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ASTHMA GENETICS: A REVIEW ON GENE EXPRESSION

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ABSTRACT

Recent research suggests that asthma genetics is significantly influenced by pathways involved in inflammation, airway remodeling, and epithelial activation. Transcriptome analyses have identified genes that are differently expressed in response to allergens or interleukins, eosinophil apoptosis, the arginase pathway, and inhaled corticosteroids. A1AR and CLCA1 genes (chromosome 1), IL-1RN and DPP10 (2q14), HLA-G and TNF-(6p21), GPR (7p14), FcRI and GSTP1 (11q13), NOS1, IFNG, STAT6, VDR, and other genes (12q13-26), PHF11 and flaking genes (13q14), AACT and PTGDR (14q), and ADAM33 (20p13) are just a few of the genetic regions that have been identified by candidate gene and genome-wide studies. Future research, ideally longitudinal in nature, is required to confirm the involvement of these and other genetic variables.

Keywords: association, asthma, atopy, expression, gene, genome, haplotype.

INTRODUCTION

Asthma is a prevalent and intricate ailment, exhibiting significant variation in its manifestation and fundamental pathophysiology. The principal asthma symptoms include coughing, wheezing, and dyspnea paroxysms. However, each patient's symptoms may be unique, and even patients with comparable symptoms may react differently to treatment.

Understanding the hereditary and environmental triggers for asthma as well as the variables that contribute to variations in the disease's natural history is a major objective of research on asthma. It is well recognized that a crucial component of the diathesis is inflammation.

CELLS AND MEDIATORS

According to recent research, one of the main elements in the pathophysiology of asthma is airway inflammation. Due to the participation of many local and recruited inflammatory cells, the condition is multifactorial (in both beginning and progression). According to Elias et al. (2003), T cells and IgE-mediated reactions are recognized as important components of the allergic response. Through the process of processing antigens, dendritic cells serve as a conduit between allergens and T cells[1]. T cells release a limited range of cytokines in reaction to allergens. In particular, the Th2 subtype of T helper cells produces pro-inflammatory cytokines. Th1 cells, the other kind, oppose the allergic response and are engaged in viral defense. An unbalanced T-cell expression pattern . Asthma pathogenesis is believed to be significantly influenced by an imbalance in T cell phenotypic expression. Interleukin 4 (IL-4) is elevated in atopic patients; this is because IL-4 stimulates the Th2 cell response, which in turn provides signals for the creation of IgE. Proallergic cytokines are not only produced by T helper cells; other sources include mast cells, basophils, eosinophils, CD8+ T cells, bronchial, fibroblast, and smooth muscle cells. These cells can produce inflammatory molecules such as IL-4, IL-5, IL-9, and IL-13, which are encoded by the 5q cytokine cluster[2].

The production of prostaglandins and leukotrienes, the transcription of cytokines, and the release of preformed vasoactive mediators are all triggered by cross-linking to the IgE on mast cell subunit of the high affinity IgE receptor (FcRI) . The interaction of the IgE with the B cell's FcRII receptor (CD23) also induces allergen-specific IgE. The generation of IgE is linked to allergic hypersensitivity reactions to allergens inhaled[3]. The generation of cytokines and adhesion molecules that specifically attract neutrophils and eosinophils—cells important to the inflammatory manifestations—is triggered by the release of neutral protease from mast cells via the IgE receptor on endothelial and epithelial cells. An important part of the pathophysiology of allergic asthma involves eosinophils. In addition to several cytokines, transforming growth factor-Π(TGF-\), prostaglandin E2 (PGE2), cysteinyl leukotriens, platelet activating factor (PAF), reactive oxygen intermediates, cytotoxic peptides, and degradation enzymes like elastase and collagenase, they secrete a variety of inflammatory mediators. Thus, both the injury and repair of the host tissue are influenced by the inflammatory response[4].

GENES

The complex and heterogeneous ethio pathology of asthma is demonstrated by the activation of numerous distinct cellular types (e.g., B and T cells, eosinophils, dendritic cells, etc.) and molecules (cytokines, intracellular mediators) in space and time (tissue remodeling, early phase, late phase). It follows that the large number of genes that have been reported and the challenging replication of association and linkage study results should not come as a surprise. Numerous genes may be involved in the variation of phenotypes based on genetic background and environmental exposure within a population[5]**.** Environmental influences could reveal susceptibility genes that were already present in a population. Furthermore, as numerous papers have started, methodological difficulties (such as sample size and structure, power of the study, definition of the phenotype, selection criteria, and DNA markers employed) that impact the reliability of the results must be taken into consideration[5]. There is compelling evidence that, unlike in Mendelian disease, genes determine vulnerability rather than the disease itself. Early genetic investigations reported linkage or correlation with the high affinity IgE receptor with a postulated maternal inheritance, the IL-4 gene cluster, and the predicted candidate MHC II area, confirming the biophysiological data. Numerous genes or chromosomal areas were reported by subsequent investigations, including those on chromosomes 12 (IFGN, ITG-7, STAT6, NOS1, STAT6), 5 (IL-4 cluster genes, ADRB2, CD14, SPINK5), 7 (TCRG), 11 (FcRI), 13 (AACT), 19 (FcRII), and many more[6].

Positional cloning and precise mapping research have recently connected asthma in multiple groups to new genes, many of which have unknown roles.

This study discusses insights into genetic pathways of disease pathogenesis using animal models of asthma generated by various allergens and protocols (exposure to cytokines, medicines, etc.). We also cover some recent findings from fine mapping and gene expression studies. Table 1 provides an overview of the genes linked to asthma that were discussed in this review.

GENE EXPRESSION STUDIES

Numerous loci can have their gene expression studied using DNA microarray technology. It is possible to compare the expression profiles in various samples and track the expression simultaneously. The time span over which gene expression is measured, treatment exposure, cell types under investigation, and other factors could all be contributing factors to the sample variation. The variability of disease phenotype can be investigated using a wide range of techniques to gather data that could further our knowledge of the condition as a whole[7]. With varying goals in mind, this technology has been applied to asthma and has proven to be a dependable means of validating earlier findings or offering fresh insights into metabolic pathways implicated in the pathophysiology of the condition.

EOSINOPHIL APOPTOSIS

Many research efforts have been conducted on the gene expression of eosinophils and their function in the pathophysiology of asthma.The study documented modifications in the messenger RNA expression profile following IL-5 therapy.

It was shown that the regulation of 80 genes differed between eosinophils that were treated with IL-5 and those that were not. Just seven of these genes were down-regulated, whereas the majority of these genes—73—were up-regulated. The up-regulated genes are thought to be related to eosinophil or hematopoietic cell adhesion (ICAM-1, CD24), migration, activation (IL-8, ERK-3, CCR-1, CD69), or survival (Pim-1, EGR-1). Four genes have been identified as being expressed (Pim-1, SLP-76, DSP-5, and CD24), two of which are specific to eosinophils and are involved in the survival of eosinophils in response to IL-5[8]. These two genes might be involved in crucial processes that govern inflammatory responses by limiting eosinophil survival.

THE ARGINASE PATHWAY

After conducting a gene expression analysis on 12422 genes, Zimmerman and colleagues discovered that 291 genes were frequently implicated in development of the disease following exposure to various allergens. They came to the conclusion that an asthmatic lung had 6.5% of the examined transcriptome changed (Zimmerman et al. 2003)[29].

Specifically, they discovered a coordinated overexpression of the genes that code for the molecules involved in arginine metabolism.

The synthesis of proline, which regulates cell proliferation and collagen creation, and polyamines (such as putrescine and spermidine) is aided by the enzyme arginase I. It might therefore have something to do with controlling apoptosis[9].

The authors suggest that arginine is degraded by arginase, which produces polyamines and proline, in addition to nitric oxide synthase (NOS) enzymes, which produce NO and L-citrulline. Manganese (Mn), an element necessary for arginase activity and stability, is correlated with arginase activity, according to research published in 2004 by Kocyigit et al. Lower arginase activity in asthma may result from lower Mn concentration, which would favor the overexpression of NO[15] .

THE RESPONSE TO ALLERGEN OR IL-4

A study using microarray technology, involving 40,000 genes, was conducted on a monkey model of allergic asthma.

Following inhalation of the Ascaris suum antigen (bronchocostriction) or IL-4 (allergic reaction), gene expression was assessed. The lung tissue's gene expression was assessed 4, 18, and 24 hours following the antigen exposure. Four hours after the challenge, there was a differential expression of 139 genes. The lungs and activation-related chemokines, vascular cell adhesion molecule 1 (VCAM1), IL-4 inducible genes (eotaxin, VCAM1, MCP-1, MCP-3), tissue remodeling factors (plasminogen activator inhibitor-1 PAI-1, tissue inhibitor of metalloproterase I TIMPI), chitinase defense against proteolytic enzyme damage, and several antioxidants (SOD1, SOD2, GPX) are among the five gene clusters that the authors described[10].

This supports the findings of Kinnula and Crapo (2003) that reactive oxygen species and oxidative stress are factors in asthma inflammation. It's important to note that alpha1-antichymotrypsin (AACT), a protease inhibitor, is one of the genes with variable expression. A sample of Italian families' increased IgE levels was linked to AACT (Malerba et al. 2001). The downregulated genes CCAAT binding transcription factor (NF-Y), SYBl1, aminopeptidase A, and SLAM promoting Th2 responses showed the biggest decrease in expression level, indicating that they react to allergen exposure rather than IL-4 treatment[11].

Additionally, distinct genes expressed differently 24 hours after inhaling IL-4, but not in response to an antigen challenge.

PROFILING ATOPY AND ASTHMA

Asthma and atopy have a high correlation. Brutsche and colleagues examined the expression of 609 genes in atopic asthmatics, non-atopic asthmatics, and healthy people in an effort to find a cluster of genes that would be useful in determining the state of the condition (Brutsche et al. 2002). They created a composite atopy gene expression (CAGE) score that takes into account the dysregulation of ten genes in atopic people. It has been found that the CAGE score is a more accurate indicator of atopic persons than IgE[12]. The score displayed a pattern of connection with the severity of asthma and linked with IgE levels. It's significant to notice that IL-1R maps to the IL-1 gene cluster on chromosome 2, which has recently been related to asthma (see chromosome 2). This gene cluster is one of the ten genes that were selected to compute the CAGE score.

INHALED CORTICOSTEROID THERAPY

In order to identify differentially expressed genes in bronchial biopsies of asthmatic patients following inhaled corticosteroid therapy (ICS), Laprise et al. published a microarray analysis using 12,000 oligonucleotide probes.

79 genes with altered expression patterns in patients compared to controls were found. A comparison of 128 genes' expression levels in the patients before and after ICS treatment suggested that the medication may

initiate novel metabolic pathways. Inhaled corticosteroid therapy resulted in partial or complete correction of expression levels for 26 out of 79 genes, including the expression of the proteolytic enzymes[12].

CANDIDATES, FINE-MAPPING AND GENOME STUDIES

CHROMOSOME 1: THE A1AR AND CLCA1 GENES

One of the regulating nucleosides produced in response to cellular stress and injury is adenosine. Diverse adenosine receptors (ARs) on various cells are expected to express differently, mediating distinct pro- and anti-inflammatory actions. A1 adenosine receptor (A1AR) signaling has been demonstrated in certain investigations to activate monocytes and neutrophils. One signaling molecule linked to the control of asthma and other lung conditions is adenosine[13].

Adenosine deaminase deficient (ADA deficient) animals with high adenosine levels have lung inflammation and injury, which Sun et al. explored as a result of A1AR signaling. Increased mucus metaplasia, alveolar injury, and excessive expression of IL-4 and IL-13 in the lungs, along with a rise in chemokine and matrix metalloproteinase expression, were all brought on by the deletion of the A1AR gene. By regulating the amounts of significant mediators of inflammation and damage, A1AR signaling may help to reduce the degree of pulmonary remodeling and inflammation in chronic lung disease[14]. Adenosine increases the expression of the mucin (MUC2) and aids in the hypersecretion of mucus by airway epithelial cells.

The route begins at the A1AR and uses the epidermal growth factor receptor (EGFR) and a Ca2++-activated Cl-channel to transmit signals. The Japanese population's association between childhood and adult asthma and CLCA1 gene polymorphisms and haplotypes was described by Kamada et al. in 2004.

The overproduction of mucus in asthmatic patients may be partially attributed to the CLCA1 channel, according to a 2002 study by Toda and colleagues that revealed the activation of CLCA1 by IL-9.

This demonstrates the importance of knowledge that may be gained from either full or partial understanding of the mechanisms involved in the creation of novel gene candidates. By encouraging the production of IL-4 and IL-13 and by controlling CLCA1, A1AR contributes to the regulation of inflammation and mucus formation. Combining several methods (gene expression, experimental models, and frequency of gene variation) has provided fresh information about a pathway that is probably involved in the production of mucus during inflammation[16].

CHROMOSOME 2: ONE OR MORE GENES?

Recently, the findings of two separate groups' positional cloning work on chromosome 2 were published. The two groups identified two distinct candidate genes that localize in the vicinity of the IL-1 cluster on chromosome 2q14: IL-R1N and DPP10. In the asthmatic populations of Germany and Italy, Gohlke and colleagues found a correlation with SNPs in the IL-1RN gene . The DPP10 gene's SNPs were not investigated. In British and German populations, Allen et al. revealed no association in the IL-1RN gene; rather, they discovered an association with SNPs of the DPP10 gene, which is located in close proximity to the IL-1RN gene . Neither study has produced a conclusive outcome. The anti-inflammatory cytokine IL-1 receptor antagonist protein, which is encoded by the IL-1RN gene, is crucial for preserving the equilibrium between pro- and anti-inflammatory cytokines. After a genome scan and subsequent fine mapping with 219 SNPs, the area was found[19]. Linkage with the human syntenic area was characterized using mice models for ovalbumin-induced airway hyperresponsiveness and metacholine-induced airway responsiveness[17]. Sequencing of the IL-1RN gene revealed 28 more DNA variations, indicating a greater relationship. Six SNPs were found to be sufficient for tagging all haplotypes with a prevalence greater than 1%, and the region displayed a strong (LD).

This indicates that the haplotype diversity in the IL-1RN gene might be captured by analyzing just 6 SNPs. In the German group, asthma was linked to three SNPs (rs2234678, rs878972, 98 G. Malerba, P.F. Pignatti, rs454078), and to two SNPs (rs2234678, rs878972) in the Italian families. The authors, however, were unable to identify a single causal mutation. The authors concluded that since all statistically linked SNPs or haplotypes are found in or near IL-1RN in the German families, it is unlikely that a gene flanking the IL-1RN gene is the cause of the association data. 800 kilobases separate DPP10 from the IL-1 gene cluster[17]. Using precise mapping and linkage analysis on 244 families in the UK, a haplotype linked to asthma was found on an LD island. In a group of 1047 German children with asthma, the same haplotype was likewise linked to asthma[22]. A haplotype (WTC122P*1 – D2S308*3) was also shown to be more common in asthmatics who were dependent on steroids. The region's solely expressed gene was MEX4FB-1, which codes for the DPP10 protein. The absence of coding variation in the DPP10 gene suggests that regulatory elements resulting in alternative splicing may be the source of the influence on asthma susceptibility[18].

CHROMOSOME 6: ONE MORE SUSCEPTIBILITY GENE AND MATERNAL EFFECT

On chromosome 6p21 are located the human major histocompatibility complex (MHC) genes as well as numerous additional genes that are crucial for immune system regulation.

Numerous studies have demonstrated a high correlation between the 6p21 region and asthma and the atopic phenotype, making it an important locus regulating allergic disorders. Additional researches have documented a correlation with the TNF-gene.

Nicolae and colleagues recently provided a description of the HLA-G relationship in three populations. They presented data from four separate samples that supported the HLA-G gene's status as a novel gene in the human leukocyte antigen area that confers vulnerability to asthma and bronchial hyperresponsiveness[21]. In two samples, they discovered a gene polymorphism (-944 A/G) linked to asthma using the positional cloning technique[20]. Additionally, they discovered a varied relationship between alleles and pediatric diseases depending on the level of maternal attachment. In children of mothers with bronchial hyperresponsiveness (BHR), the –964 GG genotype was linked to asthma; in children of mothers with a negative BHR affection status, the –964 AA genotype was linked to asthma.As a result, the complicated vulnerability to asthma associated with 6p21 may be impacted by maternal variables.

CHROMOSOME 7: THE GPRA GENE

Due to a reduced number of risk genes for a particular disease, populations that have been isolated for a long time or that originated from a relatively small number of individuals are likely to show more genetic homogeneity than outbred populations. As a result, these populations may be relevant in multigenic disease mapping[24].

A 20cM area on chromosome 7p14-p15 was linked in a 2001 genome scan for asthma and IgE in Finnish and French-Canadian families, and in 2004 the orphan G protein-coupled receptor gene (GPRA, G-protein-coupled receptor for asthma susceptibility) was linked to high IgE[23]. There is a correlation between increased IgE levels, atopy, and many haplotypes and SNPs located about 70 Kb. In each community, higher IgE levels were found to be connected with at least one haplotype. Nonetheless, the risk haplotypes varied among the various populations[25].

CHROMOSOME 11: NOT ONLY THE FcεRI GENE

Asthma and atopy have been linked to the glutatione-S-transferase (GST) genes and other oxidative stress-related genes.

Lung function, atopy, and gene polymorphisms related to the GST genes have all been linked to asthma . The extraordinary coincidence that the GSTP1 maps to the same area of the well discussed FcεRI gene has led to its proposition as a supplementary or alternative theory explaining the linkage of chromosome 11q13. A maternal link between genetic variations of the GSTP1 and asthma in children was revealed by Child and colleagues in 2003. This finding supported the theory of maternal inheritance and offered an alternative to FcεRI.

CHROMOSOME 12: OXIDATIVE STRESS AND THE VDR GENE

Numerous investigations have demonstrated a connection between asthma or associated traits in many populations and chromosome 12q13-26. The large region of linkage suggests that chromosome 12 may include many asthma susceptibility genes. The search for a gene's identity continues.

One of the main causes of inflammation is oxidative stress, which results in the production of reactive oxygen species (Barnes 1990). The process of converting arginine into nitric oxide (NO) involves the NOS enzymes. It is yet unclear how NO, a molecule with numerous vital biological activities, plays a part in asthma cases[26].

It has been suggested to be a marker for NO concentration and airway inflammation, and it is strongly connected with the proportion of eosinophils in BAL fluids. Nitric oxide synthase is a collection of enzymes that includes endotelial (eNOS, chromosome 7), neural (nNOS, chromosome 12q32), and inducibile NOS (iNOS, chromosome 17) that create NO. Certain nNOS markers have been linked to asthma or similar conditions; this link has most recently been verified in the Japanese population[27]. The area including the vitamin receptor D (with the single protein-modifying SNP FokI 46) and integrin beta-7 (ITG-7 with 7 SNP) was recently investigated by Vollmert et al. They came to the conclusion that, among 172 German families with asthma, neither the ITG-7 gene nor the Fok1 SNP in the VDR gene appeared to be linked to asthma or related symptoms. In parallel, after examining 7 potential genes (IFNG, STAT6, CPM, KITLG, IL-22, IRAK3, VDR) with 28 DNA markers in 582 family trios,. discovered the correlation between VDR gene polymorphisms with asthma in children and adults[31].

The FokI 46 SNP in the VDR gene did not exhibit any correlation with asthma and was not in linkage disequilibrium with any of the other six SNPs out of the seven SNPs.A case-control research involving 1034 people confirmed the link with the VDR SNPs; however, the related allele differed from the one seen in the trios (Poon et al. 2004). A recent investigation using animal models demonstrated the role of the vitamin D endocrine system in the development of lung inflammation driven by Th2.

CHROMOSOME 13: GENES INFLUENCING IGE LEVELS

Numerous investigations established the connection between atopy and the associated phenotype and chromosome 13q14, reporting a region associated with IgE levels in asthma. The PHF11 gene was the focal point of the area, which also included the surrounding genes SETDB2 and RCBTB1. Three distinct SNPs were found, and three marker haplotypes that consistently showed connection in three more sample sets were also identified[29]. The connection between 13q14 and IgE levels is supported by the latest genome scan in the Italian population, which revealed a multipoint linkage between D13S156 and higher IgE (Malerba, in preparation).

CHROMOSOME 14: THE PTDGR GENE

Numerous investigations have demonstrated the relationship between chromosome 14 markers and asthma or associated symptoms, and certain gene associations—like AATC—have been reported.

The connection between the D14S63 marker and total blood IgE levels in asthmatic families was recently revealed by Mansur et al. Physically, the prostaglandin D2 receptor (DP) gene (PTGDR) is 16 Mb away from marker D14S63. Mast cells and eosinophils, which produce the asthmatic diathesis' effector chemicals, have PTGDR on [them30]. Oguma and colleagues have identified a particular haplotype of the gene that is linked to asthma in both Black and White people, indicating that the gene polymorphisms are shared by several populations. The haplotype with the lower incidence of asthma, according to the investigators, had a low transcription efficiency, suggesting that the haplotype had a functional purpose.

CHROMOSOME 20: AIRWAYS REMODELING

The function of ADAM33 (chromosome 20p), a novel gene linked to asthma that was discovered by Van Eerdewegh et al. in 2002, is yet unknown. According to Bridges et al. (2004), the ADAM proteins are involved in proteolysis during extracellular signaling. ADAM33 may play a role in remodeling the airway wall and cellular adhesion, according to certain theories. While some research found no correlation, others have verified the relationship with asthma. SNPs in the ADAM33 gene have been linked to asthma in four populations: US Caucasian, US Hispanic, US Afro-American, and Dutch, according to Howard. Still, no single haplotype or SNP was linked to asthma susceptibility risk in any of the populations studied. These findings support the novel theory of asthma etiology, which holds that excessive 100 According to G. Malerba and P.F. Pignatti, aberrant damage and repair reactions result in inflammation and remodeling.

CONCLUSIONS

Several chromosomal areas and genes have been implicated in the initiation and progression of asthma symptoms, according to gene identification investigations.

On the other hand, in order to understand the intricate interplay between genetic and environmental drivers of the disease and the response to therapy in particular patients, it is necessary to ascertain the impact of environmental and lifestyle factors.

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