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Identifying the Roles of Interleukin-13 in Childhood Asthma

Kamleshun Ramphul

Department of Pediatrics, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
Email: adramphul@hotmail.com

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Abstract

Asthma is a chronic inflammatory disease of the airways manifested by reversible airflow obstruction and airway hyperresponsiveness. While recent research has mapped several genes as possible factors predisposing to asthma, interleukin-13 remains one of the most commonly found genes in various populations. IL-13 is a pleiotropic TH2 cytokine which has been linked to cause an increase in goblet cell differentiation, activation of fibroblasts, elevation of bronchial hyperresponsiveness and switching of B cell antibody from IgM to IgE. The aim of this review is to study and identify the three main single-nucleotide polymorphisms of IL-13 (IL13 R130Q, IL-13Rα1 and IL-13 A2044G) that have been linked to asthma in children, and to understand their respective roles in the pathogenesis of this disease.

Keywords

Asthma, Interleukin 13, Children

Subject Areas: **Medical Genetics, Women's Health**

1. Introduction

Asthma is one of the most common chronic respiratory diseases in childhood, characterized by the reversible airflow obstruction due to chronic inflammation of the airways [1]. It is thought to be caused by a combination of genetic and environmental factors [2] and the prevalence of this disease has been reported as increasing globally [3] [4]. Asthma presents as recurrent episodes of wheezing, chest tightness, coughing and breathlessness [5] which can be triggered by exposures to environmental factors such as allergens, pharmacological agents and pollutants as well as infectious sources or stimuli such as viruses. In the last ten years, the analysis of single-nuc-

leotide polymorphisms (SNPs) has become the newest approach in the detection and localization of the genetic determinants of asthma [6] [7] and we have been able to identify several genes predisposing to asthma in both adults and children.

Interleukin-13 is one of the most frequently reported genes in the predisposition of asthma in the whole population, irrespective of age, gender and ethnic background. There are different hypotheses that CD4+ T cells are the primary orchestrators of the immune response corresponding to the pathogenesis of asthma and IL-13 is one of the cytokines involved. Human IL-13 is a 17-kDa glycoprotein cloned mainly from activated T cells [8] and the gene is located on chromosome 5q31 which also codes for other factors linked to airway responsiveness, total serum IgE such as IL-4, IL-3, IL-5 and granulocyte-macrophage colony stimulating factor [9]-[14]. Recent studies on human subjects and animals have indicated a critical role of IL-13 in the pathogenesis of allergic disease in the whole population and can cause an increase in goblet cell differentiation, activation of fibroblasts, elevation of bronchial hyperresponsiveness and switching of B cell antibody from IgM to IgE [15]-[19]. Our main aim is to identify the different single-nucleotide polymorphisms of IL-13 which predisposes asthmatic children.

2. IL13 R130Q

IL13 R130Q is one of the single nucleotide polymorphisms of IL-13 that has been reported as a risk factor for asthma in children. R130Q (rs 20541) is a coding SNP in exon 4 (Arg 130 Gln) and the 130 Gln substitution can result in signal transducer and activation of transcription phosphorylation in monocytes. Zitnik S.E. *et al.* studied the occurance of R130Q in children suffering from atopic dermatitis up to 4-year of age and their level of total IgE. In their research they found statistical evidence that IL-13 R130Q allele was related to slightly elevated total IgE levels compared to the heterozygotes and was a risk factor in the development of allergic dermatitis [20]. In 2008 Chan *et al.* conducted a research with 18SNPs in Chinese asthmatic children and only R130Q showed a significant association with plasma total IgE ($P = 0.035$) [21] supporting the results published by Hunninghake *et al.* [22] and Leung *et al.* [23]. Recent research conducted in middle China by Wu X. *et al.* found significant differences of IL-13 R130Q in genotype and frequency distributions between the asthma group and the control group. They also noted that the A allele of IL-13 R130Q was significantly associated with an increased risk of asthma in the children from middle China (odds ratio [OR] = 1.59, 95% confidence interval [CI] 1.20 - 2.09, $P = 0.0010$) [24]. A meta-analysis performed by Cui *et al.* in 2012 provided evidence that the R130Q polymorphism in IL-13 is a risk factor of asthma. In the subgroup analysis by ethnicity, the significant association was also found in Caucasians (heterozygote comparison: OR = 1.37, 95% CI 1.01 - 1.85; and dominant model: OR = 1.38, 95% CI 1.04 - 1.83, respectively) but not in Asians [25].

3. IL-13 A2044G

IL-13 A2044G (rs20541) is another commonly seen polymorphism of interleukin 13. For the general population a meta-analysis conducted by Wei *et al.* in 2012 indicated a significant association between IL13+2044A/G polymorphism and asthma risk (OR = 1.18, 95% CI 1.08 - 1.28, $P = 0.0002$). In the subgroup analysis by ethnicity, there were significant associations between IL13+2044A/G polymorphism and asthma risk in Asians (OR = 1.19, 95% CI 1.04 - 1.36, $P = 0.01$) and Caucasians (OR = 1.22, 95% CI 1.06 - 1.40, $P = 0.005$) but not in African Americans [26]. While the amount of research for the pediatric population for this particular polymorphism is limited, Liu *et al.* proved that A2044G is closely associated with asthma in children of Chinese Han nationality ($\chi^2 = 13.112$, $P = 0.0001$). IL-13 A2044G is associated with a high eosinophil count [22] [27]. RANTES G-28C is located in the promoter region and it may enhance the transcriptional activity resulting in overexpression in lung cells. This change may lead to an increase in recruitment of neurtrophils and eosinophils in the airways, causing inflammation [28] [29]. RANTES G-28C also predisposes to airway obstruction [28]. Liu *et al.* found a relationship between the combined roles of IL-13 A2044G and RANTES G-28C in children suffering from asthma in China. the frequency of IL-13 A2044G A/A and RANTES G-28C G/G in the asthma group was significantly higher than in the control group (odds ratio [OR] = 2.59, $P = 0.0001$; OR = 3.00, $P = 0.0001$, respectively). Previous reports have shown that IL13-A2044G and RANTES G-28C were associated with an increased risk of asthma in Asian populations [30] [31]. IL13-A2044G can modify the primary structure of protein of IL-13 which is more active than WT IL-13 [32] [33]. They also suggested that the airway muscle cells and epithelial cells can overexpress RANTES by regulation of the mutant IL-13, and RANTES is greatly over ex-

pressed through interaction between the mutant IL-13 and RANTES G-28C. Carriers of both IL-13 A2044G A/A and RANTES G-28C G/G had a more significant risk for developing asthma than those with only a single polymorphism.

4. IL-13Rα1

Interleukin-13 Receptor alpha 1 (IL-13Rα1) is thought to have a major contribution to the development and maturation of cells of the immune system and it also participates in various immune responses. Recent research by Dhakal *et al.* suggested that IL-13Rα1 is expressed on the M2 but not on the M1 subset of macrophages and can specifically heterodimerize with the IL-4Rα chain to form a type II receptor [34]. Kim *et al.* studied the gene-gene interaction between IL-13 and IL-13Rα1 and their association with total IgE in asthmatic children in Korea. According to their research, the risk alleles for asthma were IL-13 A1512C, IL-13 C1112T and IL-13 Rα1 (A1398G) which showed an increased total IgE (P = 0.012, 0.015 and 0.017, respectively). They also performed a gene-gene interaction between risk alleles and it was associated with higher total IgE in children with atopic asthma (P = 0.002, 0.010) suggesting that IL-13 polymorphisms and IL-13Rα1 may interact to enhance IgE production and thus may have an important role in the pathogenesis of asthma [35]. Various reports for the general populations have shown the association of atopic asthma with IL-13 Rα1 [36]-[40]. However the number of reports for the pediatric population is limited but promising.

5. Discussion

Asthma is a common clinical syndrome resulting from several factors such as immunity, environment and heredity. Genetic predisposition is probably caused by a characteristic pattern of polymorphism in multiple genes involved in the regulation of the allergic reaction and the identification of these polymorphism patterns can be of predictive use for childhood asthma diagnosis. In our review we found that IL13 R130Q is one of the most commonly found polymorphism of interleukin-13 found in children from asthma. IL-13 A2044G can predispose children to asthma and carriers of both IL-13 A2044G A/A and RANTES G-28C G/G had a more significant risk for developing asthma than those with only a single polymorphism. IL-13Rα1 is a novel aspect of research which has not been fully explored in the pediatric population. It has shown close association with the disease in adult asthmatics and asthmatic children from Korea.

6. Conclusion

While recent research has mapped several genes as possible factors predisposing to asthma, interleukin-13 remains one of the most commonly found genes in various populations. Further research involving interleukin-13 will help us understand the pathogenesis and the polymorphisms predisposing to asthma in children even better.

Disclosure

The authors declare no conflicts of interest in this work.

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