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ORIGINAL ARTICLE

# Asthma and rhinitis have different genetic profiles for *IL13*, *IL17A* and *GSTP1* polymorphisms

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**Abstract**
*Background:* Asthma and rhinitis have a complex etiology, depending on multiple genetic and environmental risk factors. An increasing number of susceptibility genes are currently being identified, but the majority of reported associations have not been consistently replicated across populations of different genetic backgrounds.
*Purpose:* To evaluate whether polymorphisms of *IL4R* (rs1805015), *IL13* (rs20541), *IL17A* (rs2275913) and *GSTP1* (rs1695) genes are associated with rhinitis and/or asthma in adults of Portuguese ancestry.
*Methods:* 192 unrelated healthy individuals and 232 patients, 83 with rhinitis and 149 with asthma, were studied. All polymorphisms were detected by real time polymerase chain reaction (PCR) using TaqMan assays.
*Results:* Comparing to controls, significant association with asthma was observed for *GSTP1* rs1695 AA genotype (odds ratio (OR) – 1.96; 95% CI – 1.18 to 3.25; $p = 0.010$). The association sustains for allergic asthma (OR – 2.17; 95% CI – 1.23 to 3.80; $p = 0.007$). *IL13* rs20541 GG genotype was associated with less susceptibility to asthma (OR – 0.55, 95% CI – 0.33 to 0.94, $p = 0.028$). Among patients, *IL17A* rs2275913 AA genotype was less associated with asthma than with rhinitis (OR – 0.20; 95% CI of 0.07 to 0.56; $p = 0.002$). A similar association was found for *IL13* rs20541 GG genotype (OR – 0.48; 95% CI of 0.25 to 0.93; $p = 0.031$). There were no significant differences in the distribution of allelic and genotypic frequencies between patients and controls for the *IL4R* polymorphism' analyzed.

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*Conclusion:* These results support the existence of a significant association between *GSTP1* rs1695 and *IL13* rs20541 SNPs, with susceptibility to asthma, in the population studied. Different genotype profiles of *IL17A* and *IL13* genes seem to influence the clinical pattern of disease expression mainly confined to the upper airways, as rhinitis, or including the lower airways, as asthma.


## Introduction

Asthma and asthma-related disorders, such as sinusitis and rhinitis, are complex diseases with strong genetic and environmental components.[1] Over the last decades their prevalence has been increasing worldwide, with a significant economic impact on health services.

Asthma is a common chronic inflammatory disease of the lower airways, characterized by reversible airflow obstruction, inflammation, persistent hyper-reactivity and airway remodeling.[2] Rhinitis is an upper airways inflammatory disease, often associated with asthma[3] and have been recognized as a risk factor for its development and severity.[4]

Genetic contribution to these phenotypes may account for 50–60%,[5,6] so dissecting genetic susceptible profiles may provide insight into the pathogenesis, allowing us to identify different sub-phenotypes and also contribute to finding new targeted therapies.

An increasing number of asthma susceptibility loci are continuously being identified, either by candidate gene studies or, more recently, by microarray-based whole genome approach, the genome-wide association (GWA) studies. Results are hampered by difficulties common to other complex diseases: inconsistent replication of results, functional association between identified loci and phenotype is not obvious, and most of all, allele penetrance is low and phenotype variance largely remains to be explained.[7–10] Most marker SNPs (single nucleotide polymorphisms) are localized in or near-by genes encoding proteins directly or indirectly involved in immunologic response. Recently, GWAs have revealed that different allergic diseases with common immunological physiopathology, also share susceptibility loci.[10]

Interleukin-4 (IL4) mediates important pro-inflammatory functions in allergic phenotypes and has principle responsibility for the IgE isotype switch by B lymphocytes.[11] IL4 is also involved in T helper type 2 (TH2) lymphocytes activation, induction of endothelium modifications, hypersecretion of mucus and with lung remodeling in chronic asthma.[11] IL4 action is mediated through activation of its receptor IL4R, a cell-surface heterodimeric complex.

Interleukin-13 (IL13) is one of the cytokines released by IL4 mediated Th2 induced cells and shares most of IL4 functions. IL13 production in the airway promotes the survival and migration of eosinophils, activation of macrophages, increased permeability and mucus production by airway epithelial cells and stimulates airways hyperresponsiveness.[12] Huang et al.[13] found that asthmatic and rhinitis patients submitted to allergen-challenge had a significant enhancement of *IL13* gene expression at mRNA and protein levels in bronchoalveolar lavage samples compared with the saline-challenged control sites.

Interleukin-17A (IL17A) is the best studied member of IL17 family of cytokines. It is mainly produced by activated T cells. Signaling through activation NF-kappaB and mitogen-activated protein kinases, IL17A regulates local tissue inflammation inducing the expression of pro-inflammatory cytokines, neutrophil-recruiting chemokines, cyclooxygenase-2 (COX2) and nitric oxide (NO). IL17A may also modulate the activation and proliferation of B cells, thus enhancing IgE production and has been associated with airway hyperresponsiveness and remodeling.[14,15]

SNPs from *IL4*, *IL4R* and *IL13* genes are among the polymorphisms most frequently implicated in susceptibility to asthma, rhinitis and allergic phenotypes in general,[16] with some of these SNPs being associated with increased serum IgE levels.[17,18] Up to now few studies are available on the association with genetic polymorphisms of IL17A family members.[19–21]

Reactive oxygen and nitrogen species, originated from air pollutants or released by inflammatory cells and stressed bronchial epithelia, are major contributors to asthma and asthma related phenotypes.[22] Glutathione-S-transferases (GSTs) are enzymes involved in the cellular detoxification of free radicals. A missense SNP in Glutathione S-transferase P1 (*GSTP1*), rs1695 (p.Ile105Val), has been associated with differences in enzyme activity and susceptibility to environmental-induced diseases, including asthma, but results remain controversial.[23,24]

Frequencies of DNA polymorphisms vary between populations of diverse ethnical origins, as their contributions to complex diseases, therefore, it is important to study different populations. In this study we evaluate the role of *IL4R* rs1805015, *IL13* rs20541, *IL17A* rs2275913 and *GSTP1* rs1695 in the susceptibility to asthma and rhinitis in an adult population of Portuguese ancestry.

## Materials and methods

### Clinical samples

This case–control study comprises 424 non related Caucasian Portuguese individuals, including 232 patients and 192 controls, randomly selected from a larger sample that answered a home inquiry about symptoms of asthma, rhinitis and sinusitis. Individuals willing to participate were than observed at the Immunoallergology Department of Coimbra University Hospitals.

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