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

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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.

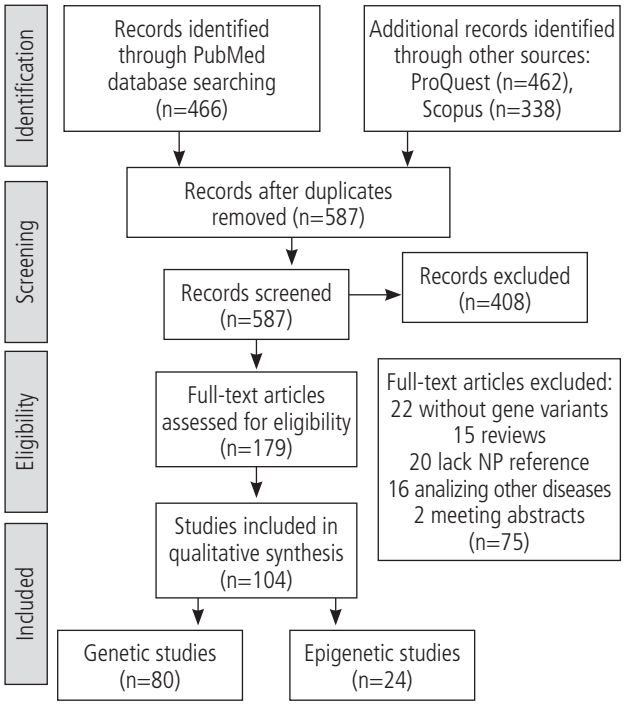

Figure 1. Flow diagram of the selection process. NP indicates nasal polyposis.

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

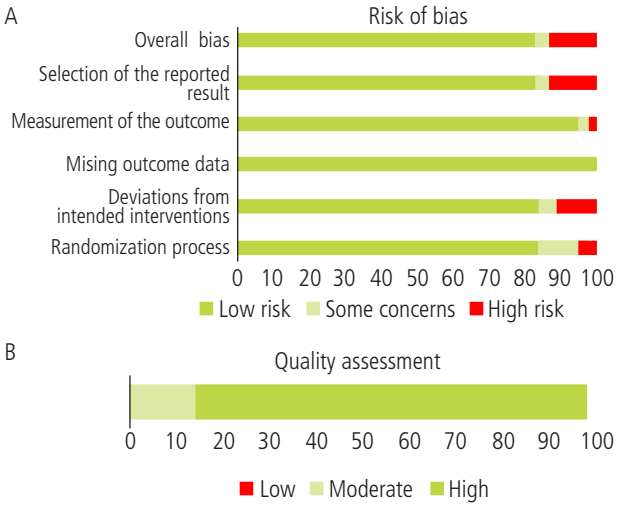

Figure 2. Risk of bias (A) and quality assessment (B) of the selected articles.

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.

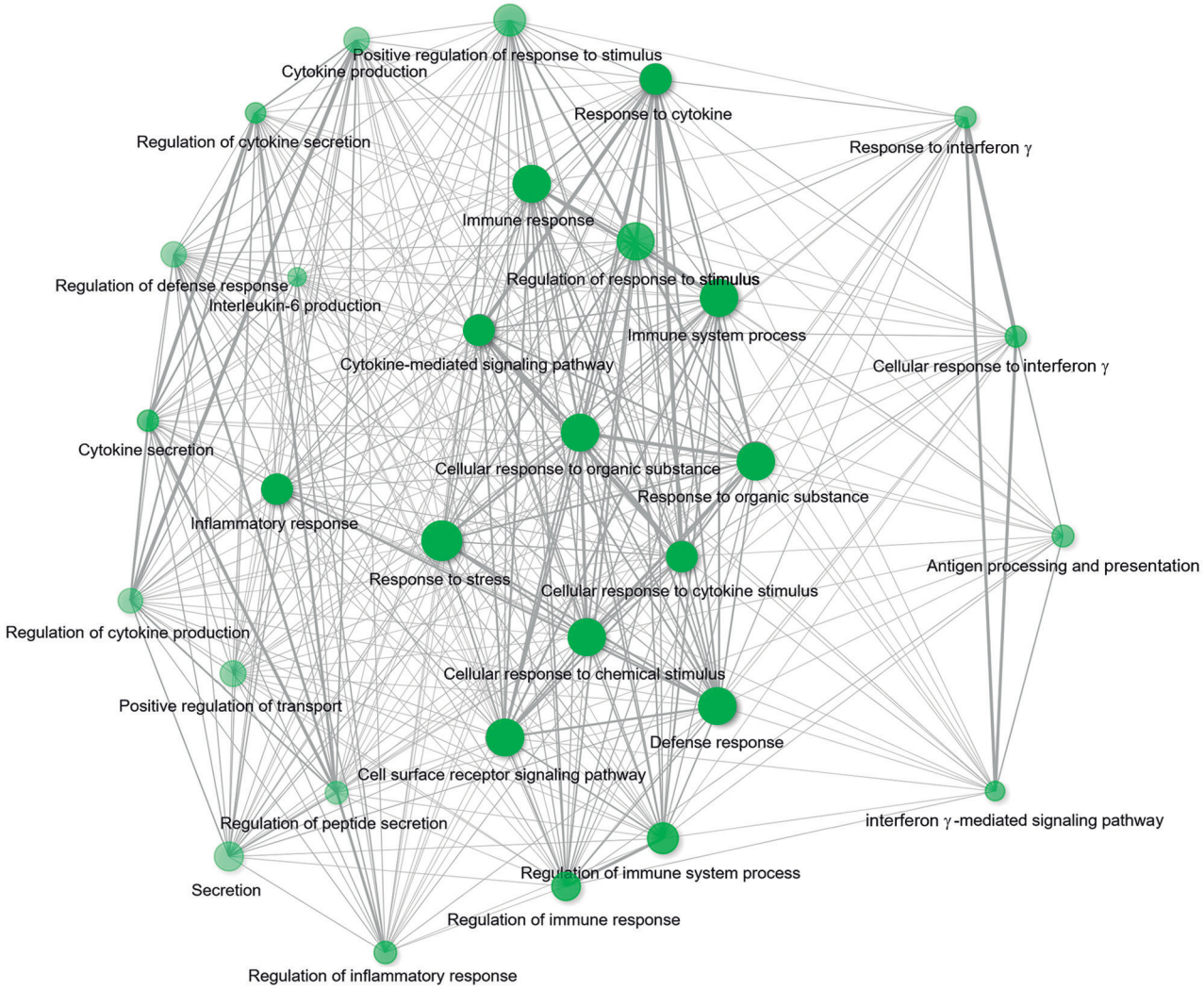

Figure 3. Main biological functions involving the genes reported as being associated with chronic rhinosinusitis with nasal polyposis.

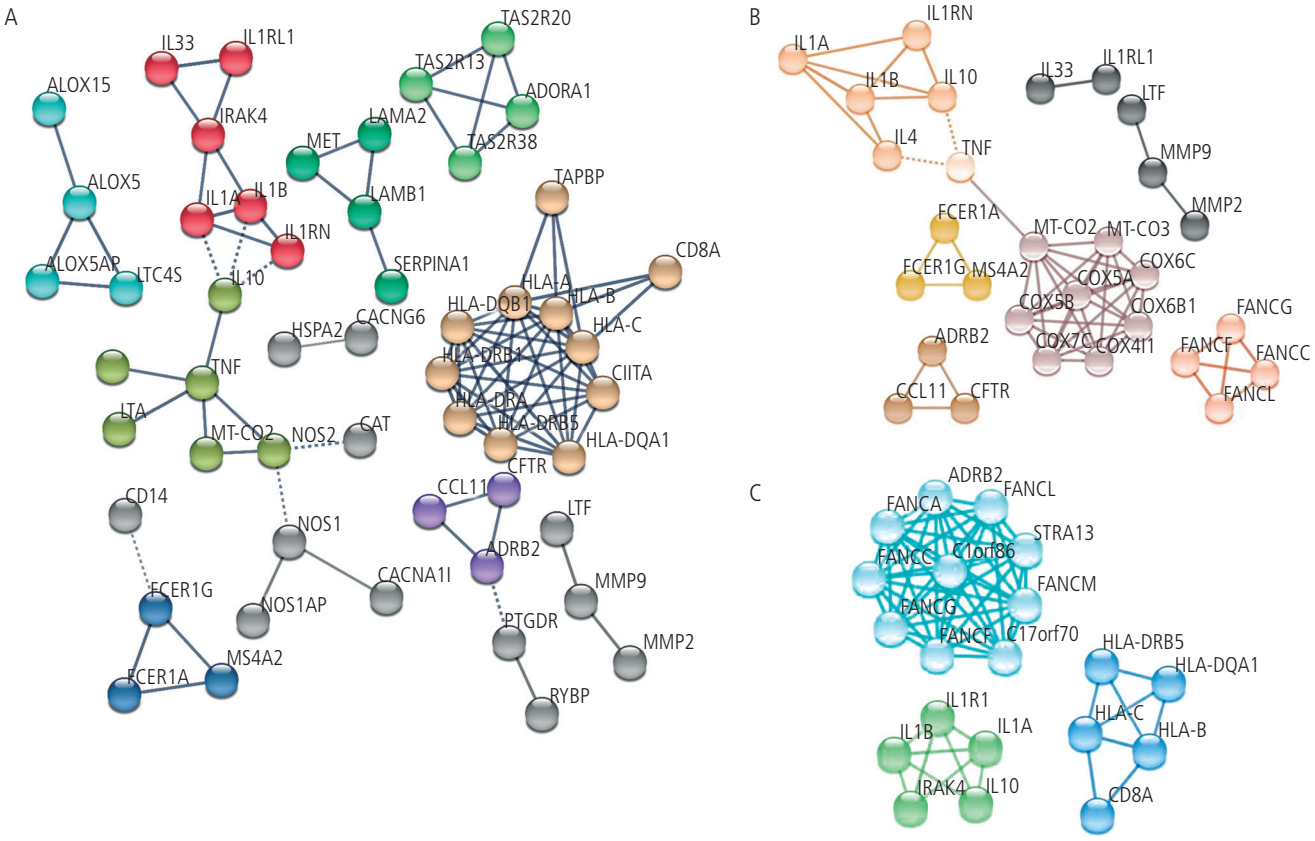

Figure 4. Clustering of genes associated with CRSwNP (A). Clusters associated with genes that increase (B) or decrease (C) the risk of chronic rhinosinusitis with nasal polyposis.

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

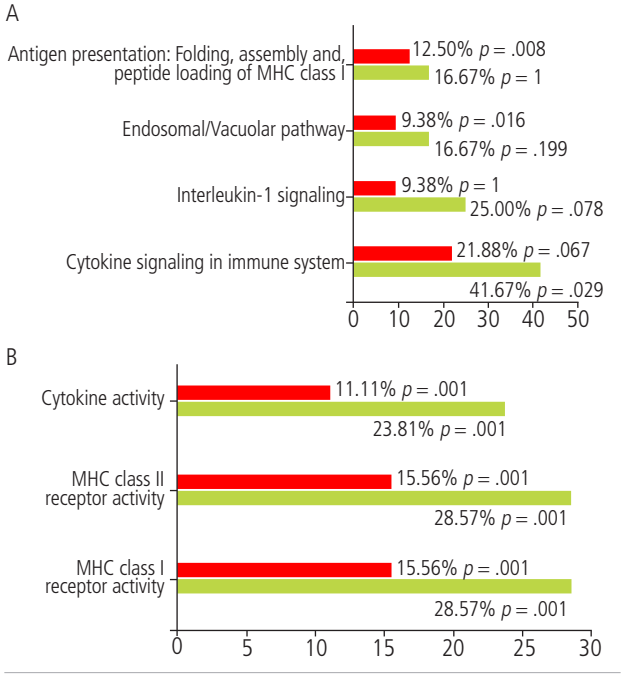

Figure 5. Gene enrichment comparison between genes that increase the risk and those that decrease the risk of chronic rhinosinusitis with nasal polyposis.

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.

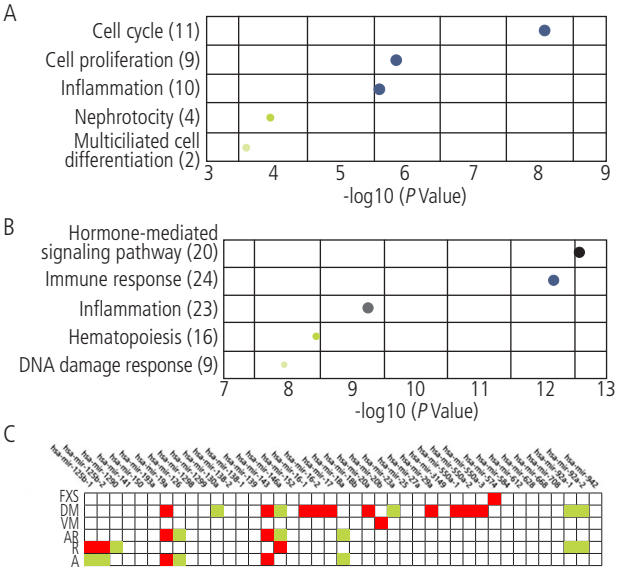

Figure 6. Enrichment of miRNAs in biological processes. A, Functions involving miRNA upregulated in CRSwNP. B, Functions involving downregulated miRNA. C, Association between miRNA and relevant diseases. FXS, indicates fragile X syndrome; DM, diabetes mellitus; VM, viral myocarditis; AR, allergic rhinitis;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

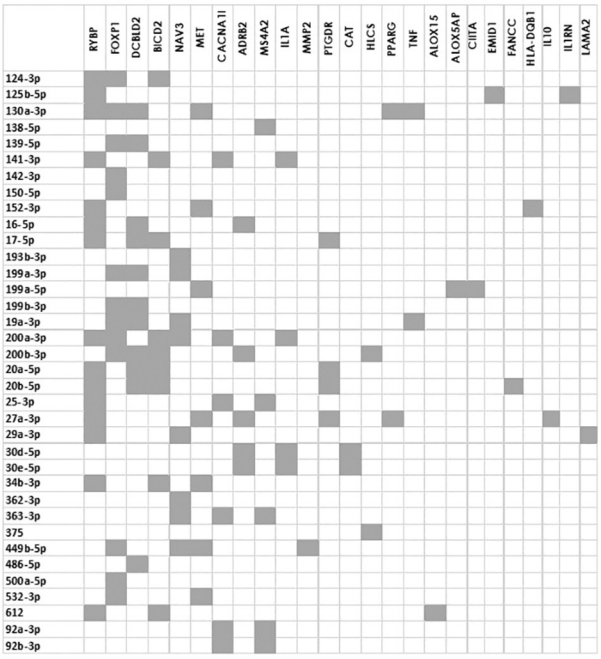

Figure 7. Relevant genes linked to miRNA. Genes found in the selected genetic articles that have been published as connected to miRNA identified by the selected epigenetic articles.

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.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Miguel Estravis

E-mail: estravis@usal.es

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1:

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Supplementary Table 1. Selected genetic studies.

Reference		Study type	Population/ Country	Objective	Sample Size	Source	Genes	SNP/Mutation	Results/conclusion
Adappa et al. 2016 [109]		CG	USA	To determine whether *TAS2R38* genetics predicts outcomes in CRS patients following sinus surgery	82 CRSwNP 41 CRSsNP	NP, sinonasal tissue	*TAS2R38*	rs713598 (G/C; Ala/Pro)) rs1726866 (G/A; Val-Ala) rs10246939 (T/C; Ile-Val)	The genotype PAV/PAV was related to lower incidence of failing therapy and less frequent sinus surgeries
Ahmed et al. 2017 [33]		CG	Iraq	To clarify the role of *IL4* polymorphism in NP	22 healthy controls (HC) 36 NP	NP, inferior turbinate mucosa (ITM)	*IL4*	?	The polymorphism was found in NP patients but not in controls
Akygit et al. 2017 [53]		CG	Turkey	To identify genetic polymorphism of *SOD2*, *CAT*, *iNOS* enzymes in E-CRSwNP and NE-CRSwNP patients.	188 HC 65 E-CRSwNP 65 NE-CRSwNP	Blood	*NOS2*	-277A/G	The GG genotype (*NOS2*) and TT genotype (CAT) distributions were different between E-CRSwNP and controls
							SOD2	16C/T	
							CAT	-21A/T	
Alromaih et al. 2013 [27]		pGWAS	Canada	To identify whether genetic factors associated with MHC1 deficiency are present in CRS	196 HC 154 CRSwNP 52 CRSsNP	Blood	*CD8A*	rs3810831	The minor allele C in *CD8A* (OR 0.706; p=0.047) and heterozygous CT (OR 0.370; p=0.012) had a protective effect on the development of CRS. The minor allele T in *TAPBP* (OR 1.53; p=0.009) and heterozygous TT (OR 2.67; p=0.042) were associated with an increased risk for CRS.
							TAPBP	rs2282851	
Al-Shemari et al. 2008 [56]		CG	Canada	To evaluate the effects of SNPs on CRS in a panel of genes related to cysteinyl leukotriene metabolism	200 HC 179 CRSwNP 27 CRSsNP	Blood	*ALOX5 AP*	rs12430915 rs9506352 rs4769870 rs9579648 rs4076128 rs9579649 rs11616333 rs9315051 rs4769055 rs4420371 rs9578196 rs4466940 rs4293222 rs9578200 rs12429692 rs9285076 rs10162089 rs9670198 rs4254165 rs4319601 rs4356336 rs4769063 rs17612127 rs4238139	Three SNPs located within the *ALOX5* (rs3780894), *CYSLTR1* (rs321090) and *ALOX5AP* (rs17612127) genes reached the nominal p-value threshold ($p < 0.05$) for association with CRS. However, none of these SNPs resisted multiple testing adjustment.
							ALOX5	rs3824612 rs12264801 rs3780894 rs3780901 rs2279435 rs7099684 rs1565096 rs1487562 rs7919239 rs2291427 rs7393696 rs2115819 rs11239523 rs4948672 rs7089063	
							CYSLTR2	rs2406939 rs9595961 rs11617224 rs17072059 rs6420296 rs7330127 rs2407249 rs7335898 rs9568087 rs9285169 rs12184704	
							CYSLTR1	rs321090 rs321007 rs321006	
							LTC4S	rs730012 rs2291418 rs166624	
Bae et al. 2013 [110]		CG	Korea	To investigate the association between *CIITA* and NP	All asthma patients: 158 CRSwNP 309 CRSsNP	Blood	*CIITA*	rs12932187 rs4781019 rs6498126 rs4781011 rs11074938 rs11074934 rs11074939 rs8043545 rs7404786 rs7201430 rs8063850 rs6498119 rs4781024 rs1139564 rs7189406 rs4774 rs6498124 rs4781016	Two SNPs (rs12932187 and rs11074938) and 2 haplotypes (*CIITA*_BL1_ht2 and *CIITA*_BL1_ht5) were demonstrated to be associated with nasal polyps (P=0.001-0.01, OR=0.53-2.35 depending on the genetic model). After multiple testing correction only rs12932187 retained the association with nasal polyps (Pcorr=0.02).

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Supplementary Table 1. Selected genetic studies.

Baldan et al. 2015 [111]		CG	Italy	To investigate the effect of 3 *IFRD1* SPNs on the development of NP in CF patients	CF patients: 40 with NP 103 without NP	Blood	*IFRD1*	rs6968084 (C>T) rs3807213 (A>C) rs7817 (C>T)	rs7817-CT showed 4-fold higher probability of NP than CC; the TT showed 7.3-fold increased probability. The CAT haplotype showed higher probability of NP (OR 2.63, p=0.004) compared to the CCC haplotype.
Batikhan et al. 2010 [47]		CG	Turkey	To investigate the possible association of *TNF* -308G/A with NP	95 HC 97 NP patients	Blood	*TNF*	rs1800629	The presence of the *TNF* -308 G/A SNP was an independent risk factor for development of NP (OR, 3.68; CI, 1.27–10.7; p = 0.016)
Benito-Pescador et al. 2012 [57]		CG	Spain	To analyze polymorphisms in *LTC4S, CYSLTR1, PTGDR,* and *NOS2* as representative genes of inflammation pathways in a population of patients with NP	245 HC 241 NP: 145 asthma 81 NSAID 75 aspirin triad	Blood	*LTC4S*	rs730012 (-444A>C)	The –444A>C *LTC4S* polymorphism was significantly associated with NP and atopy (P=.033) and with NP and atopic asthma, (P=.012). A significant association was found when the (CCTTT) repetition of the *NOS2A* gene was present more than 14 times in patients with NP and asthma (P=.034), in patients with polyposis and intolerance to nonsteroidal anti-inflammatory drugs (P=.009), and in patients with the aspirin triad (P=.005). The *PTGDR* diplotype CCCT/CCCC (–613CC, –549CC, –441CC and –197TC) was more frequent in patients with NP (P=.043), NP with asthma (P=.013), and the aspirin triad (P=.041)
							CYSLTR1	927 T>C	
							PTGDR	-613 C>T -549 T>C -441 C>T -197 T>C	
							NOS2	CCTTT	
Berghea et al. 2014 [51]		CG	Romania	To investigate the association between *TNF* SNP with NP in Romanian patients with asthma	45 NP (38 NSAID+ 7 ATA) 61 without NP (8 NSAID+ 53 ATA)	Blood	*TNF*	rs1799724 (-857 C>T) rs1800629 (-308 G>A) rs361525 (-238 G>A)	There was an association of -857C>T with NP (p=0.01 ATA; p=0.05 NSAID). The allele T was more frequent in NP patients than in non-NP patients.
Bernstein et al. 2009 [30]		CG	USA	To investigate the role of 7 proinflammatory, 4 anti-inflammatory, one Toll receptor and 2 chemokine polymorphism in patients with massive NP	153 HC 179 NP	Buccal cells	*TNF*	rs1800629	The frequency of the A allele in *TNF* is significantly higher in patients with NP versus controls (OR 1.86; 95% CI, 1.4–3.09)
							IL1A	rs3783521 rs17561	
							IL1B	rs3087258 rs1143634	
							IL6	rs13447445	
							TGFB1	rs11466315	
							IL10	rs1800895 rs1800894 rs1800896	
							CD14	rs2569190	
							CCL5/ RANTES	rs2107538	
							CCL2	rs3917882	
Bohman et al. 2017 [21]		GWAS	Sweden	To identify genetic markers and genes associated with susceptibility to CRSwNP using a family-based GWAS	393 HC 427 CRSwNP	Blood	*HLCS*		Pathway analyses using top 1000 markers with the most significant association p-values resulted in 138 target genes. Comparisons with data from expression quantitative trait loci showed the most skewed allelic distributions in cases with CRSwNP compared with HC for the genes *HLCS, HLA-DRA, BICD2, VSIR* and *SLC5A1*
							HLA-DRA		
							BICD2		
							VSIR		
							SLC5A1		
Bosse et al. 2009 [73]		GWAS	Canada	To perform pooling-based GWAS in two case-control cohorts, one of them consisting of patients with CRSwNP	189 HC 210 with severe CRS 157 CRSwNP 53 CRSsNP	Blood	*LAMA2*	rs2571584	600 SNPs from 445 genes that were potentially associated with CRS (P < 0.05). Each of these novel high-priority SNPs had allele frequency differences between cases and controls at a level worthy of additional investigation. The most significant SNP for each of the top 10 genes are shown in this table.
							PARS2	rs2873551	
							NAV3	rs1726427	
							LAMB1	rs4727695	

Supplementary Table 1. Selected genetic studies.

							CACNA1I	rs3788568	
							KIAA1456	rs11779957	
							MUSK	rs10817091	
							TRIP12	rs10535833	
							AOAH	rs4504543	
							MSRA	rs7001821	
Bussu et al. 2007 [69]		CG	Italy	To evaluate the potential involvement of ADRB2 A16G polymorphism in sinonasal polyposis	47 HC 56 NP	Blood	*ADRB2*	rs1042713 (g.5285A>G)	The presence of Arg (A allele) is significantly higher in NP patients than in controls (p=0.0386)
Buysschaert et al. 2010 [41]		GWAS	Belgium	To investigate whether certain SNPs predispose to NP	415 HC 273 NP	Blood	*IL1RL1*	rs1420101	Rs3939286 was significantly associated with NP (OR 1.60; 95% CI 1.16-2.22; p=0.0041). The A-allele conferred a risk for NP (OR 1.53; 95% CI 1.21-1.96; p=0.0041). Rs1420101 may increase risk when in combination with rs3939286
							IKZF2	rs12619285	
							GATA2	rs4431128	
							IL5	rs4143832	
							SH2B3	rs3184504	
							WDR36	rs2416257	
							MHC	rs2269426	
							MYB	rs9494145	
							GFRA2	rs748065	
							IL33	rs3939286	
Cantone et al. 2018 [61]		CG	Italy	To investigate the relevance of *TAS2R38* genetic variants in the susceptibility to bacterial infections	100 CRSwNP	Saliva, blood	*TAS2R38*	rs713598 (C145G; Pro>Ala) rs1726866 (C785T; Ala>Val) rs10246939 (G886A;Val>Ile)	The nonfunctional genotype (AVI) is more frequent among CRS patients than in the general population (25% vs. 18.4%, P=0.034). No relationship with severity was found.
Castano et al. 2009 [36]		CG	Canada	To investigate whether whether certain polymorphisms in the *IL1RL1* gene are differentially present in patients with surgery-unresponsive CRS and in control subjects	187 HC 154 CRSwNP 52 CRSsNP	Blood	*IL1RL1*	rs974389 rs10204137 rs985523 rs10208293 rs1041973 rs12105808 rs1420103 rs12712142 rs1921622 rs12996097 rs2160203 rs13431828 rs3771177 rs17696274 rs4988957	Statistically significant allelic associations with CRS were noted for 5 SNPs (rs10204137, p=0.04; rs10208293, p=0.03; rs13431828, p=0.008; rs2160203, p=0.03, and rs4988957, p=0.03). But only one SNP significantly associated with CRSwNP (rs13431828, p=0.008)
Castano et al. 2010 [71]		CG	Canada	To assess the association of polymorphisms in the *MET* gene with CRS in a Canadian population	196 HC 154 CRSwNP 52 CRSsNP	Blood	*MET*	rs38840 rs2237711 rs1024658 rs10271561 rs10243024 rs40239 rs714180 rs38855 rs38841 rs38857 rs39747 rs2237717 rs38845 rs38846 rs2299440 rs1752698 rs7798983 rs2402118 rs38849 rs193688 rs722134 rs38850 rs1621 rs42336	The genotype distribution of two SNPs in the *MET* gene (rs388840, rs38850) displayed a significantly different genotypic distribution (p≤ 0.05) between CRS patients and controls. The most significant association in the *MET* gene was found with SNP rs38850 (p=0.004).
Cheng et al. 2006 [34]		CG	Taiwan	To assess the association of *IL1B* and *IL1RN* gene polymorphisms with CRS	103 HC 88 CRS 61 CRSwNP 27 CRSsNP	Blood	*IL1B*	-511C>T +3953C>T	There were significant differences in the distribution of the *IL1RN* polymorphism between the control subjects and patients with CRS (P=.05). The II allele of *IL1RN* occurred more frequently in the CRS patient
							IL1RN	Variable number tandem repeat of an 86–base pair segment in intron 2	

Supplementary Table 1. Selected genetic studies.

									group (OR 3.3; 95% CI, 1.25-9.18, P=0.01).
Cormier et al. 2009 [112]		CG	Canada	To determine whether SNP in *TNF, TNFAIP3*, and *TNFAIP6* genes were associated with CRS	196 HC 206 CRS 154 CRSwNP	Blood	*TNF*	rs2229094 rs3093672 rs1121800 rs769177 rs1321136r rs77669888 s1800750 rs9267502 rs2256965 rs9469027 rs2256974 rs1800629 rs2857706 rs361525 rs3093561 rs4987027	Two polymorphisms in *TNFAIP3* (rs3757173 and rs5029938) are weakly associated with severe CRS but no association was found with genetic variants in TNF or *TNFAIP6*. None was associated to risk of NP.
							TNFAIP3	rs5029963 rs3757173 rs5029935 rs5029938 rs5029939 rs661561 rs610604 rs50 29965	
							TNFAIP6	rs6433371 rs16830015 rs670782 rs12466578 rs10183099 rs2342910 rs3771889 rs3771891 rs10432475	
Dar et al. 2018 [65]		CG	India	To assess the risk of CRSwNP conferred by SNPs in *FcεR1α* gene in a North Indian cohort	50 HC 100 CRSwNP	Blood	*FCER1A*	rs2427827 rs2251746 rs2298804 rs2298805 rs2269718	In those cases with high serum IgE, the T allele of rs2427827 is significantly more frequent in CRSwNP patients (OR 2.24; p=0.02)
De Alarcon et al. 2016 [58]		CG	USA	To evaluate the association of *LTC4S and PAI-1* variants with CRS	66 HC 16 CRSsNP 117 CRSwNP	Blood, polyp fibroblasts	*LTC4S*	rs730012 (-444A>C)	The C allele of *LTC4S* was more frequent in those NP patients also diagnosed with chronic hyperplastic eosinophilic sinusitis (p<0.04)
							SERPINE1 (PAI1)	rs1799762 (4G/5G ins.)	
Ekinci et al. 2011 [70]		CG	Turkey	To examine whether there is an association of eotaxin-1 (*CCL11*) gene polymorphisms with NP	93 HC 85 NP	Blood	*CCL11*	rs1490392522 (-384A>G) rs762429865 (67 G>A)	The selected SNPs are more frequent in NP patients than in HC (p=0.044 and p=0.019, respectively). However, their relation was statistically poor (association coefficient =0.18).
Erbek et al. 2007 [35]		CG	Turkey	To investigate the association between NP and SMPs of the proinflammatory cytokines *IL1A, IL1B, TNFα.*	106 HC 82 NP	Blood	*IL1A*	4845G>T	The 4845GTand 4845TTgenotypes of the *IL1A* gene were associated with NP (P<.05). The frequency of the *IL1B* –511 CC and CT were significantly higher in patients with NP than in controls (P=.01). There was a significantly high risk of susceptibility to NP in patients with the -308 GA genotype (P=.001).
							IL1B	-511C>T	
							TNF	rs361525 (-238 G>A) rs 1800629 (-308G>A)	
Esmaeilzadeh et al. 2015 [19]		CG	Iran	To investigate the association of *HLA-DRB* and *-DQ* genetic variabilities in patients with AERD	100 HC 50 CRSwNP + asthma	Blood	*HLA-DRB1*	*HLA-DRB1*0101* *HLA-DRB1*15* *HLA-DRB1*16* *HLA-DRB1*0301* *HLA-DRB1*04* *HLA-DRB1*07* *HLA-DRB1*08* *HLA-DRB1*0901* *HLA-DRB1*1001* *HLA-DRB1*11* *HLA-DRB1*12* *HLA-DRB1*1301* *HLA-DRB1*1302*	Two variations are associated with increased risk of NP: *HLA-DRB4*, OR 2.34, CI 1.37–4.00, p>0.01 *HLA-DQB1*0302*, OR 4.56, CI 2.10–9.91, p<0.01 Two variations are associated with reduced risk of NP: *HLA-DRB3*, OR 0.41, CI 0.24–0.68, p<0.01 *HLA-DQB1*0301*, OR 0.39, CI 0.21–0.73, p<0.01

Supplementary Table 1. Selected genetic studies.

								*HLA-DRB1*1305* *HLA-DRB1*14*	
							HLA-DRB3	*HLA-DRB3*	
							HLA-DRB4	*HLA-DRB4*	
							HLA-DRB5	*HLA-DRB5*	
							HLA-DQA1	*HLA-DQA1*0101* *HLA-DQA1*0102* *HLA-DQA1*0103* *HLA-DQA1*0104* *HLA-DQA1*0201* *HLA-DQA1*0301* *HLA-DQA1*0401* *HLA-DQA1*0501*	
							HLA-DQB1	*HLA-DQB1*0201* *HLA-DQB1*0301* *HLA-DQB1*0302* *HLA-DQB1*0303* *HLA-DQB1*0305* *HLA-DQB1*0401* *HLA-DQB1*0501* *HLA-DQB1*0601* *HLA-DQB1*0602* *HLA-DQB1*0604*	
Fajardo-Dolci et al. 2006 [20]		CG	Mexico	To determine the contribution of the human major histocompatibility complex *HLA-DQA1*, –*DQB1*, and *TNFα* genes with simple nasal polyposis.	151 HC 31 NP	Blood	*HLA-DQA1*	*HLA-DQA1*0101/4* *HLA-DQA1*0102* *HLA-DQA1*0103* *HLA-DQA1*0201* *HLA-DQA1*030101* *HLA-DQA1*0401* *HLA-DQA1*0501*	The allele *HLA-DQA1*0201* was found to be involved in susceptibility to develop simple NP, without asthma, aspirin intolerance, or any other allergic diseases. OR 6.79 CI (1.9-23.9) 13% etiological fraction was found for the haplotype *HLA-DQA1*0201-DQB1*0201* (P=0.016).
							HLA-DQB1	*HLA-DQB1*0201* *HLA-DQB1*0301* *HLA-DQB1*0302* *HLA-DQB1*0402* *HLA-DQB1*0501* *HLA-DQB1*0502* *HLA-DQB1*0503* *HLA-DQB1*0504* *HLA-DQB1*0601*	

Supplementary Table 1. Selected genetic studies.

								*HLA-DQB1*0602* *HLA-DQB1*0603*	
							TNF	rs1800629 (-308 G>A) rs361525 (-238 G>A)	
Fruth et al. 2011 [113]		CG	Germany	To analyze the potential association of *GST* polymorphisms and CRS.	52 HC 118 CRS 69 CRSwNP 49 CRSsNP	NP, ITM	*GST*	GST-T1 GST-M1 GST-P1	No correlation
Fruth et al. 2012 [114]		GC	Germany	To shed light on the significance of *SPINK5* and the development of inflammatory diseases of the upper respiratory tract.	30 HC 59 CRSwNP 15 CRSsNP	NP, ITM	*SPINK5*	rs17775319 (G1258A) G2475T rs1243172589 (A2915G) rs745601984 (A1103G)	No correlation
Gallo et al. 2016 [62]		CG	Italy	To confirm the proposed correlation between *TAS2R38* genotype, CRS, and related comorbidities.	39 HC 36 CRSwNP 17 CRSsNP	Blood	*TAS2R38*	rs713598 (G/C; Ala/Pro)) rs1726866 (G/A; Val-Ala) rs10246939 (T/C; Ile-Val)	No differences found in genotypic distribution
Henmyr et al. 2014 [37]		GWAS	Turkey, Finland, China, Korea, USA, Belgium	To investigate the reproducibility of previous SNP associations with CRSsNP and CRSwNP.	1588 HC from Illumina data base 613 Belgian patients: 275 CRSwNP 338 CRSsNP	Blood, database	*IL1A*	rs17561	Some SNPs are associated with increased risk of NP: *IL1A* rs17561 *RYBP* rs4532099 *TNF* rs1800629 *IL33* rs3939286 *IL10* rs1800870 *CACNG6* rs192808 *MMP9* rs3918242 Some SNPs are associated with reduced risk of NP *IL1B* rs16944 *DCBLD2* rs828618 *AOAH* rs4504543 *IRAK4* rs4251431
							IL1B	rs16944	
							RYBP	rs4532099	
							DCBLD2	rs828618	
							TNFA	rs1800629 rs361525	
							AOAH	rs4504543	
							IL33	rs3939286	
							IRAK4	rs4251431	
							IL10	rs1800870	
							CACNG6	rs192808	
							MMP9	rs3918242 rs17577	
Henmyr et al. 2016 [115]		CG	Sweden, 1000Genomes Project	To screen for rare variants in *PARS2* and to evaluate for accumulation of such variants in CRS patients.	372 HC 138 CRSwNP 172 CRSsNP	Blood	*PARS2*	rs143717155 rs116816976 rs35201073 rs12023572 rs768053281 rs370234936 rs61768813 rs2270004 rs145005088 rs563439229 rs1180946 rs1180945 rs11577368 rs116416055 rs145866387 rs74617964 rs1180947	A significant surplus of variation was observed in the CRS patients (p=0.048). Haplotype analysis of the region showed a significant excess of rare haplotypes in the CRS patients compared to HC in the following SNPs: rs2873551, rs2270004, rs11577368, rs1180946, rs1180945 TTAGC p=0.0048 TTCCC p=0.0048 TCAGT p=0.0016
Hytönen et al. 2001 [67]		CG	Finland	To investigate if the frequency of the most common *CFTR* mutations was more	135 CRS	Blood	*CFTR*	ΔF508	No abnormal distribution was observed in CFR patients

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Supplementary Table 1. Selected genetic studies.

				common among CRS patients with or without NP.	91 CRSsNP 46 CRSwNP			394delTT	
Ismi et al. 2017 [50]		CG	Turkey	To determine the genetic susceptibility of NP formation to TNF and IL1B polymorphisms	91 HC 71 CRSwNP	Blood	*TNF*	-308G>A	There was a statistically significant increase in the expression of the *TNF* -308 GG and *IL1B* -511 CC genotypes in the patients with NP
							IL1B	-511T>C	
Karjalainen et al. 2003 [38]		CG	Finland	To establish whether *IL1A* and *IL1B* have an effect on susceptibility to NP.	35 CRSwNP 210 CRSsNP	Blood	*IL1A*	4845G>T	The risk of NP was markedly increased in *IL1A* allele G homozygous subjects (OR 2.73; 95%CI 1.40–5.32, p=0.005). In the case of *IL1B* no significant associations were found.
							IL1B	-511C>T	
Keles et al. 2008 [22]		CG	Turkey	To evaluate whether there is a relationship between *HLA-A, -B, -Cw,* and *-DRB1* alleles and developing NP.	100 HC 66 NP	Blood	*HLA-A*	*HLA-A* *01 *HLA-A* *02 *HLA-A* *03 *HLA-A* *11 *HLA-A* *24 *HLA-A* *26 *HLA-A* *33	*HLA-B*07* and *-Cw*12* alleles were significantly higher in the NP patients than in the control group. *HLA-B*57* and *-Cw*04* alleles were significantly lower in the NP patients than in the control group. In the NP patients with ASA, there was a significant increased frequency of the *HLA-A*24, -Cw*01, -Cw*12,* and *-DRB1*04* alleles. *HLA-A*33* and *-Cw*12* alleles in NP patients who had polypectomy history were significantly higher than in the control group. In NP patients, a significantly decreased frequency of the *HLACw** *04* and *-DRB1*11* alleles was shown.
							HLA-B	*HLA-B* *07 *HLA-B* *15 *HLA-B* *35 *HLA-B* *44 *HLA-B* *51 *HLA-B* *57	
							HLA-Cw	*HLA-Cw* *01 *HLA-Cw* *02 *HLA-Cw* *03 *HLA-Cw* *04 *HLA-Cw* *06 *HLA-Cw* *07 *HLA-Cw* *08 *HLA-Cw* *12	
							HLA-DRB1	*HLA-DRB1**01 *HLA-DRB1**03 *HLA-DRB1**04 *HLA-DRB1**07 *HLA-DRB1**11 *HLA-DRB1**14	
Kilty et al. 2010 [116]		CG	Canada	To investigate the association between SNPs in the *SERPINA1* gene and CRS	196 HC 154 CRSwNP 27 CRSsNP	Blood	*SERPINA1*	rs11558262 rs11832 rs1243160 rs1243163 rs1243166 rs1243167 rs1243168 rs1243169 rs1243171 rs12884390 rs1303 rs17287271 rs17580 rs1956707 rs2071274 rs2230075 rs2239651 rs2749531 rs2753934 rs3748316 rs4900229 rs4900230	Two SNPs (rs1243168 and rs4900229) were associated with the disease. rs1243168 T allele was significantly associated with severity (p<0.01)

Supplementary Table 1. Selected genetic studies.

								rs17751614 rs4905198 rs17751769 rs6575424 rs17824797 rs6647 rs709932 rs7151526 rs8010121 rs877081	
Kim et al. 2007 [117]		CG	Korea	To evaluate the association of *TGFB1* polymorphisms with an AERD phenotype in the Korean population	456 HC 206 AERD 72 NP 324 ATA 10 NP	Blood	*TGFB1*	rs13447445	No association with NP
Kim et al. 2009 [64]		CG	Korea	To evaluate associations between genetic polymorphisms of adenosine deaminase and adenosine receptors with the AERD phenotype	183 HC 136 AERD 47 NP 181 ATA 10 NP	Blood	*ADA*	rs11086932 rs244076	No association with NP was described. Significant differences between normal and patients with AERD in the ADORA1 SNP genotype frequencies for rs16851030 (P=0.001) and rs6664108 (P=0.013).
							ADORA1	rs10920568 rs6664108 rs6427994 rs16851030 rs12744240	
							ADORA2A	rs5996696 rs5751876	
							ADORA3	rs2298191 rs10776727 rs1544224 rs2229155	
Kim et al. 2012 [23]		CG	Korea	To investigate the associations of HLA-DRA polymorphisms with NP in asthmatic and AERD patients.	158 CRSwNP 309 CRSsNP	Blood	*HLA-DRA*	rs9268628 A>C rs3129871 C>A rs9268633 G>A rs9405035 G>A rs14004 C>A rs9268644 C>A rs9268645 G>C rs3129878 A>C rs3135392 G>T rs6926374 G>A rs3129881 C>T rs17496549 C>T rs6911777 T>C rs3129886 C>T rs8084 C>A rs2239805 A>C rs2239804 G>A rs7192 G>T rs4935354 A>G rs7194 A>G	4 SNPs were significantly associated with NP Rs9268644 p=0.009 Rs3129878 p=0.033 Rs3129881 p=0.013 Rs2239805 p=0.029 And the haplotype (rs3129871; rs8084; rs2239805; rs2239804; rs7192; rs4935354; rs7194; rs1051336; rs1041885) TAAATGGA (p=0.029)

Supplementary Table 1. Selected genetic studies.

								rs1051336 G>A rs1041885 A>T	
Kostuch et al. 2005 [66]		CG	Poland	To determine the prevalence of the most common CFTR mutations in patients with NP without suspicion of CF.	70 human placentas 44 NP	Blood, placenta	*CFTR*	ΔF508 G551D G542X N1303K 1717-1G>A W1282X R553X ΔI507	ΔF508 is more frequent in patients than in HC (p=0.0032) and in the general Polish population as well (P =0.0059).
Kosugi et al. 2013 [118]		CG	Brazil	To analyze the relationship between an IL6 polymorphism and asthmatic NP patients.	81 HC 45 asthmatic with NP 63 non asthmatic NP 45 asthmatic without NP	Blood	*IL6*	rs374295772 (-174G>C)	Genotype distribution was non-significant, but GG genotype appeared more frequently in all inflammatory groups.
Kristjansson et al. 2019 [55]		GWAS	Iceland, UK	To search for sequence variants affecting the risk of NP or CRS	Iceland 353939 HC 3188 cases UK 406147 HC 2420 cases	Database	*HLA-DQA1*	rs1391371	The mentioned variants at ten loci were found that associate with NP at genome-wide significance. The variant with the largest effects on the risk of NP is a low-frequency missense variant rs34210653[A] (Thr560Met) in ALOX15 that confers a 68% reduction in NP risk (p= $8.0x10^{-27}$ OR 0.32, 95% CI 0.26, 0.39).
							IL33	rs1888909	
							TSLP	rs1837253	
							ALOX15	rs34210653	
							10p14	rs1444782	
							FOXP1	rs17718444	
							CYP2S1	rs338598	
							IL18R1	rs6543124	
							SLC22A4	rs1050152	
							MYRF	rs174535	
Kuran et al. 2019 [39]		CG	Turkey	To analyze possible genetic factors that increase susceptibility to NP.	98 HC 78 NP	Blood	*IL1RN*	rs2234663	Distribution of genotypes of IL1RN and IL4 was significantly different in NP vs HC (p=0.0001)
							IL4	rs8179190	
							IL2	rs206976	
Luxenberger et al. 2000 [119]		CG	Austria	To determine the association of HLA-A, -B, -DR, and –DQ with NP	1070 HC 89 NP	Blood	*HLA-A* *HLA-B* *HLA-DR* *HLA-DQ*		A significant association was seen with HLA-A74 and nasal polyposis
Mfuna Endam et al. 2009 [29]		CG	Canada	To explore association between SMPs in IL22RA1 and severe CRS	196 HC 206 CRS 154 CRSwNP 52 CRSsNP	Blood	*IL22RA1*	rs10465895 rs10751768 rs10794665 rs10903031 rs11249201 rs11577442 rs11578307 rs11579657 rs12070496 rs12092673 rs12408946 rs16829225 rs2502450 rs3795300 rs3936073 rs4292900 rs4648936 rs4648942 rs4649187 rs6424157 rs7418238 rs7513249	Three SNPs (rs4292900 Pnom =0.0006, OR 1.757; rs4648936 Pnom=0.0011, OR 1.716; rs16829225 Pnom=0.0014, OR 1.977) show significant differences in allelic frequencies between cases and controls
Mfuna Endam et al. 2010 [28]		CG	Canada	To replicate the CRS associations recorded for IL1A, IL1B, and TNF	196 HC	Blood	*IL1A*	rs17561 rs1800587 rs2048874 rs3783521 rs3783538	For rs17561, this study replicated previous results about the association of the TT homozygote genotype (OR, 3.39; P=.007). The protective effect of

Supplementary Table 1. Selected genetic studies.

				in a cohort of Canadian patients with severe CRS.	206 CRS 154 CRSwNP 52 CRSsNP			rs2856838 rs6722023	rs2856838 (OR, 0.38; P=.002) and the risk effect of rs1800587 (OR=3.16, P=.008) are enhanced with the homozygote form of the minor allele. In contrast, no association was found with SNPs in IL1B or TNF.
							IL1B	rs16944	
							TNF	rs1121800 rs3093561 rs13211368 rs3093672 rs1800629 rs1800750 rs361525 rs2229094 rs4987027 rs2256965 rs769177 rs2256974 rs2857706 rs7766988 rs9267502 rs9469027	
Mfuna Endam et al. 2014 [59]		GWAS	Canada	To identify taste receptor associated with CRS and verify whether known SNP replicated in their CRS cohort	GCRS1 196 HC 206 CRS GCRS2 190 HC 408 CRSwNP	Blood	*TAS2R1*	rs17788846 rs6874254 rs41483 rs882142 rs12374524 rs6555620 rs4272105 rs1173971 rs10746553 rs3110986 rs1015855 rs3094363	57 SNPs in TAS2Rs and 16 SNPs in TAS1Rs had allele frequency differences above 10% between controls and patients (range, 10.2% to 32.4%). Three coding SNPs associated with CRS were identified: 1 in the TAS2R13 gene (rs1015443, biallelic differences of 13.8% in GCRS1), and 2 others in the TAS2R49 gene (rs12226920, biallelic difference of 16.0% in GCRS1; and rs12226919, biallelic difference of 11.9% in GCRS1)
							TAS2R10	rs669503 rs10845219	
							TAS2R13	rs1015442 rs1015443	
							TAS2R14	rs3851586 rs1013311 rs3741843	
							TAS2R3	rs765007 rs6962760	
							TAS2R38	rs4726481 rs10246939 rs1726866	
							TAS2R39	rs11979433	
							TAS2R4	rs2234002 rs2190245	
							TAS2R41	rs2966709 rs12536735 rs2966715 rs1806578 rs2949746 rs2949770 rs2966701 rs2966699	
							TAS2R43	rs2966699 rs2708333 rs35911096 rs2597975 rs2708364 rs7313683 rs2599396 rs2597974	
							TAS2R44	rs4763616 rs2010481	
							TAS2R46	rs2708389 rs11533164 rs2708377 rs2255418	
							TAS2R48	rs10772420	

Supplementary Table 1. Selected genetic studies.

							TAS2R49	rs1463237 rs10772408 rs4298989 rs12226920 rs12581501 rs12226919 rs11054150	
							TAS2R5	rs35010424 rs11769672 rs11773137 rs1859646	
							TAS2R50	rs2900554 rs6488331	
							TAS2R7	rs7313019	
							TAS1R1	rs11122100 rs12080675	
							TAS1R2	rs28410948 rs6686865 rs7417542 rs9662598 rs7411042 rs4920566 rs6685177 rs12137730 rs6603912 rs6684577 rs12063142 rs3935570 rs12042960 rs7418296	
Molga et al. 2016 [120]		CG	Poland	To assess genetic predisposition of MMP1 -1607 G/GG polymorphism to CRSwNP	463 HC 206 CRSwNP	Blood	*MMP1*	rs199750 (-1607 G/GG)	The frequency of genotypes was not significant related to CRSwNP, but GG is relates to increases number of surgeries (p=0.002) and bronchial asthma (p=0.021)
Molnar-Gabor et al. 2000 [24]		CG	Hungary	To investigate whether there is an association between HLA-DRB1, -DQA1, and DQB1 alleles and developing NP	50 HC 50 CRSwNP	Blood	*HLA-DR5*		The odds ratios for developing nasal polyposis increased in people carrying the DR7 (OR 2.55) allele with the linked DQA1*0201 (OR 2.52) and DQB1*0202 (OR 5 2.84) alleles. On the other hand, DR5 (OR 0.66) linked with DQA1*05012 (OR 0.69), DQB1*0301 (OR 0.57) alleles showed a decreased odds ratio value.
							HLA-DR7		
							HLA-DQA1	*HLA-DQA1*0101* *HLA-DQA1*0102* *HLA-DQA1*0103* *HLA-DQA1*0104* *HLA-DQA1*0201* *HLA-DQA1*0301* *HLA-DQA1*05011* *HLA-DQA1*05012*	
							HLA-DRB1	1-10	
							HLA-DQB1	*HLA-DQB1*0201* *HLA-DQB1*0202* *HLA-DQB1*0302* *HLA-DQB1*0301* *HLA-DQB1*0303* *HLA-DQB1*0402* *HLA-DQB1*0501* *HLA-DQB1*0502* *HLA-DQB1*0503* *HLA-DQB1*0601* *HLA-DQB1*0602* *HLA-DQB1*0603*	

Supplementary Table 1. Selected genetic studies.

								*HLA-DQB1*0604*	
Mrowicka et al. 2014 [32]		CG	Poland	To investigate the relationship between IL1B and IL4 promoter polymorphisms	200 HC 208 CRSwNP	Blood	*IL1B*	rs55778004 (-511C>T)	The TT genotype for C-511T mutation associated with the risk of developing NP in a Polish population
							IL4	-590C>T	
Nakayama et al. 2020 [121]		GWAS	Japan	To perform an association study of CRSwNP and AERD with genetic variants in the TSLP locus	1908 HC 499 CRSwNP	Blood	*TSLP*	rs1751303 rs3806933 rs10056340 rs1898671 rs1837253 rs2416257 rs3806932 rs1438673	Significant association between CRSwNP and rs1837253, rs3806932 and rs3806933, with the most significant association being observed at rs1837253 ($p= 1.27x10^{-6}$; OR, 1.60; 95% CI, 1.32-1.94)
Ozdas et al. 2015 [122]		CG	Turkey	To analyze SNPs of the RYD5 gene and to determine the effect on polyp formation	238 HC 196 NP	Blood	*RYD5*	rs113795008 rs7951297 rs535294582 rs2294083 rs2280540 rs2294082 rs144999256 rs61997072 rs148962288	Four SNPs (rs113795008, rs2280540, rs2294083, and rs2294082) were significantly associated with NP. The individuals with combined genotypes of six risk alleles (rs113795008, rs2280540, rs7951297, rs2294083, and rs2294082) had significantly higher risks for NP compared with the ones with one or four risk alleles.
Palikhe et al. 2017 [123]		CG	Korea	To investigate the potential associations between ABCC4 gene polymorphisms and asthma genotype.	120HC 270 asthma 106 NP	Blood	*ABCC4*	rs868853 (A>G) rs839951 (C>G)	No significant association
Park et al. 2006 [43]		CG	Korea	To evaluate expression of cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO) associated with IL4 promoter polymorphism -590 in NP tissues	70 HC 61 NP	Blood	*IL4*	-590 C>T	A T>C exchange at -590 position was correlated with NP. The T allele was significantly more frequent in NP (p=0.028).
Pasaje et al. 2012a [124]		CG	Korea	To explore the association of DCBLD2 gene with the presence of NP in asthma patients	309 HC 158 NP+asthma	Database	*DCBLD2*	rs2439224 rs828618 rs1371687 rs828616 rs9838238 rs16840208 rs17278047 rs17270986 rs7615856 rs1062196 rs828621 rs8833	Six SNPs were associated with the presence of NP: rs1371687, rs7615856, rs828621, rs828618, rs828616, and rs8833. After multiple testing adjustment, only rs828621 remained significant (p=0.006)
Pasaje et al. 2012b [125]		CG	Korea	To investigate the association between EMID and NP	309 asthma no NP 158 asthma+NP	Database	*EMID*	rs6945102 rs1476652 rs4729697 rs6973489 rs10237610 rs7802156 rs9986717 rs10953342 rs10254516 rs12668018 rs10239458 rs1008064 rs221 rs13232646 rs10435333 rs1543883 rs6944691 rs1859625 rs6942770 rs6947089 rs9640666 rs9969331 rs6947185 rs12538381 rs11770876 rs17135512 rs11772022 rs1558015 rs11772003 rs10250055 rs10223928 rs6947735 rs4729705 rs2158739 rs10254310 rs10279545	Ten EMID2 SNPs (rs6945102, rs4729697, rs221, rs10435333, rs6947185, rs4727494, rs13233066, rs1008064, rs1543883,and rs13245946) were associated with the presence of nasal polyps (p= 0.004- 0.05, OR 0.61-1.32) depending on the genetic model. rs6945102, rs4729697, rs221, and rs10435333, were found to be significantly associated with NP in the overall Korean asthma patients even after multiple testing corrections

Supplementary Table 1. Selected genetic studies.

								rs4045 rs6945961 rs6949799 rs13245946 rs4727491 rs17470799 rs13238748 rs10237510 rs4727494 rs17135617 rs13233066 rs17135621 rs869127	
Pascual et al. 2008 [126]		CG	Spain	To analyze the (CCTTT)n polymorphism of NOS2 in patient with NP and/or asthma	98 HC 46 NP 150 asthma	Blood	*NOS2*	(CCTTT)n	Allele frequency distribution is significantly different between HC and NP (p=0.003). A 15-repeat cutoff is associated with increased risk of NP (OR 14.39; 95% CI, 3.02 - 68.60; P = .001)
Pavon-Romero et al. 2018 [54]		SNP array	Mexico	To evaluate whether contribution to susceptibility of SNPs reported in other populations are associated with AERD in Mexican patients	179 HC 120 AERD 179 asthma	Blood	*ACE*	rs4309† rs4293†	In AERD vs. HC, we identified 22 associated SNPs, with 11 SNPs associated with risk in 7 genes (ACE, MS4A2, FSIP2, IL10, FCERIG, KIFC3, and ANX4; denoted as † in the adjacent column). Two SNPs were strongly associated: ACE rs4309 (C allele p = 0.0001, OR = 1.92, CI 95% = 1.37–2.69) and MS4A2 rs573790 (C allele p = 0.0002, OR = 1.94, CI 95% = 1.35–2.79). By contrast, 11 SNPs in 5 genes (PPARG, IL10, RG7SBP, TBXAS1, and FANCC) were associated with protection.
							MS4A2	rs576790† rs502581†	
							FSIP2	rs2631700† rs2631702†	
							KIFC3	rs2285700†	
							ANX4	rs7588022†	
							FCER1G	rs4489574† rs7528588	
							IL10	rs1800896† rs3024498† rs1554286 rs1800872	
							PPARG	rs2960421 rs4135275 rs1875796	
							RGS7BP	rs6870654	
							TBXAS1	rs13239058 rs10487667 rs6962291	
							FANCC	rs1326188	
Purnell et al. 2019 [63]		CG	USA	To determine the frequency of 6 SNPs in genes with bitter taste signaling function.	1000 Genomes database 74 CRS 41 CRSwNP 33 CRSsNP	Buccal cells	*TAS2R38*	rs713598	No differences between CRSwNP and CRSsNP
							GNB3	rs5443	
							TAS2R19	rs10772420	
							TAS2R20	rs12226920	
							RGS21	rs7528947 rs1175152	
Ramirez-Anguiano et al. 2006 [25]		CG	Mexico	To determine the association of HLA-DRB1 alleles with NP in the Mexican Mestizo population.	99 HC 34 NP	Blood	*HLA-DRB1*	*HLA-DRB1**02 *HLA-DRB1**03 *HLA-DRB1**04 *HLA-DRB1**05 *HLA-DRB1**07 *HLA-DRB1**08	Significant increase in the *03 and *04 (OR 2.2, p=0.009) allele frequencies. Significant decrease in the *08 allele (OR 0.2, p=0.01)

Supplementary Table 1. Selected genetic studies.

Sachse et al. 2010 [127]		CG	Germany	To detect staphylococcal colonization in nasal polyps and controls.	51 HC 68 NP	NP, ITM	*TLR2*	rs5743708	The minor allele A is not associated with NP
Sitarek et al. 2012 [52]		CG	Poland	To investigate the association of COX-2 and MET gene polymorphisms with the risk of CRSwNP.	200 HC 195 NP	Blood	*COX2*	rs20417	Increased risk (p>0.001) of CRSwNP associated with the C allele of COX2 (OR 6.05) and G allele of MET (OR 5.52) The combined genotype GC/GG had increased risk (OR 4.07, p<0.001)
							MET	rs78116323	
Song et al. 2012 [128]		CG	Korea	To investigate the genetic contribution of ALO15 to the development of AERD.	195 HC 171 AERD (49 NP) 229 ATA (9 NP)	Blood	*ALOX15*	rs34104097 rs7220870 rs2664592	The patients carrying haplotype 1 (GCG) of Rs34104097, Rs7220870, and Rs2664592 showed a significantly higher total eosinophil count compared to the other haplotypes (p = 0.008) in the AERD group
Szabo et al. 2013 [49]		CG	Hungary	To determine whether TNFa -308G>A SMP has a role in the genetic predisposition to CRS in a Hungarian population.	169 HC 326 CRSwNP 49 CRSsNP	Buccal cells	*TNF*	rs1800629	There was a significantly higher carriage rate of the rare A allele-containing genotypes among the AIA CRSwNP patients
Szabo et al. 2015 [48]		CG	Hungary	To examine whether the association between TNFa -308A allele and AIA CRSwNP is due to this allele or to the presence of the complete 8.1 ancestral haplogroup (AH) in chromosome 6.	169 HC 244 CRSwNP 57 CRSsNP	Buccal cells	*TNF*	rs1800629	Carriers of 8.1 AH carried all 4 studied SNPs in homozygotic or heterozygotic forms. This AH is significantly associated with CRSwNP (p=0.014)
							AGER	rs1800625	
							HSP70-2	rs1061581	
							LTA	rs909253	
Tewfik et al. 2009 [31]		CG	USA	To investigate whether polymorphisms in the genes encoding key TLR signaling molecules might be associated with total serum IgE levels.	154 CRSwNP 27 CRSsNP	Blood	*TLR11*	rs4286521 rs4833095 rs5743611 rs5743594 rs4833103	Blood IgE levels have been shown to be raised in patients with CRSwNP The C allele of rs1461567, the G allele of rs4251513, and the A allele of rs4251559 of the IRAK4 gene are associated with high serum levels of IgE in the NP patients.
							TLR2	rs13150331 rs4696480 rs1898830 rs4696483 rs3804100 rs5743704 rs5743708 rs7656411 rs1339 rs17030340 rs2289318 rs7695605	
							TLR3	rs956239 rs4861699 rs5743305 rs7657186 rs6552950 rs3775296 rs35140061 rs7668666 rs3775292 rs35311343 rs5743317 rs3775291 rs5743318 rs10025405 rs4862633 rs4608848 rs6857595 rs1519309	
							TLR4	rs10983754 rs10759930 rs10759932 rs2149356 rs4986790 rs4986791 rs11536889 rs11536898 rs1554973 rs7860896 rs7037225 rs2183016	
							TLR6	rs5743810 rs5743808 rs5743794 rs5743788 rs6833914	

Supplementary Table 1. Selected genetic studies.

							TLR9	rs352162 rs352140 rs5743836 rs187084 rs352143 rs11717574	
							TLR10	rs4513579 rs11466657 rs11096955 rs11466652 rs10856839 rs7653908	
							CD14	rs7721577_TC rs4914_CG rs2569190_GA rs2569193_GA rs2563310_GA	
							MD2/LY96	rs1905045_TC rs16938755_TC rs11786591_CT rs6472812_GA rs10504554_TC rs17226566_TC rs12544736_TG rs16938766_GC	
							MYD88	rs2239621 rs4988453 rs7744 rs6767684 rs6796045	
							IRAK4	rs11182250 rs1461567 rs4251580 rs4251520 rs4251559 rs17121283 rs6582484 rs4251459 620-1delAC rs4251487 821delT rs4251583 T877C rs4251513 A1188+520G G1189-1T rs4251545	
							TRAF6	rs3740961 rs5030437 rs5030416 rs5030411 rs331455	
Tournas et al. 2010 [129]		GWAS	Canada	To verify an association between p73 and CRS.	196 HC 154 CRSwNP 52 CRSsNP	Blood	*P73*	rs3765731 rs3765692	The A allele of rs3765731 was differentially expressed in NP when compared to HC (p=0.037). The A allele has a protective effect: AA+AG vs GG OR 0.5391, p=0.0036.
Wang et al. 2000 [68]		CG	USA	To determine whether mutations in the CFTR gene, which is responsible for CF, predispose to CRS.	123 HC 147 CRS	Blood	*CFTR*	ΔF508 G542X N1303K	Only 11 patients had one of the selected mutations in the CFTR gene.
Wang et al. 2008 [130]		CG	Taiwan	To investigate the role of MMP2 tagging SNPSs and promoter functional polymorphism in the	136 HC 136 CRSwNP	Blood	*MMP2*	rs2438656 rs857403 rs1030868 rs1477017	rs857403 T allele was associated with increased risk (OR 2.07 p=0.03) but it could not be replicated with additional controls.

Supplementary Table 1. Selected genetic studies.

				development of NP.				rs1053605 rs9302671 rs2241145 rs2241146 rs243849 rs12599775 rs243847 rs243844 rs243840 rs2287076 rs11639960 rs243832 rs7201	
Wang et al. 2010 [131]		CG	Taiwan	To investigate the role of MMP9 tagging SNPSs and promoter functional polymorphism in the development of NP.	730 HC 203 CRSwNP	Blood	*MMP9*	rs3918242 rs2664538 rs3787268 rs2274756	The T allele of promoter SNP rs3918242 was associated with CRSwNP under the dominant (nominal p = 0.023, empirical p = 0.022, OR = 1.62) and additive models (nominal p= 0.012, empirical p = 0.011, OR = 1.60). The A allele of rs2274756 has a nominal p value of 0.034 under the dominant model and 0.020 under the additive model. the most significant haplotype was TGGA p=0.0045
Wang et al. 2013 [132]		CG	Taiwan	To investigate the relative expression of MMPs in the non-recurrent and recurrent NP as compared to control individuals.	31 HC 30 CRSwNP	Blood	*MMP2*	rs243865	Genetic polymorphisms of MMP-2 and MMP-9 functional promoters were not associated with the recurrence of NP.
							MMP9	rs3918242	
Yazdani et al. 2012 [133]		CG	Iran	To investigate the association between the polymorphism C-159T in CD14 gene and NP.	87 HC 107 CRSwNP	Blood	*CD14*	rs946564423	Significant association of the C allele in NP patients (or 1.88, p=0.04)
Yea et al. 2006 [45]		CG	Korea	To investigate the relationship between an IL-4 promoter polymorphism and NP.	70 HC 106 CRS 61 CRSwNP	Blood	*IL4*	-590C/T	The presence of T allele was associated with reduced risk of NP (OR TT 0.529, p=0.028)
Zhai et al. 2007 [26]		CG	China	To explore a potential association between NP and polymorphisms at loci for HLA-DR and HLA-DQ.	81 HC 30 NP	Blood	*HLA-DR*	*04 *07 *08 *09 *10 *11 *12 *13 *14 *15 *16	Frequency of allele was significantly higher in patients for DR*09 and -*16 and DQ-*08 and -*09. DQ*07 frequency was lower in patients.
							HLA-DQ	*02 *04 *05 *06 *07 *08 *09	
Zhang et al. 2008 [134]		CG	China	To examine whether there is an association between Clara cell 10kDa protein (CC10)+38A>G, plasma CC10 levels and CRS.	180 HC 90 CRSwNP 130 CRSsNP	Blood	*CC10 (SCGB1A1)*	+38A>G	No association
Zhang et al. 2011 [135]		CG	Canada	To determine whether polymorphisms in gene regulating NO synthesis	187 HC 154 CRSwNP	Blood	*NOS1*	rs1004356 rs1483757	Two SNPs in the NOS1 gene (rs1483757, p=0.0023, OR 0.62; rs9658281, p =0.0129, O 0.66) remained

Supplementary Table 1. Selected genetic studies.

				are associated with CRS.	52 CRSsNP			rs545654 rs9658281	significant after correction for multiple testing. Homozygote allele C (p=0.0017; OR 0.28) in rs1483757 locus increased the risk. rs12047527 in NOS1AP showed significant association (p<0.05) with CRS
							NOS1AP	rs10458392 rs10919117 rs12022557 rs12047527 rs12061249 rs3923367 rs4657164 rs6676638 rs6677052 rs6677606 rs7416392 rs7546353 rs6681981 rs8179404	
Zhang et al. 2012a [40]		CG	China	To replicate and extend genetic association studies in CRS in a Chinese population.	315 HC 306 CRSwNP 332 CRSsNP	Blood	*PARS2*	rs2873551	Rs4532099 SNP in RYBP increased the risk of CRSwNP (OR 2.76, $p=3.2x10^{-6}$). Selected SNPs in AOAH and IRAK4 were associated with a reduced risk of CRS (OR 0.60-0.79, p<0.05)
							IL22RA1	rs4292900 rs4648936 rs16829225	
							TNFRSF1B	rs235214 rs496888 rs652625 rs7550488	
							TRIP12	rs1035833	
							IL1RL1	rs13431828 rs10204137	
							IL1A	rs17561 rs2856838 rs2048874 rs1800587	
							FAM79B	rs13059863	
							RYBP	rs4532099	
							TSLP	rs3806932 rs2289276	
							LAMA2	rs2571584	
							TNFAIP3	rs3757173 rs5029938	
							LAMB1	rs4727695	
							AOAH	rs4504543	
							MET	rs38850	
							RAC1	rs836479	
							CACNA2D 1	rs6972720	
							KIAA1456	rs11779957	

Supplementary Table 1. Selected genetic studies.

							MSRA	rs7001821	
							MUSK	rs10817091	
							PDGFD	rs12574463	
							NOS1	rs1483757	
							NAV3	rs1726427	
							IRAK4	rs4251431 rs6582484 rs1461567 rs3794262	
							SERPINA1	rs1243168 rs4900229	
							UBE3A	rs1557871	
							SLC13A3	rs393990	
							CACNA1I	rs3788568	
Zhang et al. 2013a [136]		CG	China	To examine association between specific SNPs in/around the FOXP3 and EBI3 genes and susceptibility to CRS	315 HC 306 CRSwNP 332 CRSsNP	Blood	*EBI3*	rs428253 rs6613 rs353698 rs2302164	Risk analysis showed rs428253 of EBI3 gene to play a protective role among both CRSsNP (GG/CC) and CRSwNP (CG/CC) subjects. Haplotype analysis of the FOXP3 gene region further indicated that CRS risk was higher in individuals carrying the haplotype GG in rs2294018–rs2232365 block, compared with wild-type AG haplotype
							FOXP3	rs2294018 rs3060515 rs2232365 rs3761548 rs4824747	
Zhang et al. 2013b [137]		CG	China	To explore associations between SNPs in/around the TSLP gene and development of CRS	315 HC 306 CRSwNP 332 CRSsNP	Blood	*TSLP*	rs1545169 rs764917 rs12653736 rs1837253 rs12654933 rs10455025 rs11466741 rs13156086 rs6886755 rs252706 rs2416259	SNPs rs252706 (AA genotype: P=0.012, OR 0.552) and rs764917 (CA genotype: P=0.001, OR 0.182) displayed protective roles among CRSwNP, but not CRSsNP, subjects.
Zielinska at al. 2012 [138]		CG	Poland	To investigate the association between LF and OSF2 polymorphisms with the risk of CRSwNP in Poland	200 HC 195 CRSwNP	Blood	*LTF*	rs1126478	Rs1126478 LF (OR 4.78; 95% CI 3.07–7.24), the -33C/G OSF2 (OR 3.48; 95% CI 2.19–5.52) and the rs3829365 OSF2 (OR 16.45; 95% CI 6.71–40.30) genotypes were associated with an increased risk of CRSwNP.
							fgOSF2	rs3829365 -33C/G	

Supplementary Table 2. Selected epigenetic studies.

Reference	Objective	Tissue	Epigenetic assay	Population	Significant findings
Callejas-Diaz et al. 2020 [84]	To identify which key mRNA and miRs are regulating in vitro mucociliary differentiation of human adult basal stem cells under pathological and healthy conditions.	NP, inferior turbinate mucosa (ITM; control)	miRNA	Spain	Transcriptome related to ciliogenesis and cilia function is significantly impaired during differentiation of CRSwNP epithelium due to an altered expression of microRNAs, particularly of those belonging to mir-34 and mi-449 families
Cheong et al. 2011 [76]	To analyze the genome-wide DNA methylation levels in nasal polyps from patients with AIA.	NP, buffy coats	Genome-wide DNA methylation	China	332 loci in 296 genes were hypermethylated in AIA vs ATA. These genes are involved in ectoderm development, hemostasis, and wound healing. 158 loci in 141 genes were hypomethylated in AIA vs ATA. Relevant pathways were lymphocyte proliferation, cell proliferation, leukocyte activation, and immune response.
Cho et al. 2012 [75]	To study the effect of trichostatin A (TSA), a histone deacetylase inhibitor, on TGFβ1-induced myofibroblast differentiation and ECM accumulation in NP fibroblasts.	NP, ITM	Histone acetylation control	Korea	The expression levels of HDAC2, α-SMA and TGF-β1 were increased in NP compared to normal tissues. TSA induced hyperacetylation of histones, inhibiting them. HDAC inhibition is associated with myofibroblast differentiation and ECM accumulation in NP.
Cho et al. 2013 [75]	To investigate the inhibitory effect of TSA on myofibroblast differentiation and ECM production in nasal polyp organ cultures.	NP tissue cultures	Histone acetylation control	Korea	TSA inhibited HDAC and induced hyperacetylation of histones H4
Kidoguchi et al. 2018 [77]	To investigate the methylation levels at 3 CpG sites in the proximal PLAT promoter and their effects on gene expression in NP tissue.	NP, ITM	DNA methylation	Japan	Methylation of -618, -121, and -105 CpGs was significantly higher in NP. *PLAT* expression was lower ($p>0.001$). The methylation changes at -618 site showed a negative correlation with the gene expression changes between NP and ITM ($r=-.65$, $p<0.01$).
Kim et al. 2018 [78]	To elucidate whether DNA methylation of specific genes is involved in the development of NP.	NP, ITM	DNA methylation	Korea	The promotor regions of 10 and 30 genes were hypermethylated and hypomethylated, respectively, in NP samples compared with controls. The top four genes with altered hypomethylation in NP tissues were *KRT19*, *NR2F2*, *ADAMTS1* and *ZNF222*.
Kim et al. 2019 [79]	To investigate the expression and distribution of FZD5 and the role of eosinophil infiltration in CRSwNP pathogenesis.	NP, uncinated process tissue	Methylation profiling	Korea	397 and 387 genes were differentially hypermethylated and 399 and 208 genes were hypomethylated in the E-CRSwNP and NE-CRSwNP groups, respectively, compared to the control tissues. Most of the differentially methylated genes were associated with cancer pathways. FZD5 was significantly hypomethylated in the E-CRSwNP compared to the NE-CRSwNP group.
Li et al. 2019a [80]	To determine whether there was any association between abnormal DNA methylation of TSLP gene and CRS	NP, ethmoid mucosa (CRSsNP) patients	DNA methylation	China	There was an increase in methylation ratios of 4 CpGs (2, 22, 23, 24) of TSLP gene had increased in the CRSwNP patients compared to the CRSsNP and

Supplementary Table 2. Selected epigenetic studies.

	pathogenesis.	and ITM			control subjects, significantly related to disease status (p<0.02)
Li et al. 2019b [81]	To determine whether there was any association between abnormal DNA methylation of IL8 promoter and CRS pathogenesis.	NP, ethmoid mucosa (CRSsNP) patients and ITM	DNA methylation	China	Three CpGs (-116, -106, -31) were significantly hypomethylated in the CRSwNP group compared with CRSsNP and HC.
Liu et al. 2018 [85]	To study the role of miR124 in CRSwNP.	NP, ITM	miRNA	China	MiR124 expression was reduced in NP tissues, which negatively correlated with the expression of AHR. This may be critical to the development of inflammatory response in CRSwNP.
Liu et al. 2019 [83]	To characterize the transcriptome profiles of mRNAs and lncRNAs in patients with CRSwNP.	GEO datasets, blood samples	lncRNA	China	A total of 265 differentially expressed lncRNAs were obtained, including 56 upregulated and 209 downregulated genes.
Luo et al. 2017 [86]	To test whether miR-17-92 cluster is associated with suppressing IL-10 in peripheral DC.	Blood samples	miRNA	China	A negative correlation was found between expression of Il-10 and miR-19a in DC from NP patients. miR19-1 was upregulated while miR-17, -18a, -19b, -20a and -92a showed no differences between NP and HC.
Ma et al. 2015 [88]	To investigate miRNAs expression profiles of peripheral blood DCs in CRS patients.	Blood samples	miRNA	China	There were 31 miRNAs changed in all CRS patients with respect to HC, and 49 miRNA that changed exclusively in CRSwNP. miR-210-3p, miR-125b-5p, and miR-150-5p were upregulated in CRS, while miR-708-5p and miR-126-3p were downregulated.
Ma et al. 2018 [87]	To investigate the effects and mechanism of miR-150-5p to promote the development of CRS via the DC-Th axis.	Blood samples	miRNA	China	miR-150-5p was upregulated in DCs from CRS patients compared with HC, and DCs Promote Naïve T Cells Proliferation. MiR-150-5p further regulated EGR2 and inhibited DCs, leading to an abnormal DC-Th axis.
Qing et al. 2019 [89]	To investigate the mechanisms between the miR-142-3p and TNF-a activation in vitro and in vivo	NP, ITM	miRNA	China	miR-142-3p may participate in the regulation of the body's inflammatory response through the LPS-TLR-TNF-a signaling pathway in CRSwNP.
Seiberling et al. 2012 [95]	To determine the presence of 5-bromo-cytosine, 5-chloro-cytosine and methylated cytosine in CRSwNP.	NP, posterior ethmoid tissue (HC)	DNA modification	USA	The levels of 5-Bromocytosine were significantly higher in polyps (p=0.007). Aberrant methylation patterns in polyp eosinophils may help explain the pathogenesis of CRSwNP.
Tian et al. 2012 [96]	To explore the profiling of tandem alternative polyA (APA) sites in NP.	NP, uncinated process mucosa	Genome-wide polyadenylation site sequencing	China	There was a switching of 3'UTR lengths in NP compared with nasal uncinate process mucosa from the same patient. 105 genes were switched to distal polyA sites in the nasal polyps and 90 genes were switched to proximal poly(A) sites. Besides, 213 genes were upregulated in NP while 414 genes were downregulated.
Xuan et al. 2019 [90]	To evaluate miRNAs profiles and relevant biological pathways in CRSwNP and	Nasal mucosa	miRNA array	China	24 miRNAs showed differential expression. 5 miRNAs (miR-210-5p, miR-3178, miR-585-3p, miR-3146, and

Supplementary Table 2. Selected epigenetic studies.

	control subjects.				miR-320e) were significantly upregulated ($p < 0.05$, fold change >2), and 19 miRNAs, including miR-32-3p, miR-1299, miR-3196, miR-3924, miR-548e-3p, miR-3184-5p, miR-375, miR-23a-5p, miR-377-5p, miR-574-5p, miR-3149, miR-500a-5p, miR-125b-2-3p, miR-1914-5p, miR-532-3p, miR-612, miR-1298-5p, miR-1226-3p, and miR-668-3p, were significantly downregulated in CRSwNP tissue ($p < 0.05$, fold change <0.5).
Yan et al. 2020 [91]	To examine human neutrophil elastase-induced MUC5AC overexpression in CRS via miR-146a.	NP, uncinated process mucosa	miRNA	China	EGFR is a target of miR-146a. This miRNA is downregulated in NP reducing the inhibition of EGFR, and therefore MUC5AC expression levels were increased.
Yu et al. 2018 [92]	To evaluate the roles of TGFβ1 and miR-663 in the pathogenesis of NP in children.	Nasal mucosa, peripheral blood eosinophils (PBE)	miRNA	China	The expression of miR-633 was significantly reduced in polyps and PBE from CRS patients, while *TGFB1* mRNA was significantly increased. miR-633 binds to the 3'UTR of *TGFB1* and regulated its expression.
Zhang et al. 2012b [94]	To determine the pattern of expression and biological role of miRNAs in CRS.	NP, ethmoidal mucosa, inferior turbinate tissue	miRNA	China	miR-125b was upregulated in CRSwNP when compared to CRSsNP. This may enhance type I IFN expression through suppressing 4E-BP1 protein expression in airway epithelial cells.
Zhang et al. 2012c [97]	To investigate the expression of miRNA machinery components in CRS.	NP, ethmoid sinus mucosa	mRNA expression	China	PACT mRNA expression was found to be upregulated in CRSwNP as compared with controls. The rest of the miRNA machinery components including Drosha, Dicer, TRBP, FXR1 and E1F2C2, showed no differences between patients and controls.
Zheng et al. 2015 [82]	To identify whether DNA methylation pays a role in the pathogenesis of NP.	NP, ITM	DNA methylation	China	198 genes had a differential methylated signal in their promoter region when comparing NP samples with ITM samples. The four most changed genes were *COL18A1*, *EP300*, *GNAS* and *SMURF1*.
Zhou et al. 2020 [93]	To explore the pathogenesis of CRSwNP from the perspective of genes.	CRSwNP datasets. NP, nasal mucosa (HC)	Functional enrichment analysis, including non-coding RNAs	China	Two clusters of genes, lncRNAs and miRNAs were found to be related to CRSwNP. Main miRNA involves were: miR-130a, miR-27a-3p, miR-193-3p, miR-29a-3p, miR-18b-5p, miR-138-5p, and miR-25-3p.

Supplementary Table 3.

Functional Category	Enrichment FDR	Genes in list	Total genes	Genes
Cytokine-mediated signaling pathway	2.63e-16	29	950	IL1B IL1RN IL22RA1 CCL11 IRAK4 TSLP EBI3 IL1RL1 FCER1G IL1A PPARG TNF NOS2 ALOX5 MMP2 MMP9 IL10 IL33 ALOX15 CIITA HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Defense response	1.10e-15	38	2062	NOS2 IL33 FCER1G PTGDR CD14 CCL11 CIITA LTF IL1B IL10 TNF HLA-A ALOX5 FOXP3 IL1A IL1RL1 PPARG ALOX5AP AOAH IL1RN IL22RA1 MS4A2 ADORA1 CYSLTR1 SERPINA1 IRAK4 AGER TSLP HLA-DRB1 MMP9 ALOX15 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-DRB4
Inflammatory response	1.10e-15	27	856	IL33 PTGDR CD14 CCL11 CIITA NOS2 IL1B IL10 TNF ALOX5 FOXP3 IL1A IL1RL1 PPARG ALOX5AP AOAH IL1RN MS4A2 FCER1G ADORA1 CYSLTR1 SERPINA1 AGER TSLP HLA-DRB1 MMP9 ALOX15
Response to stress	7.689e-15	52	4507	NOS2 MMP2 CAT IL1B HSPA2 IL1RN IL33 TRIP12 FANCC FCER1G PTGDR CD14 CCL11 MSRA CIITA CFTR LTF DCBLD2 TP73 NOS1 MMP9 IL1A IL10 TNF HLA-A IFRD1 ALOX5 FOXP3 IL1RL1 PPARG ALOX5AP AOAH IL22RA1 MS4A2 ALOX15 ADORA1 ADRB2 CYSLTR1 SERPINA1 IRAK4 MT-CO2 AGER MET TSLP HLA-DRB1 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-DRB4

Supplementary Table 3.

Response to cytokine	1.04e-13	30	1372	IL1B IL1RN IL22RA1 CCL11 IRAK4 TSLP CIITA NOS2 EBI3 IL1RL1 FCER1G CD14 IL1A PPARG ALOX15 TNF ALOX5 MMP2 MMP9 IL10 IL33 HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Immune system process	1.124e-13	45	3539	RUNX2 IL1B IL1RN CD8A FCER1G CD14 CCL11 ACE LTF FOXP3 PPARG IL10 IL33 CIITA HLA-DRB1 HLA-DRA AGER TNF HLA-B HLA-A NOS2 MMP9 EBI3 TAPBP IL1A IL1RL1 MS4A2 FANCC ALOX15 ADORA1 CYSLTR1 LTA HLA-DQB1 HLA-DRB3 HLA-DQA1 IRAK4 HLA-DRB5 HLA-C HLA-DRB4 TSLP ALOX5 TP73 CAT FCER1A SERPINA1
Cellular response to cytokine stimulus	1.121e-13	29	1278	IL1B IL1RN IL22RA1 CCL11 IRAK4 TSLP NOS2 EBI3 IL1RL1 FCER1G CIITA IL1A PPARG ALOX15 TNF ALOX5 MMP2 MMP9 IL10 IL33 HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Immune response	1.41e-13	39	2602	CD8A FCER1G CD14 CCL11 IL1B LTF FOXP3 IL10 CIITA AGER TNF HLA-B HLA-A NOS2 IL1A IL1RL1 IL1RN IL33 MS4A2 ALOX15 CYSLTR1 LTA HLA-DQB1 HLA-DRB3 HLA-DRB1 HLA-DQA1 IRAK4 HLA-DRB5 HLA-DRA HLA-C HLA-DRB4 PPARG ALOX5 MMP9 EBI3 TAPBP CAT FCER1A SERPINA1
Cell surface receptor signaling pathway	2.29e-13	43	3287	MUSK MET IL1B IL1RN IL22RA1 CD8A FCER1G CD14 CCL11 ANXA4 IRAK4 LTF

Supplementary Table 3.

				TSLP TNF FOXP3 EBI3 IL1A IL1RL1 RUNX2 IL33 MS4A2 ADORA1 ADRB2 CYSLTR1 MMP9 PPARG NOS2 ALOX5 MMP2 IL10 ALOX15 CIITA FCER1A HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA AGER HLA-C HLA-B HLA-A HLA-DRB4
Cellular response to chemical stimulus	4.85e-13	44	3536	IL1B HSPA2 PPARG IL1RN IL22RA1 FANCC FCER1G CD14 CCL11 MSRA IRAK4 CFTR LTF MMP9 ALOX5AP TSLP ALOX15 AGER TNF NOS2 MMP2 NOS1 EBI3 IL1RL1 CAT RUNX2 IL10 PTGDR ADRB2 CIITA LTC4S MET IL1A HLA-DRB1 ALOX5 IL33 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Cellular response to organic substance	5.90e-12	39	2938	IL1B HSPA2 PPARG IL1RN IL22RA1 CD14 CCL11 IRAK4 CFTR LTF TSLP AGER TNF NOS2 MMP2 NOS1 EBI3 IL1RL1 CAT RUNX2 IL10 FCER1G PTGDR ADRB2 CIITA IL1A ALOX15 HLA-DRB1 ALOX5 MMP9 IL33 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Response to organic substance	1.593e-11	42	3547	NOS2 NOS1 IL1B HSPA2 PPARG IL1RN IL22RA1 CD14 CCL11 IRAK4 CFTR LTF IL10 TSLP HLCS CIITA AGER TNF TBXAS1 TP73 MMP2 MMP9 EBI3 IL1RL1 CAT RUNX2 FCER1G PTGDR ADRB2 IL1A ALOX15 HLA-DRB1 ALOX5 IL33 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Regulation of immune system process	2.414e-10	30	1909	FCER1G CD14 IL1B ACE FOXP3

Supplementary Table 3.

				IL10 IL33 AGER TNF HLA-B HLA-A IL1RL1 MS4A2 ALOX15 ADORA1 LTF PPARG TSLP HLA-DRB1 TP73 EBI3 CD8A FCER1A HLA-DRB3 HLA-DQA1 IRAK4 HLA-DRB5 HLA-DRA HLA-C HLA-DRB4
Regulation of immune response	5.63e-10	25	1325	FCER1G CD14 IL1B FOXP3 IL10 AGER TNF HLA-B HLA-A IL1RL1 IL33 MS4A2 ALOX15 LTF PPARG CD8A FCER1A HLA-DRB3 HLA-DRB1 HLA-DQA1 IRAK4 HLA-DRB5 HLA-DRA HLA-C HLA-DRB4
Regulation of response to stimulus	1.05e-09	46	4820	IL1B IL1RN IL33 FCER1G CD14 CCL11 IRAK4 NOS2 LTF FOXP3 MET IL10 TSLP ADRB2 AGER TNF HLA-B HLA-A CFTR TP73 NOS1 EBI3 IL1A IL1RL1 CAT RUNX2 PPARG ALOX5AP AOAH MS4A2 ALOX15 ADORA1 LTA RGS7BP MMP9 TRIP12 HLA-DRB1 NOS1AP CD8A FCER1A HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-DRB4
Cytokine secretion	3.78e-09	13	285	CD14 NOS2 FOXP3 IL1A IL10 IL33 TNF IL1RL1 IL1B AGER TSLP ANXA4 HLA-DRB1
Cellular response to interferon-gamma	4.23e-09	13	289	CCL11 NOS2 CIITA PPARG HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Interferon-gamma-mediated signaling pathway	4.76e-09	11	178	PPARG CIITA HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Regulation of inflammatory response	6.81e-09	15	448	IL33 NOS2 FOXP3 IL1RL1 IL1B PPARG ALOX5AP AOAH IL10 FCER1G ADORA1 AGER TSLP TNF MMP9
Antigen processing and presentation	9.27e-09	14	384	FCER1G HLA-DRB1 HLA-DRA HLA-B TAPBP

Supplementary Table 3.

				HLA-DQB1 HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-C HLA-A HLA-DRB4 CD8A ACE
Response to interferon-gamma	9.27e-09	13	312	CCL11 CIITA NOS2 PPARG HLA-DRB3 HLA-DRB1 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-C HLA-B HLA-A HLA-DRB4
Regulation of cytokine secretion	1.269e-08	12	257	CD14 FOXP3 IL1A IL10 IL33 TNF IL1RL1 IL1B AGER TSLP ANXA4 HLA-DRB1
Positive regulation of response to stimulus	1.51e-08	32	2621	IL1B IL1RN IL33 FCER1G CD14 CCL11 IRAK4 LTF IL10 TSLP ADRB2 TNF HLA-B CFTR FOXP3 TP73 NOS1 IL1RL1 CAT ALOX5AP ADORA1 AGER MMP9 MET ALOX15 HLA-DRB1 NOS1AP HLA-DRB3 HLA-DQA1 HLA-DRB5 HLA-DRA HLA-DRB4
Cytokine production	4.97e-08	19	925	IL1B IL1RN CD14 NOS2 LTF FOXP3 IL1A IL10 IL33 TSLP AGER TNF IL1RL1 FCER1G IRAK4 NAV3 ANXA4 HLA-DRB1 EBI3
Interleukin-6 production	4.97e-08	10	172	IL1B IL1RN NOS2 IL10 TNF FOXP3 IL33 FCER1G AGER TSLP
Secretion	7.35e-08	26	1861	CACNA1I CD14 NOS2 FOXP3 IL1A IL1B IL10 IL33 ACE TNF CFTR IL1RL1 IL1RN FCER1G ADORA1 MT-CO2 AGER TSLP ANXA4 HLA-DRB1 LTF ALOX5 MMP9 CAT SERPINA1 HLA-C
Positive regulation of transport	7.35e-08	20	1069	CACNA1I FCER1G CD14 CFTR IL1A IL10 IL33 TNF IL1RL1 IL1B HSPA2 PPARG ADORA1 AGER ADRB2 TSLP NOS1 HLA-DRB1 NOS1AP TP73
Regulation of cytokine production	8.36e-08	18	852	IL1B IL1RN CD14 NOS2 LTF FOXP3 IL1A IL10 IL33 TSLP AGER TNF IL1RL1 FCER1G NAV3 ANXA4 HLA-DRB1 EBI3
Regulation of defense response	8.789e-08	19	968	IL33 CD14 NOS2 HLA-A FOXP3

Supplementary Table 3.

				IL1RL1 IL1B PPARG ALOX5AP AOAH IL10 FCER1G ADORA1 AGER LTF TSLP TNF MMP9 IRAK4
Regulation of peptide secretion	9.132e-08	15	559	CD14 FOXP3 IL1A IL1B IL10 IL33 TNF CFTR IL1RL1 ADORA1 AGER NOS2 TSLP ANXA4 HLA-DRB1