Review Article

Genetic associations with asthma and virus-induced wheezing: a systematic review*, **

Associação genética da asma e da sibilância induzida por vírus: uma revisão sistemática

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Abstract

Various wheezing phenotypes can be identified based on differences in natural histories, risk factors and responses to treatment. In epidemiologic studies, atopic asthma or virus-induced wheezing can be discriminated by the presence or the absence of sensitization to allergens. Children with asthma have been shown to present lower levels of lung function. Patients with viral respiratory infections evolve from normal lung function to enhanced airway reactivity. The objective of this study was to identify genes and polymorphisms associated with different wheezing phenotypes. Using data obtained from the Genetic Association Database, we systematically reviewed studies on genes and polymorphisms that have been associated with virus-induced wheezing or atopic asthma. The research was carried out in February of 2009. Genes associated with the studied outcomes in more than three studies were included in the analysis. We found that different genes and loci have been associated with virus-induced wheezing or atopic asthma. Virus-induced wheezing has frequently been associated with *IL-8* polymorphisms, whereas atopic asthma and atopy have frequently been associated with Th2 cytokine gene (*CD14* and *IL-13*) polymorphisms on chromosome 5. This review provides evidence that different wheezing disorders in childhood can be differently affected by genetic variations, considering their role on airway inflammation and atopy. Future studies of genetic associations should consider the different wheezing phenotypes in infancy. In addition, stratified analyses for atopy can be useful for elucidating the mechanisms of the disease.

Keywords: Genetics; Polymorphism, genetic; Asthma; Interleukins; Respiratory syncytial viruses.

Resumo

Diversos fenótipos de sibilância têm sido identificados com base em diferenças na história natural, fatores de risco e resposta ao tratamento. Em estudos epidemiológicos, a asma atópica ou sibilância induzida por vírus pode ser discriminada pela presença ou ausência de sensibilização a alérgenos. As crianças com asma apresentam níveis menores de função pulmonar. Pacientes com infecções respiratórias virais apresentam-se com função pulmonar normal, mas mostram reatividade da via aérea aumentada. O objetivo deste trabalho foi identificar genes e polimorfismos associados aos diferentes fenótipos de sibilância. Utilizando dados do *Genetic Association Database*, foi realizada uma revisão sistemática de estudos sobre genes e polimorfismos associados à sibilância induzida por vírus ou à asma atópica. O levantamento foi realizado em fevereiro de 2009. Todos os genes associados com o desfecho estudado presentes em mais de três estudos foram incluídos na análise. Identificamos que diferentes genes e locos têm sido associados à sibilância induzida por vírus ou à asma atópica. Enquanto a sibilância induzida por vírus foi mais frequentemente associada a polimorfismos no gene *IL-8*, polimorfismos localizados em genes de citocinas Th2 no cromossomo 5 (*CD14* e *IL-13*) foram frequentemente associados à atopia ou à asma atópica. Esta revisão mostrou evidências de que a sibilância na infância pode ser afetada por variações genéticas de formas diferentes, dependendo de seu papel na inflamação das vias aéreas e na atopia. Estudos futuros de associação genética deverão levar em consideração os diferentes fenótipos na infância. Além disso, análises estratificadas para atopia podem ser úteis para elucidar os mecanismos da doença.

Descritores: Genética; Polimorfismo genético; Asma; Interleucinas; Vírus sinciciais respiratórios.

Introduction

Although wheezing is highly prevalent in infants and children in the first six years of life, only certain children develop persistent atopic asthma later in life.[1] Diverse wheezing phenotypes can be identified based on differences in risk factors, natural histories and responses to treatment.[2-3] International guidelines, which are based on the efficacy of systemic corticosteroids in reducing hospitalization in children with classic atopic asthma, recommend the use of oral corticosteroids for children with virus-induced wheezing who present to a hospital. However, the results of trials that have addressed the question of efficacy of systemic corticosteroids in young children with acute wheezing are contradictory. Atopic wheezing and non-atopic wheezing have contrasting natural histories and can have different etiologies. Atopic asthma has been associated with an allergic or eosinophilic response in older patients with asthma.[4] However, in young children with virus-induced wheezing, neutrophils typically predominate in BAL fluid samples.[5]

In various epidemiologic studies,[6-7] children with atopic asthma have been shown to present positive skin prick test results and increased airway responsiveness as major associated risk factors. Among such children, there is a significant association between an early onset of wheezing and the severity of the disease. Children with atopy have been shown to present lower levels of lung function by three years of age.[8] For preschool children with wheezing, early allergic sensitization increases the prevalence of respiratory symptoms, airway inflammation and the risk of asthma being diagnosed later in life. Several studies have shown that asthma during childhood is strongly associated with elevated serum IgE and positive skin prick test results.[9-11] Early sensitization to allergens is associated with an increased risk for the development of bronchial hyperresponsiveness.[12] Elevated IgE levels at nine months of age correlates directly with the risk of persistent wheezing, suggesting a form of IgE-mediated sensitization during the first years of life.[13] Children who had asthma by seven years of age were sensitized very early in life and had persistent sensitization when compared with children who did not have asthma.[14] These findings indicate that a genetic predisposition for atopy is associated with asthma symptoms that start early in life and persist into adulthood.

Lower respiratory illnesses (LRIs) caused by viral infection can also be associated with persistent wheezing in infants and preschool children. Non-atopic wheezers evolve from normal lung function to slightly impaired lung function and enhanced airway reactivity later in childhood. Stein et al.[15] examined the relationship between LRIs in infants and the subsequent development of wheezing during the first decade of life. The authors found that most wheezing episodes are due to viral respiratory infections, with respiratory syncytial virus (RSV) being detected in the majority of these episodes. Analyses demonstrated that RSV infections in infancy were associated with an increased risk of wheezing during the first ten years of life, regardless of other known risk factors for asthma or asthma-related symptoms, such as family history of asthma or atopy. However, RSV-induced wheezing has not been associated with an increased risk of atopy or higher serum IgE levels.

Children who had virus-induced wheezing early in life were more likely to have lower levels of lung function at eleven years of age when compared with controls. One can suggest that, in some children, the viral infection led to a specific inflammatory response that caused this long-term airway obstruction. Therefore, a significant number of children who present wheezing during the first decade of life do so in association with viral respiratory agents regardless of atopy. This wheezing phenotype seems to be associated with wheezing that is less severe. Among school-age children in developed countries, this phenotype is probably less prevalent than is the atopic phenotype, although this might not hold true in different environments. Findings from developing countries[16] have led to the hypothesis that different risk factors, such as recurrent or severe viral aggressions, are associated with an increased expression of this wheezing phenotype that is not associated with atopy. Genetic variants in the genes associated with the immune response can be associated with either non-atopic forms of wheezing or atopic asthma. Unless the atopic and non-atopic forms of wheezing are analyzed separately, the effects might not be detected.

Data collection

The Genetic Association Database (GAD) is an archive of human genetic association studies of complex disorders, organized by the National Institute of Health (http://geneticassociationdb. nih.gov/). This database allows researchers to identify relevant polymorphisms from the large volume of gene variations, in the context of a standardized nomenclature for genes and polymorphisms. The database includes selected published scientific papers. Study data are recorded with the official nomenclature used for the human genome. The submitted records are reviewed before their inclusion in the database.[17] In the present study, we searched the GAD, employing the following search terms: "virus and asthma"; "respiratory syncytial virus"; "asthma and atopy"; and "atopy". All searches were performed in February of 2009. Genes that were associated with the studied outcomes in more than three studies were included in the analysis.

Genetic associations with atopic asthma and virus-induced asthma

The number of studies identified for each term was the following: 2 for "virus and asthma"; 15 for "respiratory syncytial virus"; 9 for "asthma and atopy"; and 79 for "atopy". The 9 studies related to asthma and atopy were grouped together with those related to atopy alone. In addition, the 2 papers related to virus and asthma were grouped together with those related to RSV. Genes that were associated with the studied outcomes in more than three studies were further reviewed. Viral or specifically RSV-induced wheezing was associated with polymorphisms in *IL-8* in 4 different studies (Chart 1). Single nucleotide polymorphisms (SNPs) located on Th2 genes positioned on chromosome 5 (*CD14* and *IL-13*) and chro-

mosome 16 (*IL-4R*) were associated with atopy or atopic asthma in 16 studies (*CD14* in 5, *IL-13* in 4 and *IL-4R* in 7, Chart 2).

Studies on Th2 cytokines and their relationship with asthma have focused on *IL-4* and *IL-13*. This is due to the crucial role of these two cytokines in the generation of Th2 responses: IL-4 is essential for the maturation of naive T cells towards Th2 cells and the production of IgE; and IL-13 is a protein product that shares several biological profiles with IL-4, including IgE production and MHC class II expression.[18-21] However, IL-8 is a chemokine that has been associated preferentially with virus-induced inflammation and is one of the major mediators of the inflammatory response. It is secreted by several cell types and functions as a chemoattractant factor, especially for neutrophils. In addition, *IL-8* is believed to play a role in the pathogenesis of bronchiolitis, a common respiratory tract disease in infants caused by viral infections.[22,23] Considering these data, *IL-8* and other members of the chemokine gene family can be considered relevant candidate genes for non-atopic forms of wheezing in childhood.

Genetics of atopic asthma

Studies of twins have shown the importance of the genetics in asthma variance, with estimated heritability ranging from 48% to 79%. One important finding is that most of these twin studies in different parts of the developed world showed similar and consistent results and suggest that atopic asthma, in particular, has a strong genetic background. Although we can estimate to what extent genetic susceptibility contributes to the risk of asthma and atopy, all specific loci that influence this clinical phenotype are far from being clearly determined. Although a significant number of genetic association studies have described atopy susceptibility genes, these data

Chart 1 – Genes associated with virus-induced wheezing in more than three genetic studies.

Gene	Phenotype	Chr	Chr and band	Reference
IL-8	RSV-induced wheezing	4	4q13-q21	Hull et al.[32]
IL-8	RSV-induced wheezing	4	4q13-q21	Puthothu et al.[34]
IL-8	RSV-induced wheezing	4	4q13-q21	Heinzmann et al.[31]
IL-8	RSV infection	4	4q13-q21	Lu et al.[35]

Chr: chromosome; and RSV: respiratory syncytial virus.

Chart 2 – Genes associated with atopic asthma or atopy in more than three genetic studies.

Gene	Phenotype	Chr	Chr and band	Reference
CD14	Atopy (total IgE))	5	5q22-q32	Leung et al.[36]
CD14	Atopy	5	5q22-q32	Buckova et al.[37]
CD14	Atopy	5	5q22-q32	Kabesch et al.[38]
CD14	Atopy	5	5q22-q32	Leynaert et al.[39]
CD14	Atopy	5	5q22-q32	Koppleman et al.[40]
IL-13	Atopy	5	5q31	Liu et al.[41]
IL-13	Atopy (specific IgE)	5	5q31	Leung et al.[42]
IL-13	Asthma and atopy	5	5q31	Howard et al.[43]
IL-13	Atopy	5	5q31	Nieters et al[44]
IL-4R	Atopy	16	16p11-12	Ober et al[45]
IL-4R	Atopy	16	16p11	Liu et al.[41]
IL-4R	Atopy (IgE)	16	16p11	Heinzmann et al.[19]
IL-4R	Atopy	16	16p11	Nieters et al.[44]
IL-4R	Atopy	16	16p11	Deichmann et al.[46]
IL-4R	Atopic asthma	16	16p11	Isidoro-Garcia et al.[47]
IL-4R	Asthma and atopy	16	16p11	Kruse et al.[48]

Chr: chromossome; and IL-4R: IL-4 receptor.

demonstrate the extreme complexity of the trait, and the identification of these polymorphisms presents a considerable challenge.

Several candidate genes have been studied in atopic disorders, and different factors contribute to this abundance of candidates. Results from genome screens have provided evidence of linkage to multiple sites in the genome. Therefore, there are candidate genes at many positions. In addition, immunological pathways associated with the allergic response involve a large array of inflammatory mediators. However, the best replicated results in genetic association studies of atopic asthma involve the human genome regions 5q31-32 and 16p11-12 (Chart 2).

There is evidence that Th2 genes located on chromosome 5q (*IL-13* and *IL-4)* are major determinants of atopic asthma. In addition, *IL-13* encodes an immunoregulatory cytokine produced primarily by activated Th2 cells, and this cytokine promotes IgE isotype switching. Furthermore, IL-13 inhibits the production of pro-inflammatory chemokines. This cytokine is found to be critical to the pathogenesis of allergen-induced asthma. The *IL-13* and *IL-4* genes form a cytokine gene cluster on chromosome 5q. It has been reported that the promoter SNP rs1800925 of the *IL-13* gene contributes significantly to bronchial hyper-responsiveness and susceptibility to atopic asthma.[18] Heinzmann et al.[19] determined that a coding SNP of *IL-13* (rs20541) is associated with asthma in case-control populations; the variant also predicted asthma and higher serum IL-13 levels in a Japanese population. The protein encoded by the *IL-4* gene is a Th2 cytokine produced by activated T cells that influence the allergic immune response. The IL-4 receptor also binds to IL-13, which might contribute to overlapping functions of IL-4 and IL-13. It has also been suggested that SNPs in the *IL-4* gene are involved in the development of asthma and the regulation of total serum IgE.[20] Our group has shown[21] that the combined analyses of genetic alterations in the IL-4/IL-13 pathway reveal their significance for the development of atopy and childhood asthma. Moreover, other genes harbored at the same loci, such as *CD14*, might contribute to asthma and allergy.

The IL-4 receptor (*IL-4R*), on chromosome 16p, is a key component in the induction of Th2 lymphocytes. A further role that IL-4 plays in the pathogenesis of asthma has been indicated from sensitized il-4 knockout mice. Neither specific IgE induction nor bronchial hyperreactivity was detected in these mice, suggesting a critical role for the IL-4/IL-4R pathway in these phenotypes. At least 16 SNPs in the IL-4RA gene have been reported. The coding polymorphisms I50V, S478P, and Q551R have been associated with a greater risk of atopy, a greater risk of atopic asthma, and variations in IgE levels.[18]

Genetics and mechanisms of virus-induced asthma

The important role of IL-8 in the pathophysiology of bronchial inflammation has been confirmed by studies in humans and animals. Administration of IL-8 into the airways induces bronchial hyperreactivity in pigs[22,23] and increased levels of IL-8 in sputum precede wheezing exacerbation in humans.[24] In addition, IL-8 might be especially important in non-atopic wheezing, since IL-8-producing cells are more frequently found in this subgroup of patients with asthma.[25] Furthermore, IL-8 selectively inhibits IgE production in atopic patients by inhibiting IL-4 and thus might even protect against the development of atopy.[26,27]

The RSV is involved in at least 70% of the cases of bronchiolitis and has been repetitively linked to wheezing. It has been hypothesized that severe RSV infections in infancy might be associated with the development of recurrent wheezing or bronchitis.[28,29] According to the current evidence, genetic and environmental factors determine the type of immune response to RSV infections. Furthermore, this response might affect the development of control mechanisms in the regulation of airway diseases.

Increased concentrations of IL-8 have been described in BAL fluid and sputum of patients with recurrent wheezing.[30] In addition, a genetic association of IL-8 has been described with both persistent wheezing[31] and RSV bronchiolitis.[32,33] Heinzmann et al.[31] demonstrated an association between polymorphisms in *IL-8* with bronchial asthma. Furthermore, the findings suggested that RSV bronchiolitis and asthma have at least some different genetic factors: the same promoter polymorphism in *IL-8* that causes susceptibility to RSV bronchiolitis might protect against asthma. The results might suggest a distinct and even opposite role of IL-8 in atopic and non-atopic wheezing. Further studies provide evidence of a genetic susceptibility determinant for RSV bronchiolitis.[31-35] In a genetic association analyses, they investigated a SNP located–251 nt relative to the *IL-8* transcriptional start site. Hull et al. showed a trend for increased IL-8 production in association with the IL-8–251A allele when blood is stimulated with LPS.[32] Analysis of cases of RSV bronchiolitis showed that the IL-8–251A allele is significantly associated with the severity of the disease. The effect was most marked for severe disease requiring oxygen therapy for more than two days, and for cases of bronchiolitis with no other known risk factors.

Final considerations

This review demonstrated different effects of genetic variations in atopic[36-48] and non-atopic wheezing.[31-35] These differences should be interpreted considering the role of these genes on airway inflammation and atopy. Although these phenotypes can have different etiologies, no clinical index or test for the differentiation between atopic asthma and viral wheezing has proven sufficiently accurate to be useful in young children. However, future genetic association studies should systematically investigate the wheezing phenotypes separately. Such studies could identify clinical relevant genetic markers of virus-induced wheezing or atopic asthma.

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