

Review

Significance of Susceptible Gene Expression Profiles in Nasal Polyposis

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Nasal polyposis (NP) is a common chronic inflammatory disease of the rhinosinus mucosa and a complex disease with strong genetic and environmental components. During the past 10 to 20 yr, many studies have been performed to determine differential gene expression profiles between NP and normal nasal tissues, in order to identify susceptible genes that are associated with NP-related traits. Despite achievement in the identification of candidate genes and their associated pathogenic pathways, the large challenges remain as the genetic and molecular alterations required for its development and progression are still unclear. Therefore, the development of novel, powerful tools for gene discovery, and a closer integration of genetics and medical biology would provide valuable insight into the pathogenesis of NP.

Key Words. *Nasal polyposis, Genetics, Gene expression profile, Pathogenesis and pathophysiology, Susceptible genes and pathways*

INTRODUCTION

Nasal polyposis (NP) is one of the most common mass lesions of the nose and was first described 4,000 yr ago in ancient Egypt. The prevalence of NP is reported from 0.2% to 4.3% worldwide, with a ratio of 2-3:1 between males and females (1). In children, NP is relatively rare and has a close relationship with asthma and cystic fibrosis (2). NP is a multifactorial condition which is often associated with many diseases and pathogenic disorders, such as allergy, infection, cystic fibrosis, asthma, and aspirin intolerance (1). However, the underlying mechanisms interlinking these pathologic conditions to NP formation remain unclear.

NPs are outgrowths of nasal mucosa which are smooth, semi-translucent, gelatinous and pale. Histo-morphological characterization of polyp tissue reveals frequent epithelial damage, a thickened basement membrane, and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neural structure (3). Hellquist (4) divided NPs into four histological patterns. The most common type was the edematous NP with predominant eosinophilia, which constituted

85-90% of NPs. Other types include fibroinflammatory, hyperplasia of seromucinous glands and atypical stroma. It is not clear whether this classification has an impact on the differentiation of pathogenic mechanisms and clinical management of NPs.

Although the mechanisms involved in the pathogenesis of NP remain largely unclear, there are reports suggesting an underlying genetic predisposition. This concept is supported by some clinical data and genetic studies. This paper reviews recent understanding of the pathogenic mechanisms of NPs, which are influenced by a complex immune procedure including interaction of multiple genes. This review paper does not include NP in cystic fibrosis (CF), which is known to be a hereditary disease with multi-systemic involvement with genetic variations, presenting with defect in chloride transport across membranes and dehydrated secretions.

FAMILY AND TWIN STUDIES OF NPS

An interesting observation is that NP is frequently found to run in families, suggesting a hereditary or shared environmental factor. In the study by Rugina et al. (5), more than half of 224 NP patients (52%) had a positive family history of NP. The presence of NP was considered when NP had been diagnosed by an ENT practitioner or the patients had undergone sinus surgery for NP. A lower percentage (14%) of familial occurrence of NP was reported earlier by Greisner and Settupane (6) in a smaller group (n=50) of adult patients with NP. Thus, these results strongly suggest the existence of a hereditary factor in the pathogenesis of NP.

However, studies of monozygotic twins have not shown that

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both siblings always develop polyps, indicating that environmental factors are likely to influence the occurrence of NP (7, 8). NPs have been described in identical twins, but given the prevalence of nasal polyps, it might be expected that there would be more than a rare report of this finding (9).

LINKAGE ANALYSIS AND ASSOCIATION STUDIES ASSOCIATED WITH NPS

In the literature, some studies were able to show linkage of certain phenotypes of NP to candidate gene polymorphisms. Karjalainen et al. (10) reported that subjects with a single G-to-T polymorphism in exon 5 at +4,845 of the gene encoding IL-1 α (IL-1A) were found to have lower risk of developing NP as compared to subjects with common G/G genotype. In another study, polymorphism of IL-4 (IL-4/-590 C-T), a potential determinant of IgE mediated allergic disease, was also found to be associated with a protective mechanism against NPs in the Korean populations (11). Recently, another asthma-related Arg16gly polymorphism of the beta2-adrenoceptor gene (ADRBeta2) was found to be associated with an increased risk of NP (12).

A number of genetic association studies found a significant correlation between certain human leukocyte antigen (HLA) alleles and NP. HLA is the general name of a group of genes in the human major histocompatibility complex (MHC) region on the human chromosome 6 that encodes the cell-surface antigen-presenting proteins. Luxenberger et al. (13) reported an association between HLA-A74 and NPs, whereas Molnar-Gabor et al. (14) reported that subjects carrying HLA-DR7-DQA1*0201 and HLA-DR7-DQB1*0202 haplotype had a 2 to 3 times odds ratio of developing NP. The risk of developing NP can be as high as 5.53 times in subjects with HLA-DQA1*0201-DQB1*0201 haplotype (15). Although several HLA alleles were found to be associated with NP, such susceptibility can be influenced by ethnicity. In the Mexican Mestizo population, increased frequency of the HLA-DRB1*03 allele and of the HLA-DRB1*04 allele were found in patients with NP as compared to healthy controls (16).

MULTIPLE GENE EXPRESSIONS IN NASAL POLYPS

The development and persistence of mucosal inflammation in NPs have been reported to be associated with numerous genes and potential single nucleotide polymorphisms (SNPs). The products of these genes determine various disease processes, such as immune modulation or immuno-pathogenesis, inflammatory cells (e.g., lymphocytes, eosinophils and neutrophils) development, activation, migration and life span, adhesion molecule expression, cytokine synthesis, cell-surface receptor display, and processes governing fibrosis and epithelial remodelling.

Gene profiling technologies have demonstrated considerable power in generation of cell and tissue molecular signatures and identification of disease-associated gene expression changes, and represent a rapid and efficient mean to elucidate alterations in cell signalling or metabolic pathways. DNA microarray technology consists of a matrix with attached sequences that allow simultaneous analysis of expression of panels of human genes. Comparison of profiles of genes expressed in disease versus healthy tissues often highlights the involvement of both expected and unsuspected pathologic pathways.

In the literature, gene expression profiles in NPs have been performed by many studies, including the major repertoire of disease-related susceptibility genes or genotypic markers. With the advance of microassay technique, expression profiles of over 10,000 of known and novel genes can be detected. A recent study showed that in NP tissues, 192 genes were upregulated by at least 2-fold, and 156 genes were downregulated by at least 50% in NP tissues as compared to sphenoid sinuses mucosa (17). In another study (18), microarray analysis was used to investigate the expression profile of 491 immune-associated genes in NPs. The results showed that 87 genes were differentially expressed in the immune-associated gene profile of nasal polyps, and 15 genes showed differential expression in both NPs and healthy controls (turbinates). In other studies, alterations in expression profiles of susceptible genes may contribute to many putative underlying pathophysiological or pathogenic mechanisms of NPs.

Genes associated with inflammation and immunopathogenesis in NPs

NP is a chronic inflammatory disease of the mucous membranes in the nose and paranasal sinuses. The role of the immune system in the pathogenesis of this disease is still unknown. To date, many studies have reported significant changes in presence of numerous inflammatory cells, mediators, cytokines, chemokines, and other inflammatory and immune modulating components in NPs, indicating that chronic inflammation is an important factor in development of NPs irrespective of the etiology.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by a T(H)2-skewed eosinophilic inflammation, whereas chronic rhinosinusitis without nasal polyps (CRSsNP) represents a predominant T(H)1 milieu (18). In this report, the authors were able to show a significantly lower forkhead box P3 (FOXP3) mRNA and transforming growth factor beta-1 (TGF-beta1) protein expression, but a significantly higher T-bet, GATA-3, IL-5, and IL-13 mRNA expression compared with the healthy controls (Table 1). This T(H)2-skewed eosinophilic inflammation was shown by a decreased expression of multiple antimicrobial innate immune markers, including toll-like receptor 9, human beta-defensin 2 and surfactant protein A, in human sinonasal epithelial cells from CRSwNP. The authors suggested that the impaired mucosal innate immunity may contribute to microbial colonization (e.g., bacteria, fungi and etc.) and abnormal immune responses associat-

Table 1. Expression profile of genes associated with inflammation and immunopathogenesis in nasal polyposis

Pathogenic pathway	Name of genes	Potential biological/immunologic functions
High/overexpressed	• IL-17 and IL-17 receptor (18)	• Proinflammatory cytokine
	• Lysophosphatidic acid receptor (24)	• Inflammatory cascade
	• LL-37 (25)	• Antimicrobial peptide
	• Superoxide dismutases gene SOD3 and SOD1 (26)	• Increased oxidative stress
	• Human beta-defensin-2 (27)	• A key element in the innate host defence mechanism
	• Cyclooxygenase-1 (28)	• Mucosal inflammation
	• CD40 (29)	• Regulation of inflammation
	• IL-1 beta, IL-6, IL-8, and transforming growth factor beta (30)	• Pathogenesis of NP (non-allergic pattern of inflammation)
	• Granulocyte macrophage colony-stimulating factor and IL-8 (31)	• Local tissue inflammation
	• Tumor necrosis factor alpha (32)	• Pro-inflammatory activity (in particular with eosinophils)
	• T-box transcription factor (T-bet) (19)	• Transcription factors for T-cell subpopulations
	• GATA-3 (19)	• Transcription factors for T-cell subpopulations
	• Complement component C1q (21)	• Innate immunity
Low/underexpressed	• Cyclooxygenase-2 (28, 33)	• Mucosal inflammation
	• Syk (34, 35)	• Intracellular signal transduction in hemopoietic cells
	• Forkhead box P3 (FOXP3) (19)	• Transcription factors for T-cell subpopulations
	• Toll-like receptor 9 (20)	• Mucosal innate immunity
	• Human beta-defensin 2 (20)	• Mucosal innate immunity
	• Surfactant protein A (20)	• Mucosal innate immunity
	• B-Raf and Raf kinase inhibitor protein (36)	• Endogenous inhibitors of the MAPK pathway
	• Toll-like receptor 9 (22)	• Impaired innate immunity

Table 2. Expression profile of genes associated with the biological functions of inflammatory cells in nasal polyposis

Pathogenic pathway	Name of genes	Potential biological/immunologic functions
High/overexpressed	• Ragulated upon activation, normal T expressed and secreted (41, 42, 43)	• Eosinophil recruitment
	• IL-5 (44, 45, 46)	• Biological functions of eosinophils
	• Aquaporin-1 (47)	• Survival of eosinophils
	• Protein kinase C (48)	• Apoptosis inhibition (eosinophils)
	• Eotaxin (42, 49, 50)	• Enhance self-amplification process (eosinophils)
	• Growth-related oncogene-alpha (51)	• Recruitment and activation of neutrophils
	• Stem cell factor (52)	• Master cell growth and survival factor
	• C-C Chemokine ligand 2 (53)	• Recruitment of macrophages
	• Regulator of G-protein signaling 1 (54)	• Cell signal transduction
	• IL-8 (54)	• Releasing inflammatory factors
	• Survivin (55)	• Cell apoptosis

ed with CRSwNP (20). In another study, an increased expression level of complement component C1q in NPs is suggested to be indicative of an ongoing inflammatory response in the nasal mucosa of these patients (21).

Innate immune recognition of pathogens by sinonasal epithelial cells may play an important role in the pathogenesis of chronic mucosal inflammation in rhinosinusitis (CRS) (22, 23). In Table 1, alterations in expression levels of several genes associated with immunopathogenesis in nasal mucosal or NP tissues are indicative of an ongoing inflammation and impaired mucosal innate immunity in patients with CRS with or without NPs.

Biological functions of inflammatory cells in NPs

The general histopathological classification of NPs is eosinophil-dominated inflammation (80-90%), which appears to be a hallmark of Caucasian NPs (3). This statement is well supported by an increased expression of cytokines, chemokines and molecular markers, which are involved in the proliferation, migration, activation and survival of eosinophils (Table 2). In the literature, IL-5 and eotaxin are most frequently reported molecular markers in NPs, as they are essential for eosinophil development, activation and survival (3). The soluble IL-5R α expression level was also found to be dramatically higher (up to 1,200 times) than IL-5 concentrations in NP (37).

Table 3. Expression profile of genes associated with structure modification of epithelium in nasal polyposis

Pathogenic pathway	Name of genes	Potential biological/immunologic functions
High/overexpressed	• Hepatocyte growth factor and c-Met proteins (58)	• Enhancing proliferation of epithelial cells and submucosal glandular cells
	• Proliferation cell nuclear antigen, apoptosis associate gene protein (Bcl-2 and Bax) (59)	• Proliferation activity in the epithelium
	• Basic fibroblast growth factor (60)	• Endothelial and epithelial proliferation
	• Keratinocyte growth factor (61)	• Nasal epithelial proliferation
	• P53 (62)	• Epithelial proliferation activity
	• Mucin 1, MUC4, MUC5AC, MUC5B (63-68)	• Polyp formation and progression
	• Epidermal growth factor receptor (57, 69)	• Regulation of goblet cell mucins
	• Fas-L protein (70)	• Cystic degeneration of submucosal glands
	• Vascular permeability factor and vascular endothelial growth factor (71)	• Development of oedema in chronic inflammation
	• Platelet-derived growth factor-B chain (72)	• Chronic inflammation and tissue remodelling
	• Vascular endothelial growth factor A (73)	• Angiogenesis
	• Transforming growth factor beta1 (73)	• Epithelial differentiation and tissue remodelling
	• Insulin-like growth factor 1 (73)	• Angiogenesis
	• Fibroblast growth factor 2 (73)	• Angiogenesis?
	• Matrix metalloproteinase-9 (44)	• Zn ²⁺ dependent endopeptidases. Degradation extracellular matrix and tissue edema
Low/underexpressed	• Lumican and biglycan (74)	• Remodelling of the extracellular matrix
	• Carbonic anhydrase isoenzymes (56)	• Impaired electrolyte and water transport across the epithelial cells
	• S100A7, S100A8, S100A7 (75)	• Epithelial barrier maintenance and repair
	• Serine protease inhibitor kazal type 5 (75)	• Epithelial barrier maintenance and repair
	• Transforming growth factor beta1 (19, 76, 77)	• Chemoattractant and proliferation factor for fibroblasts

In addition, infiltration of other types of inflammatory cells, especially lymphocytes and neutrophils, may also play an important role in the inflammatory process underlying the pathogenesis of NPs (38-40). In Table 2, increased expression levels of growth-related oncogene-alpha (GRO-alpha), stem cell factors (SCF) and C-C chemokine ligand 2 are associated with biological functions of neutrophils, mast cells and macrophages. Therefore, in NP studies, one may not rely solely on limited type of cells and number of molecular markers (e., g., IL-5 and eotaxin) as NP is a heterogeneous disease with complex pathogenic mechanisms involved.

Genes associated with structure modification of epithelium in NPs

Histomorphological characterisation of NP tissue reveals frequent epithelial damage, a thickened membrane, and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neutral structure (3). Many genetic studies have resulted in an emphasis on the structure modification of the epithelium in NPs. Table 3 shows the changes in expression level of many important genes, which are associated with proliferations of nasal epithelial and endothelial cells, submucosal glandular cells, regulation of goblet cell mucins, tissue remodelling, angiogenesis, impaired electrolyte and water transport across the epithelial cells, epithelial barrier maintenance and

repair, and etc. However, pathogenic mechanisms underlying the changes of these structural gene functions are not clear.

There are a number of genes which are involved in epithelial barrier maintenance and repair in the inflammatory state of chronic rhinosinusitis (CRS) with NPs. For example, carbonic anhydrase (CA) is a zinc metalloenzyme that participate in the biological processes of various fluid transporting epithelia, including ion and water transport. In this study, a decreased expression level of CA was found to be associated with impaired electrolyte and water transport across the epithelial cell, which will result in oedema of NP tissue (56). In another study, the level of epidermal growth factor receptor (EGFR) mRNA in human sinus mucosa was found to be statistically significantly increased compared with that in the healthy controls (57). It is therefore suggested by the authors that up-regulation of the EGFR cascade may have an important role regarding mucus production in the sinus mucosa of patients with CRS and CRS with NP associated with hyperplasia and metaplasia of epithelial goblet cells.

Epithelial differential and tissue remodelling is also reported to be involved in the development and pathogenic characterization of NPs. It was reported that an increased expression level of PDGF-B, TGF-beta1, and lower expressions of lumican and biglycan were found in NPs as compared to the healthy controls (Table 3). However, controversial results of TGF-beta1 expression level were also reported by other studies, where the expression levels

Table 4. Significant genes with other or unclear biological functions in nasal polyposis

Pathogenic pathway	Name of genes	Potential biological/immunologic functions
High/overexpressed	• Statherin; prolactin-induced protein; lactoferrin, and deleted in malignant brain tumor 1 (17)	• To be identify
	• Mammaglobin (80)	• Polyp growth (to be confirmed)
	• Met proto-oncogene (MET) (79)	• Aspirin sensitivity
	• Protein phosphatase 1 regulatory subunit 9B (79)	• Aspirin sensitivity
	• K- and H-ras (78)	• Tumourigenesis
Low/underexpressed	• Clara cell 10-kd protein (17)	• To be identify
	• Human glucocorticoid receptors-alpha (45, 81)	• Inflammation and response to glucocorticosteroid treatment
	• Prolactin-induced protein (79)	• Aspirin sensitivity
	• Zinc alpha2-glycoprotein (AZGP1) (79)	• Aspirin sensitivity
	• H-ras (78)	• Tumourigenesis

of TGF-beta1 in NPs appeared to be low in NPs (Table 3).

Significant genes with other or unclear biological functions in NPs

Using a genome-wide expression microarray, some studies have reported a few genes with significant changes in expression profiles in NP tissue as compared to healthy controls (Table 4). However, the biological functions of some of these genes (e.g., plasma membrane intrinsic protein [PIP], deleted in malignant brain tumors 1 [DMBT1], Mammaglobin and CC10) underlying the pathogenic mechanisms of NP development are unclear and need to be investigated in future.

Mutation and differential expression of the ras family genes contributing to tumourigenesis either through the accumulation of mutations or by aberrant expression in a wide range of human cancers has been well demonstrated. However, a recent study found that K- and H-ras expression levels were elevated, whereas N-ras mRNA levels were lower in NPs and adjacent turbinates as compared to the healthy control tissues. K-ras mRNA levels were up-regulated in advanced-stage polyps, while N-ras levels were found elevated in small polyps (78). These findings suggest a potential key role for activated members of ras family genes in terms of their contribution to the development of NPs as well as to the hypertrophy of adjacent turbinates.

The presence of aspirin-intolerance in a patient with CRS with or without NPs is associated with a particularly persistent and treatment-resistant form of disease, coexisting usually with severe asthma and referred to as the “aspirin triad” (3). In a recent study, genome-wide expression microarray study was performed in 57 patients with three distinct phenotypes: 1) patients with chronic rhinosinusitis and sinonasal polyposis without a history of aspirin allergy (CRS group); 2) patients with chronic rhinosinusitis and sinonasal polyposis with a history of asthma and aspirin allergy (ASA group); and 3) patients with no history or clinical evidence of sinusitis, asthma, or aspirin allergy (control group) (79). This study was able to identify five genes (POSTN, MET, PIP, AZGP1, and PPP1R9B) that are likely to play a role in the pathogenesis

of sinonasal polyps associated with CRS and ASA (Table 4).

CONCLUSION

The expression of gene products is regulated at multiple levels, such as during transcription, mRNA processing, translation, phosphorylation and degradation. Although some studies were able to show certain NP associated polymorphisms and genotypes, the present data is still fragmented. Same as for many common human diseases, inherited genetic variation appears to be critical but yet still largely unexplained. Future studies are needed to identify the key genes underlying the development or formation of NP and to investigate the interactions between genetic and environmental factors that influence the complex traits of this disease. Identifying the causal genes and variants in NP is important to the path towards improved prevention, diagnosis and treatment of NPs.

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