REVIEWS

Genetics and Epigenetics of Nasal Polyposis: A Systematic Review

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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. Rinosinusitis 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, non-eosinophilic 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 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 9.05e-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 stimulus.

In the case of genes linked to the risk of developing disease, we decided to expand the network with the 5 most closely
| Increase Risk | SNP/Variant | Decrease Risk | SNP/Variant | Associated | SNP/Variant |
|---------------|-------------|-------------|-------------|------------|------------|
| ACE [54]      | rs4309      | ALOX15 [55] | rs34210653  | ADORA1 [64]| rs16851030 |
|               | rs4293      |             |             |            | 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]| rs17612127 |
|               |             |             |             | ALOX15 [128]| rs34210653 |
| CCL11 [68,70]| rs1490392522(G)| EBI3 [136]| rs428253    | AOAH [73]  | rs4504543  |
|               | rs762429865(5G)|             |             |            |            |
| CFTR [66]     | ΔF508       | FANCC [22,54]| rs1326188   | BICD2 [21] | rs3788568  |
| CIITA [110]   | rs12932187  | HLA-B [22]   | *57         | CACNA1I [73]| rs3788568  |
| COX2 [52]     | rs20417(A)  | HLA-Cw [22]  | *04         | CAT [53]   | -21(TT)    |
|               | rs20417(C)  |             |             |            |            |
| FCER1A [65]   | rs2427827(T)| HLA-DQA1 [24]| *05012     | CD14 [133] | rs94656423 |
|               |             |             |             | (C)        |            |
| FCER1G [54]   | rs4489574   | HLA-DQB1 [19,24]| *0301     | CYSLTR1 [56]| rs321090  |
| FOXP3 [136]   | rs2294018   | HLA-DQ [26]  | *07         | CYP2S1 [55] | rs338598  |
|               | rs2232365   |             |             |            |            |
| FSIP [54]     | rs502581    | HLA-DR7 [24] |              | DCBLD2 [124]| rs828621  |
|               | rs6531700   |             |             |            | rs1371687 |
|               | rs6231702   |             |             |            | rs7615856 |
|               |             |             |             |            | rs828618  |
|               |             |             |             |            | rs8833    |
| HLA-A [22]    | *24         | HLA-DRB1 [22,25]| *08     | EMID [125] | rs6945102 |
|               | *33         |             | *11         |            | rs4729697 |
|               |             |             |             |            | rs221     |
|               |             |             |             |            | rs10435333|
|               |             |             |             |            | rs6947185 |
|               |             |             |             |            | rs4727494 |
|               |             |             |             |            | rs13233066|
|               |             |             |             |            | rs1008064 |
|               |             |             |             |            | rs1543883 |
|               |             |             |             |            | rs13245946|
| HLA-B [22]    | *07         | HLA-DRB3 [19]|            |            |            |
| HLA-Cw [22]   | *01         | IL10 [34]   | rs1800872   |            |            |
|               | *12         |             | rs1554286   |            |            |
| HLA-DQB1 [19,24]| *0202      | IL1A [139]  | rs2856838   | FOXP1 [55] | rs17718444|
|               | *0302       |             |             |            |            |
| HLA-D [26]    | *08         | IL1B [37]   | rs16944     | HLA-A74 [119]|            |
|               | *09         |             |             |            |            |
| HLA-DR [24,26]| *09         | IL4 [45]    | -590C/T     | HLA-DRA [21,23]| rs9268644 |
|               | *07         |             |             |            | rs3129878 |
|               | *16         |             |             |            | rs2239805 |
| HLA-DRB1 [25] | *03         | IRAK4 [37,40]| rs4251431   | HLA-DQA1 [55]| rs1391371 |
|               | *04         |             | rs4251559   |            |            |
|               |             |             | rs4251513   |            |            |
|               |             |             | rs146567    |            |            |
| 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   |
| IFNRD1 [111]  | rs7817 (T)  | PPARG [140]  | rs2960421   | IL2 [39]   | rs6432292   |
|               |             |               | rs4135275   |            | rs180976    |
| IL10 [37,54]  | rs1800870   | P73 [129]    | rs3765731 (A)| IL22RA1 [29]| rs4292900   |
|               | rs1800896   |               | rs10487667  |            | rs4648936   |
|               | rs3024498   |               | rs6962291   |            | rs16829225  |
| IL1A [28,35,37,38]| 4845 (G/T) | RG7SBP [54] | rs6870654   | IL33 [55]  | rs1888909   |
|                | rs17561     |               |            |            |             |
|                | rs1800587   |               |            |            |             |
| IL1B [32,35,50]| -511(C/T)   | TBXAS1 [54]  | rs13239058  | IL4 [39]   | rs8179190   |
|                | rs10487667  |               | rs6962291   |            |             |
| IL1RL1 [36,41]| rs1420101   | TSLP [137]   | rs252706    | IRAK4 [31] | rs1461567   |
|                | 86-bp       |               | rs764917    |            | rs4251559   |
|                | intron2     |               |            |            |             |
|                | rs13431828  |               |            |            |             |
| IL1RN [34]    | KIAA1456 [73]|           | rs11779957  |            |             |
| IL22 [29]     | rs4292900   | LAMA2 [73]   | rs2571584   |            |             |
|                | rs4648936   |               |            |            |             |
|                | rs16829225  |               |            |            |             |
| 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)|         | MUSK [73]   | rs10817091|             |
| MMP2 [132]    | rs857403    | MYRF [55]    | rs174535    |            |             |
| MMP9 [37,131]| rs3918242   | NAV3 [73]    | rs1726427   |            |             |
|                | rs2274756   |               |            |            |             |
| MS4A2 [54]    | rs573790    | NOS1AP [135]| rs12047527  |            |             |
| OSF2 [138]    | -33C/G     | NOS2 [53,57,126]| -277(GG) | CTTT      |            |
|                | rs3829365   |               |            |            |             |
| PARS2 [115]   | rs2873551   | PARS2 [73]   | rs2873551   |            |             |
|                | rs2270004   |               |            |            |             |
|                | rs11577368  |               |            |            |             |
|                | rs1180946   |               |            |            |             |
|                | rs1180945   |               |            |            |             |
| RYBP [37,40]  | rs4532099   | PTGDR [57]   | -613 (C)    |            |
|                |             |               | -549(C)     |            |
|                |             |               | -441(C)     |            |
|                |             |               | -197(C/T)   |            |

(continued)
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 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 showed to have 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-27a-3p [84,94]             | hsa-miR-29a-3p [84,94]               |
| hsa-miR-141-3p [84]                | hsa-miR-124 [85]                     | hsa-miR-30c-3p [89]                | hsa-miR-30e-3p [89]                  |
| hsa-miR-142-3p [90]                | hsa-miR-125b-2-3p [84]               | hsa-miR-30e-5p [89]                | hsa-miR-3149 [91]                    |
| hsa-miR-150-5p [88,89]             | hsa-miR-125b-5p [84]                 | hsa-miR-3184-5p [91]               | hsa-miR-3196 [91]                    |
| hsa-miR-193a-5p [84]               | hsa-miR-126-3p [84,89]               | hsa-miR-3196 [91]                   | hsa-miR-32-3p [91]                   |
| hsa-miR-19a [87]                   | hsa-miR-1273h-3p [89]                | hsa-miR-3196 [91]                   | hsa-miR-364-5p [89]                  |
| hsa-miR-200a-3p [84]               | hsa-miR-1298-5p [91]                 | hsa-miR-364-5p [89]                | hsa-miR-362-3p [89]                  |
| hsa-miR-200b-3p [84]               | hsa-miR-1299 [91]                    | hsa-miR-364-5p [89]                | hsa-miR-363-3p [89]                  |
| hsa-miR-210-3p [89]                | hsa-miR-130a [84,94]                 | hsa-miR-375 [91]                    | hsa-miR-377-5p [91]                  |
| hsa-miR-210-5p [91]                | hsa-miR-130a-3p [89]                 | hsa-miR-3924 [91]                   | hsa-miR-486-5p [89]                  |
| hsa-miR-30d-5p [84]                | hsa-miR-130b-3p [84]                 | hsa-miR-500a-5p [91]               | hsa-miR-532-3p [91]                  |
| hsa-miR-30e-5p [84]                | hsa-miR-138-5p [94]                  | hsa-miR-532-3p [91]                | hsa-miR-548e-3p [91]                 |
| hsa-miR-3146 [91]                  | hsa-miR-139-5p [89]                  | hsa-miR-548e-3p [91]               | hsa-miR-550a-3p [89]                 |
| hsa-miR-3178 [91]                  | hsa-miR-143-3p [89]                  | hsa-miR-548e-3p [91]               | hsa-miR-574-5p [91]                  |
| hsa-miR-320e [91]                  | hsa-miR-146a [92]                    | hsa-miR-548e-3p [91]               | hsa-miR-584-5p [89]                  |
| hsa-miR-342-3p [89]                | hsa-miR-152-3p [89]                  | hsa-miR-548e-3p [91]               | hsa-miR-612 [91]                     |
| hsa-miR-34b-3p [84]                | hsa-miR-16-5p [89]                   | hsa-miR-612 [91]                    | hsa-miR-628-3p [89]                  |
| hsa-miR-34b-5p [84]                | hsa-miR-17-5p [84]                   | hsa-miR-628-3p [89]                | hsa-miR-650-3p [89]                  |
| hsa-miR-4485 [89]                  | hsa-miR-18a-5p [84]                  | hsa-miR-663 [93]                    | hsa-miR-668-3p [91]                  |
| hsa-miR-449b-5p [84]               | hsa-miR-18b-5p [84,94]               | hsa-miR-668-3p [91]                | hsa-miR-6867-5p [89]                 |
| hsa-miR-449c-5p [84]               | hsa-miR-19a-3p [89]                  | hsa-miR-6867-5p [89]               | hsa-miR-708-5p [89]                  |
| hsa-miR-585-3p [91]                | hsa-miR-1914-5p [91]                 | hsa-miR-708-5p [89]                | XLOC_005882 [83]                    |
| hsa-miR-92b-3p [84]                | hsa-miR-193-3p [84,94]               | XLOC_010305 [83]                   | XLOC_010540 [83]                    |
| XLOC_000122 [83]                  | hsa-miR-193b-3p [84]                 | XLOC_015712 [83]                   | XLOC_018024 [83]                    |
| XLOC_003006 [83]                  | hsa-miR-199a-3p [89]                 | XLOC_018529 [83]                   | XLOC_018529 [83]                    |
| XLOC_011814 [83]                  | hsa-miR-199a-5p [89]                 | XLOC_019396 [83]                   | XLOC_025155 [83]                    |
| XLOC_015500 [83]                  | hsa-miR-199b-3p [89]                 |                                   |                                      |

Abbreviation: CRSwNP, chronic rhinosinusitis with nasal polyposis.

3) Olive cluster: \( \text{TNF} \) 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 \( \text{IL10} \) as the connecting node. IL10 rs1800870 [54] and rs1800896 [37] have been reported to be associated with increased risk of NP.
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 2. Risk of bias (A) and quality assessment (B) of the selected articles.

Figure 3. Main biological functions involving the genes reported as being associated with chronic rhinosinusitis with nasal polyposis.
Several authors have focused on 3 SNPs of \textit{TAS2R38}, ie, rs713598 (C145G; Pro>Ala), rs1726866 (C785T; Ala>Val), and rs10246939 (G886A; Val>Ile). The PA V 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 \textit{ADORA1}, differences in allele frequencies were reported only for NP patients with AERD [64].

6) Other clusters

The blue cluster genes \textit{FCER1A}, \textit{FCER1G}, and \textit{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, \textit{CFTR}, and the variant AF508, 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 \textit{ADRB2} rs10452713 appeared to be more frequent in NP patients [69], while the association between \textit{CCL11} and NP was described as statistically weak [70]. Regarding the green cluster, \textit{MET} has been associated with an increased risk of NP [52,71], while the \textit{SERPIN A1} [72] and

![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.](image)

![Figure 5. Gene enrichment comparison between genes that increase the risk and those that decrease the risk of chronic rhinosinusitis with nasal polyposis.](image)
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], EGRF [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, p33RPF, 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.
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), and CFTR. 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 chemooattraction 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 (FEV1) 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 other epigenetic traits have been identified as differentially increased and reduced. Furthermore, several miRNAs and clusters of genes and the network with increased coverage, supporting functional enrichment and interaction network analysis tool. String v11: a protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019;47:D607-13.

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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