/Servicio de Bioquímica Clínica, Hospital Universitario de Salamanca, Salamanca, Spain
[7]Department of Medicine, University of Salamanca, Salamanca, Spain
[8]Department of Microbiology and Genetics, University of Salamanca, Salamanca, Spain
[9]Department of Immunoallergy/Servicio de Inmunoalergia, Hospital Universitario de Salamanca, Salamanca, Spain

J Investig Allergol Clin Immunol 2021; Vol. 31(3): 196-211
doi: 10.18176/jiaci.0673

Abstract

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nose and paranasal sinuses that is often associated with nasal polyposis (CRSwNP) in the most severe cases. As in other complex diseases, genetic factors are thought to play an important role in the risk and development of the disease. Environment may also modulate the epigenetic signature in affected patients. In the present systematic review, we aimed to compile all published data on genetic and epigenetic variations in CRSwNP since 2000. We found 104 articles, 24 of which were related to epigenetic studies. We identified more than 150 genetic variants in 99 genes involved in the pathogenesis of nasal polyposis. These were clustered into 8 main networks, linking genes involved in inflammation and immune response (eg, *MHC*), cytokine genes (eg, *TNF*), leukotriene metabolism, and the extracellular matrix. A total of 89 miRNAs were also identified; these are associated mainly with biological functions such as the cell cycle, inflammation, and the immune response. We propose a potential relationship between genes and the miRNAs identified that may open new lines of investigation. An in-depth knowledge of gene variants and epigenetic traits could help us to design more tailored treatment for patients with CRSwNP.

Key words: Nasal polyposis. Gene variants. Polymorphisms. Epigenetics. Chronic rhinosinusitis. Systematic review.

Resumen

La rinosinusitis crónica (CRS) es una enfermedad inflamatoria de las fosas nasales y los senos paranasales que, en los casos más graves, suele estar asociada a poliposis nasosinusal (CRSwNP). Al igual que otras enfermedades complejas, los factores genéticos podrían contribuir de forma notable, tanto al riesgo de padecerla como a su desarrollo; por su parte, los factores ambientales modularían la huella epigenética de los pacientes. El objetivo de esta revisión sistemática es recopilar toda la información publicada desde 2000 hasta mayo de 2020 sobre las variaciones genéticas y epigenéticas relacionadas con CRSwNP, extraída de un total de 104 artículos, 24 de ellos referentes a estudios epigenéticos. En estos artículos se han identificado más de 150 variantes genéticas en 99 genes implicados en la patogénesis de la CRSwNP, que se han agrupado en ocho redes funcionales principales, relacionadas con la inflamación, la respuesta inmune (incluyendo genes como MHC, TNF o genes de citocinas), el metabolismo de leucotrienos y con genes relacionados con la matriz extracelular. También se han identificado 89 miRNA asociados a funciones biológicas, como el ciclo celular, la inflamación y la respuesta inmune. Gracias al uso de herramientas bioinformáticas, se sugieren relaciones potenciales entre genes y miRNA relevantes para la enfermedad, lo que puede constituir nuevas líneas de investigación. Un conocimiento en profundidad de las variantes genéticas y las huellas epigenéticas de los pacientes con CRSwNP podría contribuir al diseño de tratamientos más personalizados y eficaces.

Palabras clave: Poliposis nasosinusal. Variantes genéticas. Polimorfismos. Epigenética. Rinosinusistis crónica. Revisión sistemática.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nose and paranasal sinuses defined by the presence of 2 or more symptoms, 1 of which should be either nasal blockage, obstruction, congestion, or nasal discharge, in combination with facial pain or pressure, and/or reduction in or loss of smell for at least 12 weeks [1,2]. Two primary forms are widely recognized, namely, CRS with nasal polyposis (NP) in the middle meatus (CRSwNP) and CRS without NP (CRSsNP). Eosinophilic CRS is a subtype of CRSwNP associated with severe eosinophilic infiltration in sinus tissue, which is more common in Western countries. In contrast, noneosinophilic CRSwNP, which is characterized by neutrophil-dominant inflammatory infiltration, is much more prevalent in Asian countries such as China, Korea, and Japan, although the prevalence of eosinophilic CRSwNP is rising [3].

The prevalence of CRSwNP in the general population is around 4%, with the disease being more likely in males than females [4]. Onset is primarily in adulthood, on average at around 42 years [3]. Based on the 22-item Sinonasal Outcome Test score, CRS has a negative impact on quality of life compared with controls (42.0 vs 9.3). An increase in health care expenditure has also been reported, with estimated annual direct costs per patient of $2609 in the US and €1861 in Europe. The indirect costs, ie, those derived from absenteeism and decreased productivity at work, are even greater, and CRS has been identified as one of the top 10 most costly health conditions for US employers (>$20 billion per year) [2].

CRSwNP is often associated with asthma (26%-48% of patients), and a subset of patients develop aspirin exacerbated respiratory disease (AERD), which negatively affects the course of CRSwNP [5].

Early studies have reported an unusually high prevalence of CRSwNP within some families, pointing towards a genetic component [6,7]. Given that CRSwNP is a complex disease, we expect a plethora of variants in multiple genes, but not in a single gene. Technical approaches such as genome-wide association studies may provide an extensive overview of the genes associated with the disease when performed in large cohorts of well-characterized patients and appropriate controls. However, since only a few such studies have been performed to date, current knowledge of the genetic basis of CRSwNP comes mainly from candidate gene approaches [8].

As the interface between genes and environment, epigenetic modifications may help us to understand the etiology of complex traits and diseases, such as CRS, leading to a more in-depth knowledge of the clinical and molecular factors involved [9], allowing for the identification of different clusters of patients in different geographical areas, and, therefore, enabling us to select the most effective therapeutic intervention [10]. Authors have undertaken this approach by focusing on the 3 main epigenetic mechanisms, ie, DNA methylation, histone modifications, and noncoding RNAs, mostly microRNAs (miRNAs). Thus, by investigating regulation of gene expression in both CRSwNP patients and controls it will be possible to identify disease-specific epigenetic markers.

Considering the large amount of information published in the last 20 years, we aimed to clarify the field by systematically reviewing all articles on the genetics and epigenetics of NP.

Methods

This systematic review was performed using the PRISMA guidelines for Systematic Reviews and Meta-Analysis and 2009 checklist and the GRADE recommendations [11].

We searched for original articles indexed from January 2000 to May 2020 describing genetic or epigenetic aspects of NP. We identified eligible studies using the following inclusion criteria: (*1*) primary study or meta-analysis; (*2*) written in English, French, or Spanish; (*3*) human participants (both children and adults); (*4*) patients with CRSwNP; and (*5*) description of mutations, single-nucleotide polymorphisms (SNPs), genetic variants, or epigenetic modifications in association with disease onset, severity, or population prevalence. The exclusion criteria were as follows: (*1*) animal, histological, in vitro, or in silico studies; (*2*) review articles; (*3*) transcriptomic or expression analysis without epigenetic/genotyping analysis; (*4*) articles focused on other diseases, in which NP was merely mentioned; (*5*) studies about CRS without specific reference to NP or those in which the CRSwNP patients were not explicitly identified; and (*6*) articles whose full-text version was not available to us or that were written in other languages.

The literature search was performed between May and June 2020 in PubMed, the Cochrane Library, and Scopus databases using the following terms: “nasal polyps” or “chronic rhinosinusitis” or “CRSwNP” and “gene” or “genetic” or “mutation” or “epigenetic” or “DNA methylation” or “sequencing” or “microRNA” or “polymorphism” or “genome-wide association study” or “microarray” or “gene profiling”.

Three authors independently reviewed database search results, assessed titles, evaluated abstracts, and considered the study for full review. Any disagreements in either the title/abstract or the full manuscript review phases were resolved by consensus. All eligible studies were formally evaluated and included in this systematic review.

The authors independently evaluated the quality appraisal and graded the risk of bias of the studies included.

The risk of bias was assessed using Rob2, the tool recommended for this purpose in randomized trials included in Cochrane Reviews [12], albeit slightly modified to fit the nature of the articles selected. Studies were classified as having low, moderate, or high risk of bias.

Quality was assessed using the Newcastle-Ottawa scale (NOS) [13]. Each study was awarded 1 point per positive item, according to the scale. Scores over 6 were classified as “high quality”, those below 4 “low quality”, and the remainder “moderate”.

Gene pathway analysis of the genes found was performed using ShinyGO [14], FunRich 3.1.3 [15], and STRING [16]. miRNAs were analyzed using the online tool TAM2.0 [17] and miRSystem [18].

Results

Selection, Bias, and Quality of Articles

Our database search yielded 587 articles after removal of duplicates (Figure 1). After the title and abstract review, 408 articles were excluded since they did not fulfill the eligibility criteria. Therefore, 179 articles qualified for full-text review. Of those, we eliminated 22 studies that did not include any gene variant or polymorphism, 20 articles that considered CRS patients as a whole (without differentiating between those with and those without NP), 15 reviews, 16 that analyzed other diseases (eg, asthma or cystic fibrosis), and merely mentioned NP concerning such diseases, and 2 that were meeting abstracts.

Finally, 104 articles were evaluated. Of these, 24 were related to epigenetics, 70 were candidate gene studies, 9 were genome-wide association studies (GWAS), and 1 was based on a SNP array.

A description of the 80 selected nonepigenetic studies is presented in Supplementary Table 1. Epigenetic articles are summarized in Supplementary Table 2.

We followed the Cochrane guidelines to assess the risk of bias of the studies selected using an adapted version of the Rob2 tool that fit the specific nature of the genetic analysis. Since our primary concern for bias referred to the lack of appropriate controls or techniques that were inappropriate for the intended aim, we responded to questions about intervention or randomization. Consequently, studies classified as being at high risk of bias were those in which healthy controls were missing or the methodology was not clearly explained in the text.

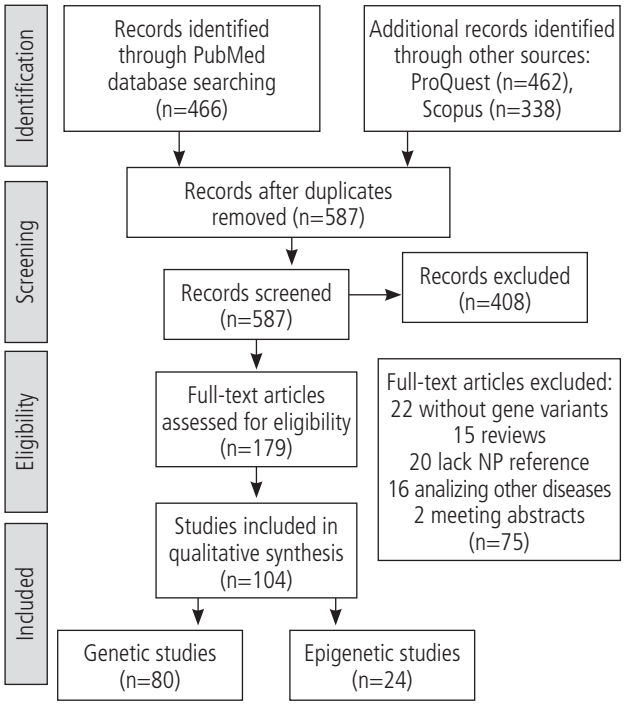

Figure 1. Flow diagram of the selection process. NP indicates nasal polyposis.

Under these conditions, 12.7% of the studies were considered at high risk of bias according to the algorithm (Figure 2A). The leading causes for qualifying a study as being at high risk included issues with the randomization process, ie, lack of healthy controls to compare with and poorly described methods. Two studies used public databases for information on the healthy population, thus raising concerns about the methodology applied to obtain these raw data. In summary, healthy controls were missing in 10 studies, and 1 article included human placenta as a control instead of nasal mucosa, which would be a more suitable tissue for comparison.

Consistently, 84.1% of the articles were considered to be of high quality after running the NOS questionnaire (Figure 2B). Overall, adequate case definition and nonresponse rate were the better scored categories. Fourteen articles were considered to be of moderate quality, mainly due to failed selection and definition of relevant controls. Only 1 study scored below 4.

Genetic Studies

A total of 99 genes and over 150 SNPs and genetic variants were identified as being related to NP in the selected articles and classified into those related to an increased risk of NP, those related to a reduced risk of NP, and those described as associated with the disease (Table 1).

A preliminary study of functional categories and GO pathways was performed using the ShinyGO v0.61 tool (Figure 3). The main functional categories included the cytokine-mediated signaling pathway, defense response, inflammatory response, response to cytokines, and immune response (FDR<1.5e-13), while the top high-level GO categories were response to stress, regulation of response to stimulus, and immune system process (Supplementary Table 3).

We also submitted the data for gene clustering using the STRING software. Figure 4 shows the results for the whole gene list cluster (Figure 4A), as well as clusters for those genes that increased the risk of NP (Figure 4B) and those that decreased the risk (Figure 4C). For purposes of clarity, those genes that failed to be connected were hidden.

Eight clusters were identified in the general list of genes. The most highly populated was the brown cluster (1), which mainly included *HLA* genes. An enrichment study showed this cluster to be associated with the immune response (FDR 3.67e-15), the cell surface receptor signaling pathway (FDR 7.49e-15), immune system processes (FDR 1.92e-12), and antigen processing and presentation (FDR 9.05e-10). The red cluster (2), consisting of cytokines and related genes, was accordingly associated with the cytokine-mediated signaling pathway (FDR 4.19e-17) and also with the response to stress (FDR 5.75e-13) and immune system processes (FDR 1.92e-12). The olive cluster (3) was related to the response to stress (FDR 5.75e-13) and, together with the turquoise cluster (4), to response to chemical stimulus (FDR 1.36e-11). The light green (5) and blue (6) clusters were involved mainly in signal transcription (FDR 1.42e-10), among other functions. Genes from the purple cluster (7) were implicated in general processes such as response to stimuli.

In the case of genes linked to the risk of developing disease, we decided to expand the network with the 5 most closely

Table 1. Genes and Corresponding Single-Nucleotide Polymorphisms (SNPs) Reported as Being Related to CRSwNP

Increase Risk	SNP/Variant	Decrease Risk	SNP/Variant	Associated	SNP/Variant
ACE [54]	rs4309 rs4293	*ALOX15 [55]*	rs34210653	*ADORA1 [64]*	rs16851030 rs6664108
ADRB2 [69]	rs1042713(A)	*AOAH [37,40]*	rs4504543	*AGER [48]*	rs1800625
ANX4 [54]	rs7588022	*CD8A [27]*	rs3810831(C)	*ALOX5 [56]*	rs3780894
CACNG6 [37]	rs192808	*DCBLD2 [37]*	rs828618	*ALOX5AP [56]* *ALOX15 [128]*	rs17612127 rs34210653
CCL11 [68,70]	rs1490392522 (G) rs762429865 (5G)	*EBI3 [136]*	rs428253	*AOAH [73]*	rs4504543
CFTR [66]	ΔF508	*FANCC [22,54]*	rs1326188	*BICD2 [21]*	
CIITA [110]	rs12932187	*HLA-B [22]*	*57	*CACNA1I [73]*	rs3788568
COX2 [52]	rs20417(A) rs20417 (C)	*HLA-Cw [22]*	*04	*CAT [53]*	-21(TT)
FCER1A [65]	rs2427827(T)	*HLA-DQA1 [24]*	*05012	*CD14 [133]*	rs946564423 (C)
FCER1G [54]	rs4489574	*HLA-DQB1 [19,24]*	*0301	*CYSLTR1 [56]*	rs321090
FOXP3 [136]	rs2294018 rs2232365	*HLA-DQ [26]*	*07	*CYP2S1 [55]*	rs338598
FS1P [54]	rs502581 rs2631700 rs2631702	*HLA-DR7 [24]*		*DCBLD2 [124]*	rs828621 rs1371687 rs7615856 rs828618 rs8833
HLA-A [22]	*24 *33	*HLA-DRB1 [22,25]*	*08 *11	*EMID [125]*	rs6945102 rs4729697 rs221 rs10435333 rs6947185 rs4727494 rs13233066 rs1008064 rs1543883 rs13245946
HLA-B [22]	*07	*HLA-DRB3 [19]*			
HLA-Cw [22]	*01 *12	*IL10 [54]*	rs1800872 rs1554286		
HLA-DQB1 [19,24]	*0202 *0302	*IL1A [139]*	rs2856838	*FOXP1 [55]*	rs17718444
HLA-D [26]	*08 *09	*IL1B [37]*	rs16944	*HLA-A74 [119]*	
HLA-DR [24,26]	*09 *07 *16	*IL4 [45]*	-590C/T	*HLA-DRA [21,23]*	rs9268644 rs3129878 rs3129881 rs2239805
HLA-DRB1 [25]	*03 *04	*IRAK4 [37,40]*	rs4251431 rs4251559 rs4251513 rs146567	*HLA-DQA1 [55]*	rs1391371
				HLCS [21]	
				HSP70-2 [48]	rs1061581

(*continued*)

Table 1. Genes and Corresponding Single-Nucleotide Polymorphisms (SNPs) Reported as Being Related to CRSwNP (continued)

Increase Risk	SNP/Variant	Decrease Risk	SNP/Variant	Associated	SNP/Variant
HLA-DRB4 [19]		*NOS1 [135]*	rs9658281 rs1483757	*IL1RN [39]*	rs2234663
				IL18R1 [55]	rs6543124 rs206976
IFNRD1 [111]	rs7817 (T)	*PPARG [140]*	rs2960421 rs4135275 rs1875796	*IL2 [39]*	
IL10 [37,54]	rs1800870 rs1800896 rs3024498	*P73 [129]*	rs3765731 (A)	*IL22RA1 [29]*	rs4292900 rs4648936 rs16829225
IL1A [28,35,37,38]	4845 (G/T) rs17561 rs1800587	*RG7SBP [54]*	rs6870654	*IL33 [55]*	rs1888909
IL1B [32,35,50]	-511(C/T)	*TBXAS1 [54]*	rs13239058 rs10487667 rs6962291	*IL4 [39]*	rs8179190
IL1RL1 [36,41]	rs1420101 86-bp intron2 rs13431828	*TSLP [137]*	rs252706 rs764917	*IRAK4 [31]*	rs1461567 rs4251559
IL1RN [34]				*KIAA1456 [73]*	rs11779957
IL22 [29]	rs4292900 rs4648936 rs16829225			*LAMA2 [73]*	rs2571584
IL33 [37,41]	rs3939286 (A)			*LAMB1 [73]*	rs4727695
IL4 [32,43]	-590C>T (C)			*LTA [48]*	rs909253
KIFC3 [54]	rs2285700			*LTC4S [56,57]*	rs730012 (A)
LTF [138]	rs1126478			*MET [71]*	
LTC4S [57,58]	rs730012 (C)			*MSRA [73]*	rs7001821
MET [52,71]	rs78116323(G) rs38850			*MUSK [73]*	rs10817091
MMP2 [132]	rs857403			*MYRF [55]*	rs174535
MMP9 [37,131]	rs3918242 rs2274756			*NAV3 [73]*	rs1726427
MS4A2 [54]	rs573790			*NOS1AP [135]*	rs12047527
OSF2 [138]	-33C/G rs3829365			*NOS2 [53,57,126]*	-277(GG) CCTTT
PARS2 [115]	rs2873551 rs2270004 rs11577368 rs1180946 rs1180945			*PARS2 [73]*	rs2873551
				PTGDR [57]	-613 (C) -549(C) -441(C) -197(C/T)
RYBP [37,40]	rs4532099				

(*continued*)

Table 1. Genes and Corresponding Single-Nucleotide Polymorphisms (SNPs) Reported as Being Related to CRSwNP (continued)

Increase Risk	SNP/Variant	Decrease Risk	SNP/Variant	Associated	SNP/Variant
RYD5 [122]	rs113795008 rs2280540 rs2294083 rs2294082			*SERPINA1 [72]*	rs1243168 rs4900229
				SLC5A1 [21]	
SERPINA1 [40,72]	rs1243168 (T) rs4900229			*SLC22A4 [55]*	rs1050152
TAPBP [27]	rs2282851(T)			*TAS2R13*	rs1015443
TAS2R38 [59,61,141]	rs713598 (C) rs1726866 (A) rs10246939(C)			*TAS2R20*	rs12226920 rs12226919
TNF [30,35,37,47,49-51]	rs1800629 (A) rs1799724 (C)			*TRIP12 [73]*	rs10535833
				TNF [48]	rs1800629
TSLP [121]	rs1837253			*TSLP [55]*	rs1837253
				VSIR [21]	

linked genes to obtain a broader view of their functions. Five clusters were found for genes related to an increased risk of NP. The most highly populated corresponded to that including *COX* genes, which are mainly involved in aerobic electron transport chains (FDR 2.26e-08). A cytokine cluster was also identified. Three clusters were defined for genes associated with a reduced risk. One included the Fanconi anemia family (*FAN*), which could be implicated in DNA interstrand cross-link repair (FDR 1.32e-15). The other 2 clusters—*ILs* and *HLAs*—have already been mentioned. It should be noted that some genes, eg, *IL1A* and *IL10*, have been related to both higher and lower risk of NP, depending on the SNP studied (Table 1).

We further explored the influence on biological functions of the genes that increase the risk by comparing them with the protective genes using the FunRich software application (Figure 5). Thus, differences in gene enrichment were noticeable for cytokine signaling and activity, IL-1 signaling, and MHC receptor activity, suggesting that activation of these pathways and processes may be linked to a reduced risk of disease.

Overview of Studies

Since the list of selected studies is extensive, we review them according to the clusters mentioned above in order to facilitate reading (Figure 4).

1) Brown cluster: *HLA* genes

Eight articles were dedicated to analyzing the association between *HLA* gene variants and NP [19-26]. Most of the variants described increased the risk of NP, and some have been confirmed in 2 different populations, namely, *DQA1*0201* in Hungarian [24] and Mexican [20] patients and *HLA-DRB1*03* and **04* in Turkish [22] and Mexican [25] patients. *HLA-DQB1*0301*, on the other hand, was reported to be linked to a reduced risk of NP in both Hungarian [24] and Iranian [19] cohorts.

Alromaih et al [27] studied the 2 related genes *TAPBP* and *CD8*, which are also included in this cluster, reporting that the minor allele C in *CD8* rs3810831 would reduce the risk of NP, while the minor allele T in *TAPBP* rs2282851 would increase it.

2) Red cluster: *IL* and associated genes

Fourteen articles studied *IL* and related genes, although not all of them reported a significant association between the SNPs and the variants analyzed [28,29,38-41,30-37]. Thus, Erbek et al [35] and Mrowicka et al [32] found a positive correlation between *IL1B* –511C>T and NP, while others reported no association [34,38]. *IL1B* rs16944 was reported both as not associated [28] and associated with a reduced risk of NP [37].

The association has been shown to depend on the SNP. Thus, *IL1A* rs17561 [28,35,38,42], rs13431828 [40], and rs21800587 [28] have been associated with an increased risk of NP, while *IL1A* rs2856838 [28] was linked to a reduced risk.

Tewfik et al [31] studied a wide range of *IRAK4* SNPs, reporting that the C allele of rs1461567, the G allele of rs4251513, and the A allele of rs4251559 of the *IRAK4* gene were associated with high serum levels of IgE in NP patients. Likewise, Zhang et al [40] found an association between IgE levels and rs4251513, and reported that rs4251431, rs6582484, rs1461567, and rs3794262 were linked to a reduced risk of NP.

Despite not being included in the red cluster, *IL4* was linked to other ILs that increased the risk of NP (Figure 4B) [33,39,43]. However, published data are controversial since the same SNP (–590C>T) has been reported to increase the risk [44], reduce the risk [45], and even not to be associated with NP [46].

Table 2. Noncoding Sequences With Differential Expression in CRSwNP Patients

Upregulated	Downregulated	Upregulated	Downregulated
ENSG00000248810.1 [83]	ENSG00000181123.4 [83]	XLOC_016248 [83]	hsa-miR-20a-5p [84]
ENSG00000253339.1 [83]	ENSG00000250360.1 [83]	XLOC_017561 [83]	hsa-miR-20b-5p [84]
hsa-miR-125b [86]	hsa-miR100-5p [84]	XLOC_018649 [83]	hsa-miR-23a-3p [84]
hsa-miR-125b-5p [84,89]	hsa-miR106a-5p [84]	XLOC_018891 [83]	hsa-miR-23a-5p [91]
hsa-miR-1290 [89]	hsa-miR-1226-3p [91]		hsa-miR-25-3p [94]
hsa-miR-141-3p [84]	hsa-miR-124 [85]		hsa-miR-27a-3p [84,94]
hsa-miR-142-3p [90]	hsa-miR-125b-2-3p [84]		hsa-miR-29a-3p [84,94]
hsa-miR-150-5p [88,89]	hsa-miR-125b-5p [84]		hsa-miR-30e-3p [89]
hsa-miR-193a-5p [84]	hsa-miR-126-3p [84,89]		hsa-miR-30e-5p [89]
hsa-miR-19a [87]	hsa-miR-1273h-3p [89]		hsa-miR-3149 [91]
hsa-miR-200a-3p [84]	hsa-miR-1298-5p [91]		hsa-miR-3184-5p [91]
hsa-miR-200b-3p [84]	hsa-miR-1299 [91]		hsa-miR-3196 [91]
hsa-miR-210-3p [89]	hsa-miR-130a [84,94]		hsa-miR-32-3p [91]
hsa-miR-210-5p [91]	hsa-miR-130a-3p [89]		hsa-miR-3614-5p [89]
hsa-miR-30d-5p [84]	hsa-miR-130b-3p [84]		hsa-miR-362-3p [89]
hsa-miR-30e-5p [84]	hsa-miR-138-5p [94]		hsa-miR-363-3p [89]
hsa-miR-3146 [91]	hsa-miR-139-5p [89]		hsa-miR-375 [91]
hsa-miR-3178 [91]	hsa-miR-143-3p [89]		hsa-miR-377-5p [91]
hsa-miR-320e [91]	hsa-miR-146a [92]		hsa-miR-3924 [91]
hsa-miR-342-3p [89]	hsa-miR-152-3p [89]		hsa-miR-486-5p [89]
hsa-miR-34b-3p [84]	hsa-miR-16-5p [89]		hsa-miR-500a-5p [91]
hsa-miR-34b-5p [84]	hsa-miR-17-5p [84]		hsa-miR-532-3p [91]
hsa-miR-4485 [89]	hsa-miR-18a-5p [84]		hsa-miR-548e-3p [91]
hsa-miR-449b-5p [84]	hsa-miR-18b-5p [84,94]		hsa-miR-550a-3p [89]
hsa-miR-449c-5p [84]	hsa-miR-19a-3p [89]		hsa-miR-574-5p [91]
hsa-miR-585-3p [91]	hsa-miR-1914-5p [91]		hsa-miR-584-5p [89]
hsa-miR-92b-3p [84]	hsa-miR-193-3p [84,94]		hsa-miR-612 [91]
XLOC_000122 [83]	hsa-miR-193b-3p [84]		hsa-miR-628-3p [89]
XLOC_003006 [83]	hsa-miR-199a-3p [89]		hsa-miR-6503-3p [89]
XLOC_011814 [83]	hsa-miR-199a-5p [89]		hsa-miR-663 [93]
XLOC_015500 [83]	hsa-miR-199b-3p [89]		hsa-miR-668-3p [91]
			hsa-miR-6867-5p [89]
			hsa-miR-708-5p [89]
			hsa-miR-92a-3p [84,87]
			hsa-miR-942-3p [89]
			XLOC_005882 [83]
			XLOC_010305 [83]
			XLOC_010540 [83]
			XLOC_015712 [83]
			XLOC_018024 [83]
			XLOC_018529 [83]
			XLOC_019396 [83]
			XLOC_025155 [83]

Abbreviation: CRSwNP, chronic rhinosinusitis with nasal polyposis.

3) Olive cluster: *TNF* and related genes

The olive cluster is organized around TNF. Many studies have focused on this crucial gene, showing a positive correlation between rs1800629 and the risk of NP [35,37,42,47-50], although other authors failed to find such a correlation [28,51]. Thus, Mfuna-Endam et al [28] did not find an association for any of the 16 SNPs studied, while Berghea et al [51] reported rs1799724, but not rs1800629, as being associated with increased risk. Moreover, Szabo et al [48] reported that the association with NP was linked to an ancestral haplotype (8.1), including rs1800629, *AGER* rs1800625, *HSP70-2* rs1061581, and *LTA* rs909253.

MT-CO2 (COX2) rs20417 [52] and *NOS-2* and *CAT* [53] have also been related to NP. Data and pathway analysis supported the association between *COX* genes and increased risk of NP, as shown in Figure 4B.

The olive cluster is closely related to the red cluster, with *IL10* as the connecting node. *IL10* rs1800870 [54] and rs1800896 [37] have been reported to be associated

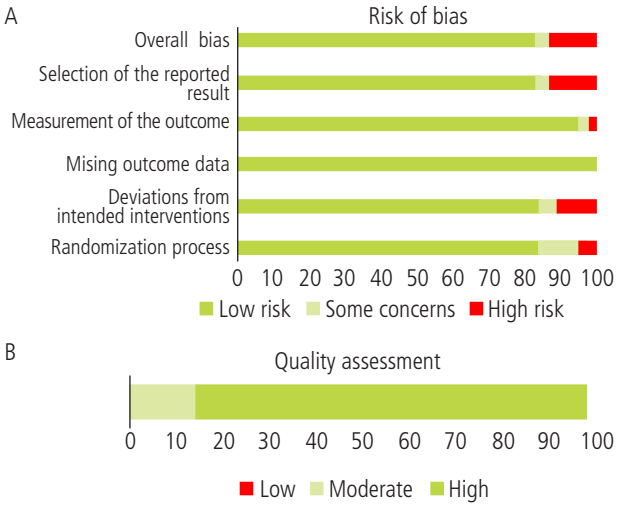

Figure 2. Risk of bias (A) and quality assessment (B) of the selected articles.

with an increased risk of NP, whereas *IL10* rs1800872 and rs1554286 [54] seemed to confer protection against NP.

4) Turquoise cluster

In the case of *ALOX* genes, the missense variant rs34210653[A] (Thr560Met) in *ALOX15* would confer a 68% reduction in the risk of NP [55]; *ALOX5* rs3780894 and *ALOX5AP* rs17612127 have been associated with the disease [56]. While an association with NP has been published for LTC4S rs730012 [57,58], other authors did not find such a relationship [56].

5) Light green cluster: *TAS* genes

Taste receptor genes (*TAS*) have also been extensively studied in relation to NP. Mfuna-Endam et al [59] published an exhaustive overview of 19 TAS receptor genes, showing different allele frequencies between patients and controls for 57 SNPs in *TAS2R* genes and 16 SNPs in *TAS1R* genes.

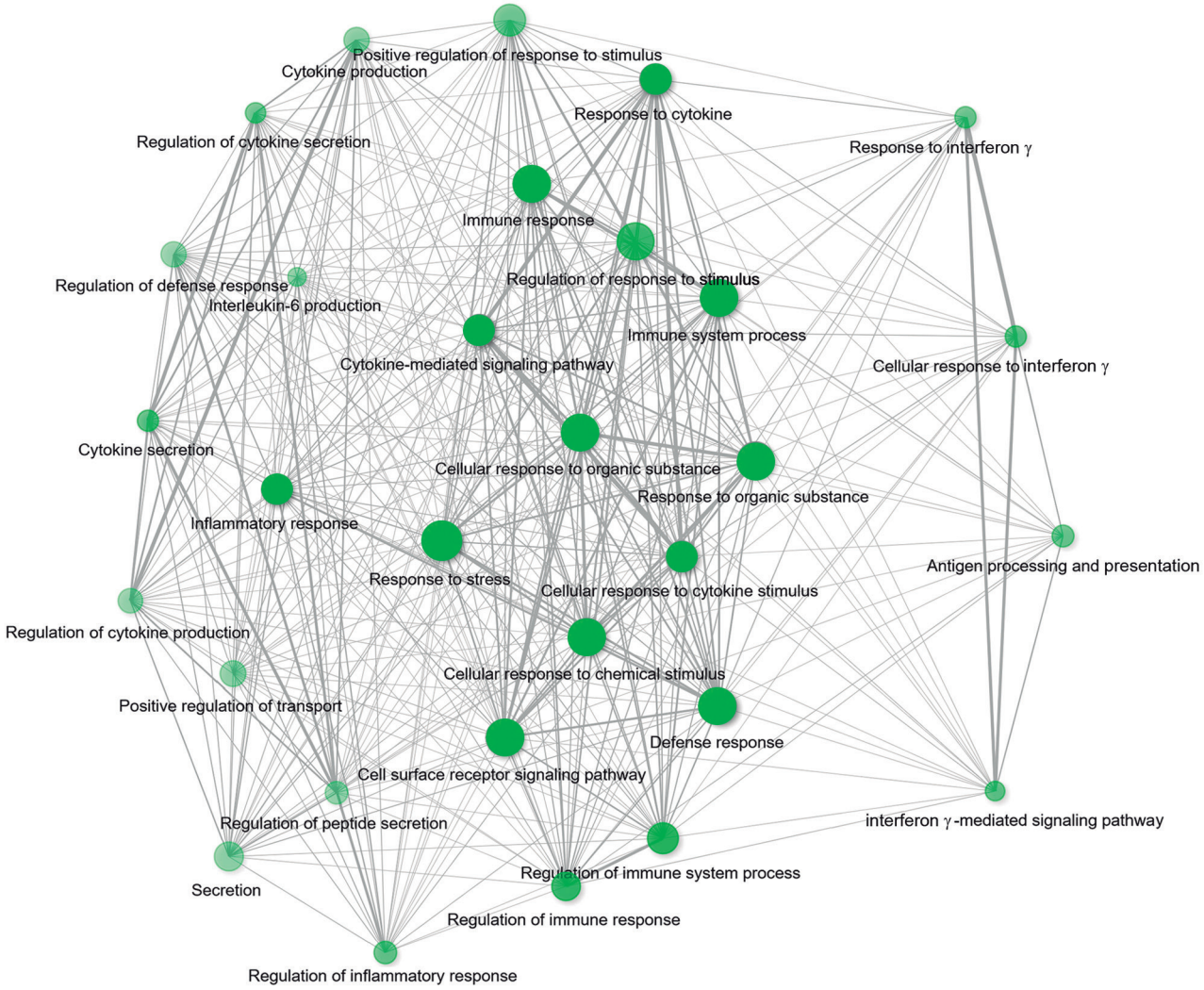

Figure 3. Main biological functions involving the genes reported as being associated with chronic rhinosinusitis with nasal polyposis.

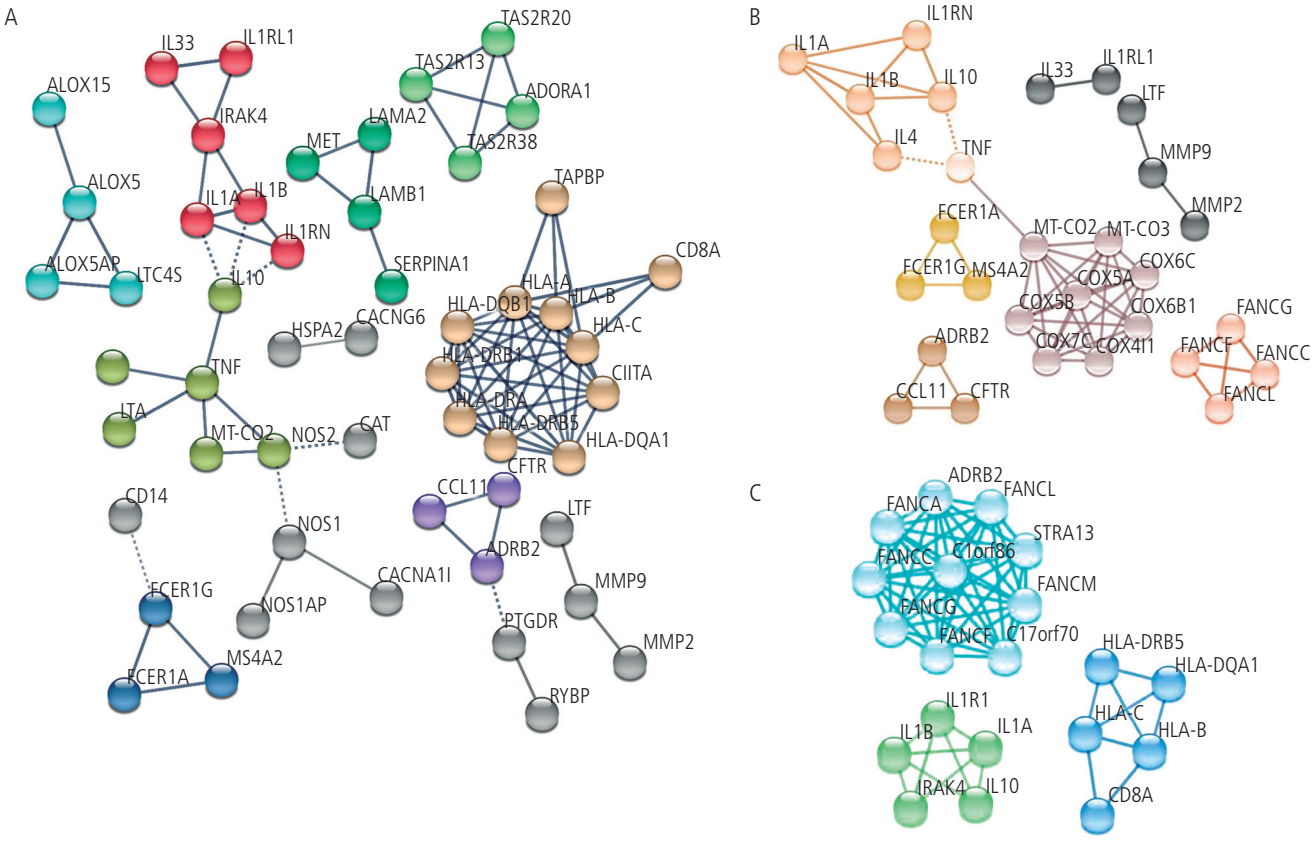

Figure 4. Clustering of genes associated with CRSwNP (A). Clusters associated with genes that increase (B) or decrease (C) the risk of chronic rhinosinusitis with nasal polyposis.

Several authors have focused on 3 SNPs of *TAS2R38*, ie, rs713598 (C145G; Pro>Ala), rs1726866 (C785T; Ala>Val), and rs10246939 (G886A; Val>Ile). The PAV genotype has been associated with better outcomes [60], while the alternate genotype AVI has been related to an increased risk of NP [61]. Other studies did not find any association between these variants and the disease [62,63].

With respect to *ADORA1*, differences in allele frequencies were reported only for NP patients with AERD [64].

6) Other clusters

The blue cluster genes *FCER1A*, *FCER1G*, and *MS4A2* have been associated with an increased risk of NP [54,65].

In the purple cluster, it is worth mentioning a gene related to cystic fibrosis that has also been studied in NP, namely, *CFTR*, and the variant ΔF508, albeit with contrasting results. While it was significantly associated with NP in a Polish population [66], data from a Finnish cohort did not show any differences compared with healthy controls [67], and Wang et al [68] reported its presence in only 7% of American patients tested. Allele A of *ADRB2* rs10452713 appeared to be more frequent in NP patients [69], while the association between *CCL11* and NP was described as statistically weak [70].

Regarding the green cluster, *MET* has been associated with an increased risk of NP [52,71], while the *SERPINA1* [72] and

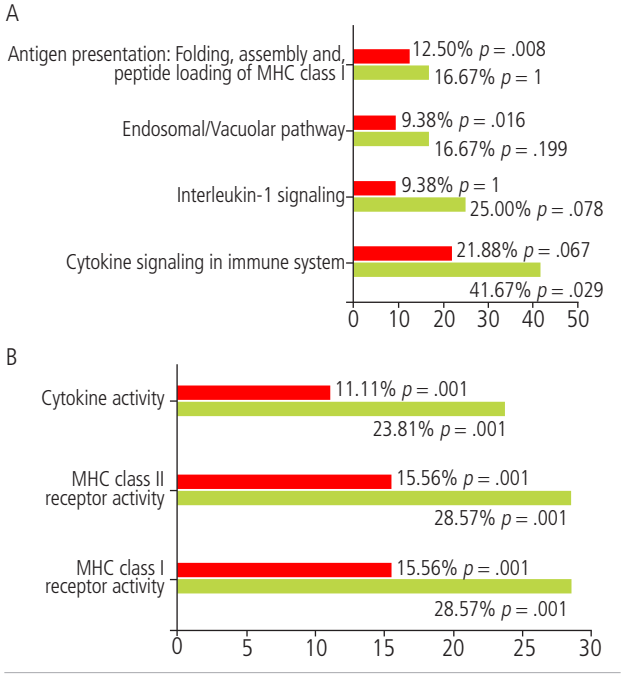

Figure 5. Gene enrichment comparison between genes that increase the risk and those that decrease the risk of chronic rhinosinusitis with nasal polyposis.

LAM genes [73] seemed to be associated with NP. However, Zhang et al [40] could not replicate the *LAM* results in a Chinese population.

Epigenetic Studies

Two of the selected studies focused on histone acetylation [74,75], 7 on DNA methylation [76-82], and 12 on ncRNAs, both lnc- [83] and miRNAs [84,85,94,86-93]. One article aimed to determine varying DNA modifications [95], and another explored polyadenylation [96]. We also included an mRNA expression study because it investigated miRNA machinery components in CRSwNP [97].

Histone Acetylation

Two studies by the same group examine hyperacetylation of histone H4 due to inhibition of histone deacetylase 2 (HDAC), which seemed to be associated with myofibroblast differentiation and extracellular matrix accumulation in NP (Supplementary Table 2).

DNA Modifications

While most articles refer to DNA methylation, Seiberling et al [95] also explored other modifications, such as bromination and chlorination of cytosines, and found significantly higher levels of 5-bromocytosine in polyps when compared with healthy ethmoid tissue.

Cheong et al [76] performed a genome-wide DNA methylation assay, comparing NP and blood samples from aspirin-intolerant asthma patients and aspirin-tolerant asthma patients. While several differentially methylated loci were found, the results must be interpreted with caution, given the purpose of this current systematic review and the lack of proper healthy controls.

Kim et al [79] performed a methylation profiling study comparing NP with uncinate process tissue and found that 397 and 387 genes were hypermethylated in patients with eosinophilic CRSwNP and noneosinophilic CRSwNP, respectively, and that 399 and 208 genes were hypomethylated compared with healthy controls. Most genes were involved in cancer pathways.

Specific genes involved in NP were selected to determine the degree of methylation in their promoter regions. *KRT19*, *NR2F2, ADAMTS1*, and *ZNF222* were the top 4 genes whose promoters were significantly hypomethylated in NP in Korean patients [78], whereas *COL18A1, EP300, GNAS*, and *SMURF1* were reported to be the 4 most changed genes in Chinese CRSwNP patients [82]. DNA methylation has also been studied in individual genes, such as *PLAT* [77], *TSLP* [80], and *IL8* [81].

RNAs

Most studies on noncoding RNAs focus on miRNA. Table 2 shows all the available lcnRNAs and miRNAs published in the selected articles (25 upregulated and 62 downregulated RNAs). Interestingly, in 1 study, not all the entities analyzed were accessible to us [93]. Therefore, we would suggest the interested reader check the original article for a complete overview.

We then analyzed the list of miRNAs using the online tool TAM 2.0. The results are shown in Figure 6. First, we analyzed upregulated and downregulated miRNAs and plotted them using bubble plots (Figure 6A and B, respectively). The size of the bubble indicates the number of input miRNAs present in each set. As shown, the top functions related to upregulated miRNAs were cell cycle (*P*-value 8.28e-9; FDR 3.34e-6), cell proliferation (*P*-value 1.42e-6; FDR 1.73e-4), and inflammation (*P*-value 2.60e-6; FDR 2.25e-4), while the top functions related to downregulated miRNAs were hormone-mediated signaling pathways (*P*-value 2.82e-13; FDR 8.55e-11), immune response (*P*-value 7.00e-13; FDR 1.41e-10), and inflammation (*P*-value 5.68e-10; FDR 3.27e-8). We also include correlations (Figure 6C) between deregulated miRNAs found in the studies selected and deregulated miRNAs in relevant disease conditions, such as allergic rhinitis and rhinosinusitis. However, the indexes were low compared with the top 3 diseases (also included in the plot).

The role of miRNAs in the development of NP has been reported through regulation of the expression of relevant genes, including *IL10* [86], *AHR* [85], *EGR2* [87], *EGFR* [91], *TGFB* [92], and *4E-BP1* [94].

In relation to miRNA processing, Zhang et al [97] studied the components of miRNA machinery and found that PACT mRNA expression was upregulated in CRSwNP compared with controls, while no differences were observed for other components.

Tian et al [98] demonstrated switching of 3′UTR lengths in nasal polyps when compared with uncinate process mucosa from the same patient. The authors also described a switch to distal or proximal polyA sites in several genes, including *DEDD*, *p53RPF*, *SOD1*, and *SOD2*, which may affect regulation of their expression.

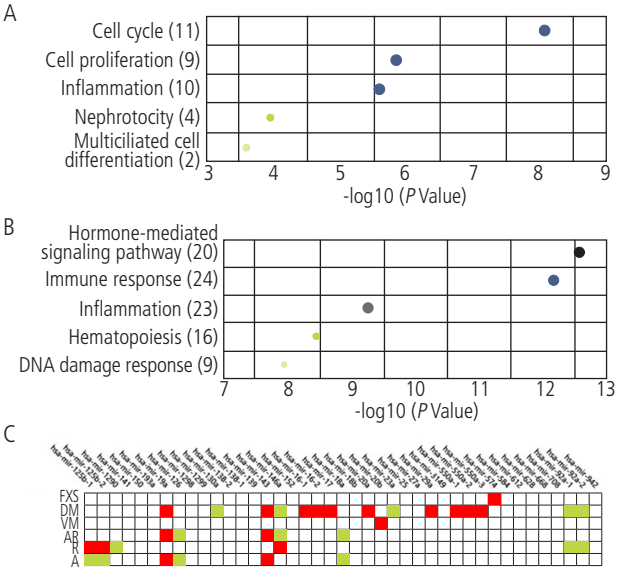

Figure 6. Enrichment of miRNAs in biological processes. A, Functions involving miRNA upregulated in CRSwNP. B, Functions involving downregulated miRNA. C, Association between miRNA and relevant diseases. FXS, indicates fragile X syndrome; DM, diabetes mellitus; VM, viral myocarditis; AR, allergic rhinitis; R, rhinosinusitis; A, asthma.

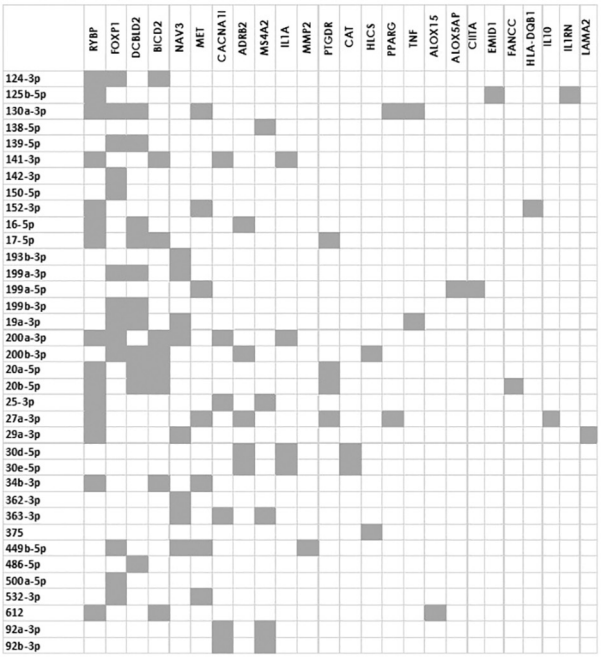

Figure 7. Relevant genes linked to miRNA. Genes found in the selected genetic articles that have been published as connected to miRNA identified by the selected epigenetic articles.

Genes to miRNA

In an attempt to combine the information obtained from genetics and epigenetics studies, we ran the list of miRNAs and the list of genes using the online tool miRSystem to investigate synergies between the two. We found links for 25 genes out of 99 and 37 miRNAs out of 87 (Figure 7). Among them, *RYP* and *FOXP1* were connected with the largest number of miRNAs (15 and 14 miRNAs, respectively). The miRNAs that appeared to be associated with more genes in the list were hsa-miR-17-5p, hsa-miR-19a-3p, hsa-miR-20a-5p, and hsa-miR-27a-3p.

Discussion

In this systematic review, we bring together all the information on the genetics and epigenetics of NP published since 2000. Following the PRISMA guidelines for systematic reviews and meta-analysis, we found 104 articles published between 2000 and May 2020 that fulfilled our inclusion criteria. We identified more than 150 genetic variants in 99 genes involved in the pathogenesis of NP; these variants increase and decrease the risk of developing NP or are associated with the disease. Most of the studies were of good quality, with a low risk of bias. We also included a search for epigenetic mechanisms that may underlie the pathogenesis of NP. These epigenetic studies focused mainly on describing the miRNAs involved in NP or risk of NP. The 87 miRNAs identified are associated with biological functions such as cell cycle, inflammation, and immune response. DNA methylation has also been compared in NP patients and healthy controls. Both hypomethylated and hypermethylated genes and gene promoters have been identified and are mostly associated with cancer pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) [78].

To obtain a more in-depth knowledge of the published data, we analyzed the information compiled using the many tools available online. Our analysis of genetic studies was based on more than 13 000 healthy controls and over 9600 CRSwNP patients, as well as on 2 large database studies. Previous reviews [2,8] had already analyzed altered genes and associated functions in CRSwNP, although no thorough study of clusters has been performed to date. Eight main clusters were identified. Of these, the *HLA* gene cluster was the most populated one and appeared only as a cluster when analyzing those SNPs associated with reduced risk of CRSwNP, with a clear dominance of class II *HLA* genes over class I. In fact, the MHC class profile could be used to differentiate CRSsNP from CRSwNP, since upregulation of MHC-class I–mediated antigen presentation has been associated with CRSsNP [99].

Other critical functional clusters were those including *IL* genes (in association with *TNF* and *NOS*), leukotriene-related genes (*ALOX5* and *-15*), IgE receptor-related genes (*FCER*), taste receptors (*TAS-R*), and *CFRT*. Data for several genes, such as *TNF*, *TAS2R38*, and *NOS2*, were extracted from several studies performed in different populations, thus reinforcing the role of these genes in NP. Although the role of other genes has not been confirmed to date, recent studies on the efficacy of anti-IgE omalizumab [100], anti-IL4R dupilumab [101,102], and anti-IL5 mepolizumab [103] suggest the involvement of the *FCER* and *IL* genes in NP. Mechanisms depending on Fc epsilon receptor (FcεR) activation have been reported to underlie airway inflammation and airway remodeling [102]. On the other hand, taste receptors seem to be associated more clearly with CRS [59].

It is worth mentioning the increased risk of CRSwNP associated with airway inflammation and extracellular matrix remodeling as per clustering analysis, which is consistent with the literature on relevant genes, ie, cyclooxygenase 2 (*COX2*) [99], matrix metalloproteinase (*MMP*) 2 and 9 [100,101], and cystic fibrosis transmembrane regulator (*CFTR*) [104]. Moreover, a transcriptomic analysis of the different stages of CRS, ranging from rhinitis to severe NP, has identified elevated expression of transcripts in polyps involved in extracellular matrix remodeling and chemoattraction of effector cells, strong induction of a combined IL4/IL13 signature, and decreased protease-inhibitor expression and metabolic genes [105].

Another strength of the current systematic review is the inclusion of genetic and epigenetic mechanisms and our tentative approach to interconnect them. While we are aware that this approach is theoretical and based on software analysis and must be confirmed experimentally, it could be a good starting point for future research on the molecular mechanisms involved in CRSwNP. Interestingly, in the articles we reviewed, some of the miRNAs encoded in the MHC genes have been identified as being related to NP, namely, miR-152, miR-20a, and miR-19a. These may affect the expression of class I MHC molecules such as HLA-B [98].

Conversely, as a limitation of the present review, we must address the lack of proper controls in 10 of the 80 genetic studies, while most of the epigenetic articles include healthy tissues as controls. Furthermore, since over 80% of the genes were mentioned in only 1 study, their role in NP remains to be confirmed. Another limitation of some studies was the use of databases as a source of genetic data in healthy controls. While databases are easily accessible repositories of gene variation, critical clinical information about the patients is likely ignored. Therefore, it cannot be ruled out that the "supposedly" healthy population included mild cases of relevant atopy or asthma that could undermine the conclusions.

As CRS is a feature of cystic fibrosis in White populations, mutations in the cystic fibrosis transmembrane regulator gene (*CFTR*), a chloride channel of the plasma membrane, have also been associated with NP [68]. However, other authors did not find such an association [69]. For patients who were heterozygous for ΔF508 and a residual function allele, tezacaftor plus ivacaftor was found to improve lung function (FEV_1) when compared with placebo and ivacaftor alone [106]. This treatment has already been approved for ΔF508 carriers [2]. In a prospective study in the Netherlands, ivacaftor proved efficacious in NP in patients harboring the S125N mutation [107].

Finally, we cannot forget the new field of medical care resulting from exploration the therapeutic potential of miRNAs. Several ongoing clinical trials are testing the safety and efficacy of miRNAs for the diagnosis and treatment of diverse cancers [108]. Opening the field to other diseases, such as CRS, will undoubtedly be worth the effort.

Final Remarks

This systematic review aimed to bring together all the available information on the genetics and epigenetics of CRSwNP. The more than 100 articles reviewed provided data on multiple SNPs and genetic variants associated with the risk of developing the disease, which was both increased and reduced. Furthermore, several miRNAs and other epigenetic traits have been identified as differentially expressed in CRSwNP patients. Clusters of genes and the potential relationship between miRNAs and genes have been proposed. New lines of research are open for further investigation.

Funding

This research was funded by the Thematic Network of Cooperative Research in Health - RETICS (Red temática de investigación en salud Asma, Reacciones Adversas y Alérgicas, ARADYAL) of the Instituto de Salud Carlos III, grant number RD16/0006/0019.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Schleimer RP. Immunopathogenesis of Chronic Rhinosinusitis and Nasal Polyposis. Annu Rev Pathol Mech Dis. 2017;12:331-57.
2. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusistis and Nasal Polyps 2020. Rhinol Suppl. 2020;58:1-464.
3. Fujieda S, Imoto Y, Kato Y, Ninomiya T, Tokunaga T, Tsutsumiuchi T, et al. Eosinophilic chronic rhinosinusitis. Allergol Int. 2019;68:403-12.
4. Newton JR, Ah-See KW. A review of nasal polyposis. Ther Clin Risk Manag. 2008;4:507-12.
5. Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusistis with nasal polyps. J Allergy Clin Immunol. 2016;4:565-72.
6. Grüneberg H. The inheritance of a disease of the accesaory nasal cavities. J Genet. 1934;29:367-74.
7. Lockey RF, Rucknagel DL, Vanselow NA. Familial Occurrence of Asthma, Nasal Polyps, and Aspirin Intolerance. Ann Intern Med. 1973;78:57-63.
8. Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. Genetics of chronic rhinosinusitis: State of the field and directions forward. J Allergy Clin Immunol. 2013;131:977-93. e5.
9. Petronis A. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature. 2010;465:721-7.
10. Feinberg AP. The key role of epigenetics in human disease prevention and mitigation. N Engl J Med. 2018;378:1323-34.
11. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1 Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383-94.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019:l4898.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.
14. Ge SX, Jung D, Yao R. ShinyGO: a graphical gene-set enrichment tool for animals and plants. Bioinformatics. 2019;36:2628-9.
15. Pathan M, Keerthikumar S, Ang C, Gangoda L, Quek CYJYJ, Williamson NAA, et al. FunRich: An open access standalone functional enrichment and interaction network analysis tool. Proteomics. 2015;15:2597-601.
16. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019;47:D607-13.
17. Li J, Han X, Wan Y, Zhang S, Zhao Y, Fan R, et al. TAM 20: tool for MicroRNA set analysis. Nucleic Acids Res. 2018;46:W180-5.
18. Lu T-P, Lee C-Y, Tsai M-H, Chiu Y-C, Hsiao CK, Lai L-C, et al. miRSystem: An Integrated System for Characterizing Enriched Functions and Pathways of MicroRNA Targets. PLoS One. 2012;7:e42390.
19. Esmaeilzadeh H, Nabavi M, Amirzargar AA, Aryan Z, Arshi S, Bemanian MH, et al. HLA-DRB and HLA-DQ Genetic Variability in Patients with Aspirin-Exacerbated Respiratory Disease. Am J Rhinol Allergy. 2015;29:e63-9.

20. Fajardo-Dolci G, Solorio-Abreu J, Romero-Álvarez JC, Zavaleta-Villa B, Cerezo-Camacho O, Jiménez-Lucio R, et al. DQA1 and DQB1 association and nasal polyposis. Otolaryngol Head Neck Surg. 2006;135:243-7.
21. Bohman A, Juodakis J, Oscarsson M, Bacelis J, Bende M, Torinsson Naluai Å. A family-based genome-wide association study of chronic rhinosinusitis with nasal polyps implicates several genes in the disease pathogenesis. PLoS One. 2017;12:e0185244.
22. Keles B, Cora T, Acar H, Arbag H, Inan Z, Ozturk K, et al. Evaluation of HLA-A, -B, -Cw, and -DRB1 alleles frequency in Turkish patients with nasal polyposis. Otolaryngol Head Neck Surg. 2008;139:580-5.
23. Kim J-H, Park B-L, Cheong HS, Pasaje CFA, Bae JS, Park JS, et al. HLA-DRA polymorphisms associated with risk of nasal polyposis in asthmatic patients. Am J Rhinol Allergy. 2012;26:12-7.
24. Molnar-gabor E, Endreffy E, Rozsasi A. HLA-DRB1, -DQA1, and -DQB1 Genotypes in Patients With Nasal Polyposis. Laryngoscope. 2000;110:422-5.
25. Ramírez-Anguiano J, Yamamoto-Furusho JK, Barquera R, Beltrán O, Granados J. Association of HLA-DR3 and HLA-DR4 with sinonasal polyposis in Mexican Mestizos. Otolaryngol Head Neck Surg. 2006;135:90-3.
26. Zhai L, Sun Y, Tang L, Liu H. Polymorphism between loci for human leukocyte antigens DR and DQ in patients with nasal polyps. Ann Otol Rhinol Laryngol. 2007;116:66-8.
27. Alromaih S, Mfuna-Endam L, Bosse Y, Filali-Mouhim A, Desrosiers M. CD8A gene polymorphisms predict severity factors in chronic rhinosinusitis. Int Forum Allergy Rhinol. 2013;3:605-11.
28. Mfuna Endam L, Cormier C, Bossé Y, Filali-Mouhim A, Desrosiers M. Association of IL1A, IL1B, and TNF Gene Polymorphisms With Chronic Rhinosinusitis With and Without Nasal Polyposis. Arch Otolaryngol Neck Surg. 2010;136:187.
29. Endam LM, Bossé Y, Filali-Mouhim A, Cormier C, Boisvert P, Boulet L-P, et al. Polymorphisms in the interleukin-22 receptor alpha-1 gene are associated with severe chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2009;140:741-7.
30. Bernstein JM, Anon JB, Rontal M, Conroy J, Wang C, Sucheston L. Genetic polymorphisms in chronic hyperplastic sinusitis with nasal polyposis. Laryngoscope. 2009;119:1258-64.
31. Tewfik MA, Bossé Y, Lemire M, Hudson TJ, Vallée-Smejda S, Al-Shemari H, et al. Polymorphisms in interleukin-1 receptor-associated kinase 4 are associated with total serum IgE. Allergy. 2009;64:746-53.
32. Mrowicka M, Zielinska-Blizniewska H, Milonski J, Majsterek I, Olszewski J. Association of IL1β and IL4 gene polymorphisms with nasal polyps in a Polish population. Mol Biol Rep. 2014;41:4653-8.
33. Ahmed SAJ, Yas NK, Hatem HA. DNA Polymorphism of Interleukin IL-4 of Nasal Mucosal Stem Cells in Nasal Polyps of Iraqi Patients. Int J Bio Tech Res. 2017;7(3):11-6.
34. Cheng Y-K, Lin C-D, Chang W-C, Hwang G-Y, Tsai S-W, Wan L, et al. Increased prevalence of interleukin-1 receptor antagonist gene polymorphism in patients with chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2006;132:285-90.
35. Erbek SS, Yurtcu E, Erbek S, Atac FB, Sahin FI, Cakmak O. Proinflammatory Cytokine Single Nucleotide Polymorphisms in Nasal Polyposis. Arch Otolaryngol Neck Surg. 2007;133:705.
36. Castano R, Bossé Y, Endam LM, Desrosiers M. Evidence of association of interleukin-1 receptor-like 1 gene polymorphisms with chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23:377-84.
37. Henmyr V, Vandeplas G, Halldén C, Säll T, Olze H, Bachert C, et al. Replication study of genetic variants associated with chronic rhinosinusitis and nasal polyposis. J Allergy Clin Immunol. 2014;133:273-5.
38. Karjalainen J, Joki-Erkkila V-P, Hulkkonen J, Pessi T, Nieminen MM, Aromaa A, et al. The IL1A genotype is associated with nasal polyposis in asthmatic adults. Allergy. 2003;58:393-6.
39. Kuran G, Aslan H, Haytoglu S, Özalp Yuregir Ö, Tug Bozgodan S. IL-1RN VNTR, IL-2(-330), and IL-4 VNTR gene polymorphisms in patients with chronic rhinosinusitis with sinonasal polyposis. Turkish J Med Sci. 2019;49:1411-7.
40. Zhang Y, Endam LM, Filali-Mouhim A, Zhao L, Desrosiers M, Han D, et al. Polymorphisms in RYBP and AOAH Genes Are Associated with Chronic Rhinosinusitis in a Chinese Population: A Replication Study. PLoS One. 2012;7:e39247.
41. Buysschaert ID, Grulois V, Eloy P, Jorissen M, Rombaux P, Bertrand B, et al. Genetic evidence for a role of IL33 in nasal polyposis. Allergy. 2010;65:616-22.
42. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008;100:S1-148.
43. Park SK, Heo KW, Jung H, Yea SS, Yang Y Il. Expression of cyclooxygenase-2 and 5-lipoxygenase in nasal polyps associated with interleukin-4 promoter polymorphism -590. Otolaryngol Head Neck Surg. 2006;135:928-32.
44. Kim S-H, Park H-S, Holloway JW, Shin H-D, Park C-S. Association between a TGF [beta] 1 promoter polymorphism and rhinosinusitis in aspirin-intolerant asthmatic patients. Respir Med. 2007;101:490-5.
45. Yea SS, Yang Y-I, Park SK, Jang WH, Lee SS, Seog D-H, et al. Interleukin-4 C-590T Polymorphism is associated with Protection against Nasal Polyps in a Korean Population. Am J Rhinol. 2006;20:550-3.
46. Mrowicka M, Zielinska-Blizniewska H, Milonski J, Olszewski J, Majsterek I. Evaluation of oxidative DNA damage and antioxidant defense in patients with nasal polyps. Redox Rep. 2015;20:177-83.
47. Batikhan H, Gokcan MK, Beder E, Akar N, Ozturk A, Gerceker M. Association of the tumor necrosis factor-alpha –308 G/A polymorphism with nasal polyposis. Eur Arch Otorhinolaryngology. 2010;267:903-8.
48. Szabó K, Polyánka H, Kiricsi Á, Révész M, Vóna I, Szabó Z, et al. A conserved linkage group on chromosome 6, the 81 ancestral haplotype, is a predisposing factor of chronic rhinosinusitis associated with nasal polyposis in aspirin-sensitive Hungarians. Hum Immunol. 2015;76:858-62.
49. Szabó K, Kiricsi Á, Révész M, Vóna I, Szabó Z, Bella Z, et al. The -308 G>A SNP of TNFA is a factor predisposing to chronic rhinosinusitis associated with nasal polyposis in aspirin-sensitive Hungarian individuals: conclusions of a genetic study with multiple stratifications. Int Immunol. 2013;25:383-8.
50. Ismi O, Ozcan C, Polat G, Kul S, Gorur K, Puturgeli T. TNF-α and IL-1 β Cytokine Gene Polymorphism in Patients with Nasal Polyposis. Turk Arch Otolaryngol. 2017;55:51-6.

51. Berghea EC, Popa OM, Meirosu M, Popa LO, Bara C, Bumbacea RS. Association of TNF-alpha gene polymorphism with nasal polyposis in Romanian asthmatic patients. Rom J Rhinol. 2014;4.
52. Sitarek P, Zielinska-Blizniewska H, Dziki L, Milonski J, Przybylowska K, Mucha B, et al. Association of the −14C/G MET and the −765G/C COX-2 Gene Polymorphisms with the Risk of Chronic Rhinosinusitis with Nasal Polyps in a Polish Population. DNA Cell Biol. 2012;31:1258-66.
53. Akyigit A, Keles E, Etem EO, Ozercan I, Akyol H, Sakallioglu O, et al. Genetic polymorphism of antioxidant enzymes in eosinophilic and non-eosinophilic nasal polyposis. Eur Arch Otorhinolaryngology. 2017;274:267-73.
54. Pavón-Romero GF, Pérez-Rubio G, Ramírez-Jiménez F, Ambrocio-Ortiz E, Bañuelos-Ortiz E, Alvarado-Franco N, et al. MS4A2-rs573790 Is associated with aspirin-exacerbated respiratory disease: Replicative study using a candidate gene strategy. Front Genet. 2018;9.
55. Kristjansson RP, Benonisdottir S, Davidsson OB, Oddsson A, Tragante V, Sigurdsson JK, et al. A loss-of-function variant in ALOX15 protects against nasal polyps and chronic rhinosinusitis. Nat Genet. 2019;51:267-76.
56. Al-Shemari H, Bossé Y, Hudson TJ, Cabaluna M, Duval M, Lemire M, et al. Influence of leukotriene gene polymorphisms on chronic rhinosinusitis. BMC Med Genet. 2008;9:21.
57. Benito Pescador D, Isidoro-García M, García-Solaesa V, Pascual de Pedro M, Sanz C, Hernández-Hernández L, et al. Genetic association study in nasal polyposis. J Investig Allergol Clin Immunol. 2012;22:331-40.
58. Alarcón A de, Steinke JW, Caughey R, Barekzi E, Hise K, Gross CW, et al. Expression of Leukotriene C 4 Synthase and Plasminogen Activator Inhibitor 1 Gene Promoter Polymorphisms in Sinusitis. Am J Rhinol. 2006;20:545-9.
59. Mfuna Endam L, Filali-Mouhim A, Boisvert P, Boulet L-P, Bossé Y, Desrosiers M. Genetic variations in taste receptors are associated with chronic rhinosinusitis: a replication study. Int Forum Allergy Rhinol. 2014;4:200-6.
60. Adappa ND, Zhang Z, Palmer JN, Kennedy DW, Doghramji L, Lysenko A, et al. The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery. Int Forum Allergy Rhinol. 2014;4:3-7.
61. Cantone E, Negri R, Roscetto E, Grassia R, Catania MR, Capasso P, et al. In Vivo Biofilm Formation, Gram-Negative Infections and TAS2R38 Polymorphisms in CRSw NP Patients. Laryngoscope. 2018;128:E339-45.
62. Gallo S, Grossi S, Montrasio G, Binelli G, Cinquetti R, Simmen D, et al. TAS2R38 taste receptor gene and chronic rhinosinusitis: new data from an Italian population. BMC Med Genet. 2016;17:54.
63. Purnell PR, Addicks BL, Zalzal HG, Shapiro S, Wen S, Ramadan HH, et al. Single Nucleotide Polymorphisms in Chemosensory Pathway Genes GNB3, TAS2R19, and TAS2R38 Are Associated with Chronic Rhinosinusitis. Int Arch Allergy Immunol. 2019;180:72-8.
64. Kim S-H, Kim Y-K, Park H-W, Kim S-H, Kim S-H, Ye Y-M, et al. Adenosine deaminase and adenosine receptor polymorphisms in aspirin-intolerant asthma. Respir Med. 2009;103:356-63.
65. Dar SA, Rai G, Ansari MA, Akhter N, Gupta N, Sharma S, et al. FcεR1α gene polymorphism shows association with high IgE and anti-FcεR1α in Chronic Rhinosinusitis with Nasal Polyposis. J Cell Biochem. 2018;119:4142-9.
66. Kostuch M, Klatka J, Semczuk A, Wojcierowski J, Kulczycki L, Oleszczuk J. Analysis of most common CFTR mutations in patients affected by nasal polyps. Eur Arch Otorhinolaryngol. 2005;262:982-6.
67. Hytönen M, Patjas M, Vento SI, Kauppi P, Malmberg H, Ylikosk J, et al. Cystic fibrosis gene mutations δF508 and 394delTT in patients with chronic sinusitis in Finland. Acta Otolaryngol. 2001;121:945-7.
68. Wang X, Moylan B, Leopold DA, Kim J, Rubenstein RC, Togias A, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. J Am Med Assoc. 2000;284:1814-9.
69. Bussu F, Tiziano FD, Giorgio A, Pinto AM, Corso E De, Angelozzi C, et al. Arg16gly Polymorphism of the beta2-Adrenoceptor Gene (ADRBeta2) as a Susceptibility Factor for Nasal Polyposis. Am J Rhinol. 2007;21:378-82.
70. Ekinci S, Erbek SS, Yurtcu E, Sahin FI. Lack of Association between Eotaxin-1 Gene Polymorphisms and Nasal Polyposis. Otolaryngol Neck Surg. 2011;145:1036-9.
71. Castano R, Bossé Y, Endam LM, Filali-Mouhim A, Desrosiers M. c-MET pathway involvement in chronic rhinosinusitis: A genetic association analysis. Otolaryngol Neck Surg. 2010;142:665-71.
72. Kilty SJ, Bossé Y, Cormier C, Endam LM, Desrosiers MY. Polymorphisms in the SERPINA1 (Alpha-1-Antitrypsin) Gene are Associated with Severe Chronic Rhinosinusitis Unresponsive to Medical Therapy. Am J Rhinol Allergy. 2010;24:e4-9.
73. Bossé Y, Bacot F, Montpetit A, Rung J, Qu H-Q, Engert JC, et al. Identification of susceptibility genes for complex diseases using pooling-based genome-wide association scans. Hum Genet. 2009;125:305-18.
74. Cho J-S, Moon Y-M, Park I-H, Um J-Y, Moon J-H, Park S-J, et al. Epigenetic regulation of myofibroblast differentiation and extracellular matrix production in nasal polyp-derived fibroblasts. Clin Exp Allergy. 2012;42:872-82.
75. Cho J-S, Moon Y-M, Park I-H, Um J-Y, Kang J-H, Kim TH, et al. Effects of Histone Deacetylase Inhibitor on Extracellular Matrix Production in Human Nasal Polyp Organ Cultures. Am J Rhinol Allergy. 2013;27:18-23.
76. Cheong HS, Park S-M, Kim M-O, Park J-S, Lee JY, Byun JY, et al. Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics. Allergy. 2011;66:637-44.
77. Kidoguchi M, Noguchi E, Nakamura T, Ninomiya T, Morii W, Yoshida K, et al. DNA Methylation of Proximal PLAT Promoter in Chronic Rhinosinusitis With Nasal Polyps. Am J Rhinol Allergy. 2018;32:374-9.
78. Kim JYJ-Y, Kim DKD-K, Yu MS, Cha MJM-J, Yu SLS-L, Kang J. Role of epigenetics in the pathogenesis of chronic rhinosinusitis with nasal polyps. Mol Med Rep. 2018;17:1219-27.
79. Kim JYJ-Y, Cha MJM-J, Park YSY-S, Kang J, Choi JJJ-J, In SM, et al. Upregulation of FZD5 in Eosinophilic Chronic Rhinosinusitis with Nasal Polyps by Epigenetic Modification. Mol Cells. 2019;42:345-55.
80. Li J, Jiao J, Gao Y, Zhang Y, Zhang L. Association between methylation in nasal epithelial TSLP gene and chronic rhinosinusitis with nasal polyps. Allergy, Asthma Clin Immunol. 2019;15:71.

81. Li J, Jiao J, Wang M, Gao Y, Li Y, Wang Y, et al. Hypomethylation of the IL8 promoter in nasal epithelial cells of patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2019;144:993-1003.e12.
82. Zheng YB, Zhao Y, Yue LY, Lin P, Liu YF, Xian JM, et al. Pilot study of DNA methylation in the pathogenesis of chronic rhinosinusitis with nasal polyps. Rhinology. 2015;53:345-52.
83. Liu M, Guo P, An J, Guo C, Lu F, Lei Y. Genome-wide profiling of lncRNA and mRNA expression in CRSwNP. Mol Med Rep. 2019;49:3855-63.
84. Callejas-Díaz B, Fernandez G, Fuentes M, Martínez-Antón A, Alobid I, Roca-Ferrer J, et al. Integrated mRNA and microRNA transcriptome profiling during Differentiation of Human Nasal Polyp Epithelium reveals an altered Ciliogenesis. Allergy. 2020:0-1.
85. Liu CC, Xia M, Zhang YJ, Jin P, Zhao L, Zhang J, et al. Micro124-mediated AHR expression regulates the inflammatory response of chronic rhinosinusitis (CRS) with nasal polyps. Biochem Biophys Res Commun. 2018;500:145-51.
86. Luo X-Q, Shao J-B, Xie R-D, Zeng L, Li X-X, Qiu S-Q, et al. Micro RNA-19a interferes with IL-10 expression in peripheral dendritic cells of patients with nasal polyposis. Oncotarget. 2017;8:48915-21.
87. Ma Z, Shen Y, Zeng Q, Liu J, Yang L, Fu R, et al. MiR-150-5p regulates EGR2 to promote the development of chronic rhinosinusitis via the DC-Th axis. Int Immunopharmacol. 2018;54:188-97.
88. Ma Z-X, Tan X, Shen Y, Ke X, Yang Y-C, He X-B, et al. MicroRNA expression profile of mature dendritic cell in chronic rhinosinusitis. Inflamm Res. 2015;64:885-93.
89. Qing X, Zhang Y, Peng Y, He G, Liu A, Liu H. Mir-142-3p Regulates Inflammatory Response by Contributing to Increased TNF-α in Chronic Rhinosinusitis With Nasal Polyposis. Ear Nose Throat J. 2019:1-7.
90. Xuan L, Luan G, Wang Y, Lan F, Zhang X, Hao Y, et al. MicroRNAs regulating mucin type O-glycan biosynthesis and transforming growth factor β signaling pathways in nasal mucosa of patients with chronic rhinosinusitis with nasal polyps in Northern China. Int Forum Allergy Rhinol. 2019;9:106-13.
91. Yan D, Ye Y, Zhang J, Zhao J, Yu J, Luo Q. Human Neutrophil Elastase Induces MUC5AC Overexpression in Chronic Rhinosinusitis Through miR-146a. Am J Rhinol Allergy. 2020;34:59-69.
92. Yu H, Ju J, Liu J, Li D. Aberrant expression of miR-663 and transforming growth factor-β1 in nasal polyposis in children. Exp Ther Med. 2018;15:4550-6.
93. Zhou X, Zhen X, Liu Y, Cui Z, Yue Z, Xu A, et al. Identification of Key Modules, Hub Genes, and Noncoding RNAs in Chronic Rhinosinusitis with Nasal Polyps by Weighted Gene Coexpression Network Analysis. Biomed Res Int. 2020;2020:1-20.
94. Zhang X-H, Zhang Y-N, Li H-B, Hu C-Y, Wang N, Cao P-P, et al. Overexpression of miR-125b, a Novel Regulator of Innate Immunity, in Eosinophilic Chronic Rhinosinusitis with Nasal Polyps. Am J Respir Crit Care Med. 2012;185:140-51.
95. Seiberling KA, Church CA, Herring JL, Sowers LC. Epigenetics of chronic rhinosinusitis and the role of the eosinophil. Int Forum Allergy Rhinol. 2012;2:80-4.
96. Tian P, Sun Y, Li Y, Liu X, Wan L, Li J, et al. A Global Analysis of Tandem 3'UTRs in Eosinophilic Chronic Rhinosinusitis with Nasal Polyps. PLoS One. 2012;7:e48997.
97. Zhang Y-N, Cao P-P, Zhang X-H, Lu X, Liu Z. Expression of MicroRNA machinery proteins in different types of chronic rhinosinusitis. Laryngoscope. 2012;122:2621-7.
98. Tian P, Li J, Liu X, Li Y, Chen M, Ma Y, et al. Tandem alternative polyadenylation events of genes in non-eosinophilic nasal polyp tissue identified by high-throughput sequencing analysis. Int J Mol Med. 2014;33:1423-30.
99. Bassiouni A, Ou J, Schreiber A, Geoghegan J, Tsykin A, Psaltis AJ, et al. The global transcriptomic signature in sinonasal tissues reveals roles for tissue type and chronic rhinosinusitis disease phenotype. Rhinology. 2020;58:273-83.
100. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146:595-605.
101. Jonstam K, Swanson BN, Mannent LP, Cardell LO, Tian N, Wang Y, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy Eur J Allergy Clin Immunol. 2019;74:743-52.
102. Sastre J, Dávila I. Dupilumab: A New Paradigm for the Treatment of Allergic Diseases. J Investig Allergol Clin Immunol. 2018;28:139-50.
103. Gevaert P, Bruaene N Van, Cattaert T, Steen K Van, Zele T Van, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128:989-95.e8.
104. Aghasafari P, George U, Pidaparti R. A review of inflammatory mechanism in airway diseases. Inflamm Res. 2019;68:59-74.
105. Ordovas-Montanes J, Dwyer DF, Nyquist SK, Buchheit KM, Vukovic M, Deb C, et al. Allergic inflammatory memory in human respiratory epithelial progenitor cells. Nature. 2018;560:649-54.
106. Johnson BJ, Choby GW, O'Brien EK. Chronic rhinosinusitis in patients with cystic fibrosis—Current management and new treatments. Laryngoscope Investig Otolaryngol. 2020;5:368-74.
107. Gostelie R, Stegeman I, Berkers G, Bittermann J, van der Drift IL, van Kipshagen PJ, et al. The impact of ivacaftor on sinonasal pathology in S1251N-mediated cystic fibrosis patients. PLoS One. 2020;15:1-14.
108. Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee SS. Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine. Mol Ther - Nucleic Acids. 2017;8:132-43.
109. Adappa ND, Farquhar D, Palmer JN, Kennedy DW, Doghramji L, Morris SA, et al. TAS2R38 genotype predicts surgical outcome in nonpolypoid chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6:25-33.
110. Bae JS, Pasaje CFA, Park BL, Cheong HS, Kim J-H, Uh S-T, et al. Genetic association analysis of CIITA variations with nasal polyp pathogenesis in asthmatic patients. Mol Med Rep. 2013;7:927-34.
111. Baldan A, Presti AR Lo, Belpinati F, Castellani C, Bettin MD, Xumerle L, et al. IFRD1 gene polymorphisms are associated with nasal polyposis in cystic fibrosis patients. Rhinology. 2015;53:359-64.
112. Cormier C, Bossé Y, Mfuna L, Hudson TJ, Desrosiers M. Polymorphisms in the tumour necrosis factor alpha-induced protein 3 (TNFAIP3) gene are associated with chronic rhinosinusitis. J Otolaryngol Head Neck Surg. 2009;38:133-41.

113. Fruth K, Best N, Amro M, Ingel K, Gosepath J, Mann WJ, et al. No evidence for a correlation of glutathione S-tranferase polymorphisms and chronic rhinosinusitis. Rhinology. 2011;49:180-4.
114. Fruth K, Goebel G, Koutsimpelas D, Gosepath J, Schmidtmann I, Mann WJ, et al. Low SPINK5 expression in chronic rhinosinusitis. Laryngoscope. 2012;122:1198-204.
115. Henmyr V, Lind-Halldén C, Halldén C, Säll T, Carlberg D, Bachert C, et al. Chronic Rhinosinusitis Patients Show Accumulation of Genetic Variants in PARS2. PLoS One. 2016;11:e0158202.
116. Kilty SJ, Desrosiers MY. Chronic sinusitis and α 1-antitrypsin deficiency: Potential role for protease in rhinosinusitis? J Otolaryngol - Head Neck Surg. 2008;37:E179-82.
117. Kim S-H, Park H-S, Holloway JW, Shin H-D, Park C-S. Association between a TGFβ1 promoter polymorphism and rhinosinusitis in aspirin-intolerant asthmatic patients. Respir Med. 2007;101:490-5.
118. Kosugi EM, Camargo-Kosugi CM De, Weckx LLM, Guerreiro-da-Silva IDC, Gregório LC. Interleukin-6 -174 G/C promoter polymorphism and nasal polyposis. Rhinology. 2009;47:400-4.
119. Luxenberger W, Posch U, Berghold A, Hofmann T, Lang-Loidolt D. HLA patterns in patients with nasal polyposis. Eur Arch Otorhinolaryngol. 2000;257:137-9.
120. Molga P, Fendler W, Borowiec M, Pietruszewska W. Impact of -160701G/2G MMP1 gene polymorphism on morbidity and clinical course in patients with chronic rhinosinusitis with nasal polyps. Otolaryngol Pol. 2016;70:23-32.
121. Nakayama T, Hirota T, Asaka D, Sakashita M, Ninomiya T, Morikawa T, et al. A genetic variant near TSLP is associated with chronic rhinosinusitis with nasal polyps and aspirin-exacerbated respiratory disease in Japanese populations. Allergol Int. 2020;69:138-40.
122. Özdaş S, İzbirak A, Özdaş T, Özcan KM, Erbek SS, Köseoğlu S, et al. Single-Nucleotide Polymorphisms on the RYD5 Gene in Nasal Polyposis. DNA Cell Biol. 2015;34:633-42.
123. Palikhe S, Uuganbayar U, Trinh HKT, Ban G-Y, Yang E-M, Hae-Sim P, et al. A Role of the ABCC4 Gene Polymorphism in Airway Inflammation of Asthmatics. Mediators Inflamm. 2017;2017.
124. Pasaje CFA, Bae JS, Park B-L, Cheong HS, Kim J-H, Jang A-S, et al. DCBLD2 gene variations correlate with nasal polyposis in Korean asthma patients. Lung. 2012;190:199-207.
125. Pasaje CFA, Bae JS, Park BL, Cheong HS, Kim JH, Jang AS, et al. Possible role of EMID2 on nasal polyps pathogenesis in Korean asthma patients. BMC Med Genet. 2012;13:2.
126. Pascual M, Sanz C, Isidoro-García M, Dávila I, Moreno E, Laffond E, et al. (CCTTT)n polymorphism of NOS2A in nasal polyposis and asthma: a case-control study. J Investig Allergol Clin Immunol. 2008;18:239-44.
127. Sachse F, Becker K, Rudack C. Incidence of Staphylococcal Colonization and of the 753Q Toll-like Receptor 2 Variant in Nasal Polyposis. Am J Rhinol Allergy. 2010;24:e10-3.
128. Song Y, Yang E, Kim S, Jin HJ, Park H. Effect of Genetic Polymorphism of ALOX15 on Aspirin-Exacerbated Respiratory Disease. Int Arch Allergy Immunol. 2012;159:157-61.
129. Tournas A, Mfuna L, Bossé Y, Filali-Mouhim A, Grenier J-P, Desrosiers M. A pooling-based genome-wide association study implicates the p73 gene in chronic rhinosinusitis. J Otolaryngol Head Neck Surg. 2010;39:188-95.
130. Wang L-F, Chien C-Y, Kuo W-R, Tai C-F, Juo S-HH. Matrix Metalloproteinase-2 Gene Polymorphisms in Nasal Polyps. Arch Otolaryngol Head Neck Surg. 2008;134:852.
131. Wang L-F, Chien C-Y, Tai C-F, Kuo W-R, Hsi E, Juo S-HH. Matrix metalloproteinase-9gene polymorphisms in nasal polyposis. BMC Med Genet. 2010;11:85.
132. Wang L-F, Chien C-Y, Chiang F-Y, Chai C-Y, Tai C-F. Expression of matrix metalloproteinase-2 and matrix metalloproteinase-9 in recurrent chronic rhinosinusitis with nasal polyposis. Kaohsiung J Med Sci. 2013;29:26-31.
133. Yazdani N, Amoli MM, Naraghi M, Mersaghian A, Firouzi F, Sayyahpour F, et al. Association between the functional polymorphism C-159T in the CD14 promoter gene and nasal polyposis: Potential role in asthma. J Investig Allergol Clin Immunol. 2012;22:406-11.
134. Zhang F, Xiong Z-G, Cao P-P, You X-J, Gao Q-X, Cui Y-H, et al. Lack of Association of Clara Cell 10-kDa Protein Gene Variant with Chronic Rhinosinusitis in a Chinese Han Population. Am J Rhinol. 2008;22:376-80.
135. Zhang Y, Endam LM, Filali-Mouhim A, Bossé Y, Castano R, Desrosiers M. Polymorphisms in the nitric oxide synthase 1 gene are associated with severe chronic rhinosinusitis. Am J Rhinol Allergy. 2011;25:e49-54.
136. Zhang Y, Wang C, Zhao Y, Zhang L. Some Polymorphisms in Epstein-Barr Virus-induced Gene 3 Modify the Risk for Chronic Rhinosinusitis. Am J Rhinol Allergy. 2013;27:91-7.
137. Zhang Y, Wang X, Zhang W, Han D, Zhang L, Bachert C. Polymorphisms in thymic stromal lymphopoietin gene demonstrate a gender and nasal polyposis-dependent association with chronic rhinosinusitis. Hum Immunol. 2013;74:241-8.
138. Zielinska-Blizniewska H, Sitarek P, Milonski J, Dziki L, Przybylowska K, Olszewski J, et al. Association of the −33C/G OSF-2 and the 140A/G LF gene polymorphisms with the risk of chronic rhinosinusitis with nasal polyps in a Polish population. Mol Biol Rep. 2012;39:5449-57.
139. Mfuna Endam L, Cormier C, Bossé Y, Desrosiers M. Genetic Variants in IL1A but not TNFA are Associated with Severe Chronic Rhinosinusitis: A Replication Study. J Allergy Clin Immunol. 2009;123.
140. Bardy JJ, Sarovich DS, Price EP, Steinig E, Tong S, Drilling A, et al. Staphylococcus aureus from patients with chronic rhinosinusitis show minimal genetic association between polyp and non-polyp phenotypes. BMC Ear Nose Throat Disord. 2018;18.
141. Adappa ND, Truesdale CM, Workman AD, Doghramji L, Mansfield C, Kennedy DW, et al. Correlation of T2R38 taste phenotype and in vitro biofilm formation from nonpolypoid chronic rhinosinusitis patients. Int Forum Allergy Rhinol. 2016;6:783-91.

Manuscript received December 29, 2020; accepted for publication January 22, 2021.

Miguel Estravis

E-mail: estravis@usal.es