

# Genetics and the occupational environment

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## Purpose of review

This article will focus on the role of risk factors including genetic factors in the development of sensitization and occupational asthma.

## Recent findings

We will review the recent literature published on the genetics of occupational asthma, especially on genes coding for class II human leukocyte antigen and on respiratory antioxidant mechanisms. We will also discuss published work on non-occupational asthma and on allergic rhinitis because this information may contribute to a better understanding of the mechanisms involved in occupational asthma and serve to confirm data obtained on the disease. To date, although some progress has been made in the field of occupational asthma genetics, most studies were based on small sample sizes, findings were not replicated, and gene–environment interactions have not yet been established.

## Summary

Occupational asthma is a widespread and frequent condition and has relevant long-term adverse health and economic consequences. The search for risk factors including genetic factors in the development of the disease and an understanding of the mechanisms of interaction between genes and environment are important because the identification of individuals who are susceptible to occupational asthma together with an effective control of exposure to respiratory sensitizers in the workplace may be helpful in preventing the disease.

## Keywords

genetics, occupational asthma, risk factors, susceptibility, workplace

## Abbreviations

|             |                            |
|-------------|----------------------------|
| <b>AHR</b>  | airway hyperresponsiveness |
| <b>GST</b>  | glutathione-S transferase  |
| <b>HDI</b>  | hexamethylene diisocyanate |
| <b>HLA</b>  | human leukocyte antigen    |
| <b>LMWA</b> | low-molecular-weight agent |
| <b>TDI</b>  | toluene diisocyanate       |
| <b>TNF</b>  | tumour necrosis factor     |

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## Introduction

Bronchial asthma is common, affecting children and adults of all ages. Occupational factors account for 9–15% of the cases of asthma in adults of working age. Workplace agents induce asthma through two mechanisms: an allergic or presumed allergic mechanism which accounts for almost 90% of the cases of occupational asthma; or an irritant inflammatory mechanism, which occurs within a few hours of a high concentration exposure to an irritant gas, fume or vapour at work. Asthma is a multifactorial condition and is a good model for studying complex gene–environment interactions. Occupational asthma, like the non-occupational form, is a complex disease and is a valid model for studying the natural history of adult-onset asthma and examining gene–workplace interactions [1,2]. The genetics of asthma and allergy, current approaches to the analysis of gene–environment interactions, and strategies for examining the aetiology of complex traits have all been examined in books and reviews published in recent years [3,4<sup>•</sup>,5<sup>•</sup>,6<sup>•</sup>,7<sup>•</sup>]. This article will focus on risk factors and on genetic susceptibility in developing sensitization and occupational asthma.

## Risk factors

Most studies of risk factors for occupational asthma are of cross-sectional design. This design has two main disadvantages. The first is that, by examining only a current workforce, the results obtained may reflect the resulting survivor effects; the second is that this method does not distinguish cause from effect or from association.

However, factors increasing the risk of developing occupational asthma – such as level of exposure to a specific sensitizing agent in the workplace, atopy, smoking, rhinitis, and genetic predisposition – have been identified for a number of occupational agents.

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### Exposure to agents in the workplace

In most of the studies on the subject, a positive exposure–response relationship has been demonstrated to exist both for occupational asthma and for sensitization with allergen exposure in the workplace [8–11]. A relationship between occupational asthma and the level of allergen exposure has been demonstrated with colophony, flour allergens, isocyanates, western red cedar, cimetidine, crab, green coffee and castor bean. These studies indicate that the risk of sensitization and occupational asthma is increased by higher exposures to many occupational agents.

### Atopy

Atopy is a condition characterized by the propensity to develop clinical manifestations of IgE-mediated allergy such as eczema, asthma and rhinitis on exposure to common allergens present in the environment. It should be emphasized that conflicting results from different studies on the role of atopy in contributing to occupational asthma could be due to the different methods used to demonstrate its presence, which range from skin prick testing to levels of serum total IgE, to reports of a personal or family history of allergic disease: asthma, hayfever or eczema.

Atopy has been associated with an increased risk of both sensitization and occupational asthma in workers exposed to enzymes, bakery allergens, crab, acid anhydrides, green coffee and castor bean. Most studies reporting a relationship between the risk of being atopic and the development of occupational asthma have investigated disease caused by exposure to high-molecular-weight agents that induce the production of specific IgE [12]. For isocyanates, low-molecular-weight agents (LMWAs), evidence of both an increased risk and of no association between atopy and occupational asthma has been reported. However, patients with western red cedar asthma caused by the LMWA plicatic acid, are mostly non-atopic, and the pathogenic mechanisms responsible for occupational asthma arising from these two LMWAs are almost identical.

### Smoking

As with atopy, conflicting results have been obtained by some studies that examined the role of smoking in the development of occupational asthma induced by exposure to isocyanates. Similarly, inconsistencies between studies have been reported for laboratory animal allergens, acid anhydrides, and detergent enzymes. Smoking increases the risk of occupational asthma in workers exposed to platinum salts, snow crab, and salmon. In summary, the role of cigarette smoking is unclear for asthma caused by most occupational agents [13].

### Rhinitis

An increased interest in the role of rhinitis has been evoked by the epidemiological evidence obtained in

the general population of a strong association between a previous history of either allergic or perennial rhinitis and the development of asthma. Is occupational rhinitis a risk factor for developing occupational asthma? A number of studies have shown that occupational rhinitis and occupational asthma frequently occur as a morbid condition in occupational asthma induced by an IgE mechanism; rhinoconjunctivitis is more likely to occur before the onset of occupational asthma; and the risk of developing occupational asthma is highest in the year after the onset of occupational rhinitis [14•].

In summary, occupational rhinitis is a risk factor for the development of occupational asthma, especially for high-molecular-weight agents.

To date, there have been no studies to determine susceptibility genes in the case of occupational rhinitis. However, for non-occupational allergic rhinitis, a number of genetic studies have been published. It was shown that mRNA expression of PAF acetylhydrolase, a family of enzymes that play different roles in inflammation, is lower in the nasal mucosa of patients with seasonal allergic rhinitis than in healthy participants [15]. The frequencies of two polymorphisms of the RANTES (a chemokine linked to allergic diseases) promoter region (–403 G/A and –28 C/G) were significantly higher in patients with allergic rhinitis than in control participants [16•]. In a German study, it was shown that homozygotes of the G-allele in IL-2-330 T/G were at increased risk of hayfever. In another study performed in Germany on a population of 105 families, the authors found that a single-nucleotide polymorphism (SNP) +127 (g/t) in exon 1 was a susceptibility locus for seasonal allergic rhinitis ( $P = 0.008$ , OR 3.22). In the Chinese population, human leukocyte antigen (HLA) *DQA1* and *DQB1* genes are associated with the development of artemisia pollen-induced allergic rhinitis. HLA *DQA1*\*0201 and *DQB1*\*0602 alleles were protective whereas *DQA1*\*0302 was a susceptible factor for the development of rhinitis. Another interesting observation comes from a study performed in Taiwan [17]. The authors showed that females, but not males, with allergic rhinitis, had a significantly higher frequency of A/A genotype in the cytotoxic T lymphocyte antigen (*CTLA*)-4 (+49) polymorphism than those without atopic disease. No association was found for the IL-4 promoter (–590) polymorphism. This study showed a sex-linked genetic relationship with allergic disease [17•]. In a population-based and cross-sectional study conducted in Finland, the IL-1 gene complex polymorphism was strongly associated with allergic rhinitis in non-asthmatic individuals.

### Sex

There are sex differences in specific occupations and there are sex differences in overall prevalence of adult

asthma, with a high rate in women, but to date, there is no evidence for sex differences in response to the same workplace exposures [18•]. Using data from the Epidemiological study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy, Siroux and co-workers [19•] suggested a correlation between hormone-related events and asthma-related traits. Prostaglandins, via the COX pathways, are important mediators of inflammation in bronchial asthma. A study conducted in Poland on patients with aspirin-induced asthma, showed that the COX-2-765C homozygosity is associated with females, and the CC homozygosity has functional effects resulting in an increased capacity of monocytes to produce prostaglandins [20•]. Recently, in contrast to previous findings, it was shown that methylprednisolone clearance in women was significantly slower than in men. Women were evaluated during the luteal phase of the menstrual cycle [21•].

These preliminary data indicate that sex is likely to be associated with different prevalence of disease and with different pharmacokinetics of drugs used in therapy.

#### Genetic predisposition

Little is known about people's susceptibility to occupational asthma. A previous history of asthma is not significantly associated with occupational disease. An underlying susceptibility to occupational asthma is likely to exist because only a proportion of workers exposed to similar exposures, develop the condition. Susceptibility has also been suggested by the observation that the time course for the development of occupational asthma has the pattern of an epidemic curve, with a median period of about 1 year, consistent with the development of sensitization and asthma in a susceptible population. Most reported genetic studies of occupational asthma have been performed on small sample sizes and, sometimes, the findings have not been replicated and are fragmentary.

Asthma is a multifactorial condition, and the influence of the environment is mainly evident in the determination of multifactorial characteristics. A previous study [7•] emphasized that, in detecting a gene–environment interaction, it is important to measure both the genotype and the environmental risk factor. Moreover, large sample sizes need to be used to detect interactions. Unfortunately, these steps, important for the study of complex diseases, i.e. asthma, are difficult to follow in performing genetic studies on both occupational and non-occupational asthma. However, the field of asthma genetics has advanced considerably in recent years with the cloning of two asthma genes, *ADAM33* and *PHF11*. This has generated new information and interest in the study of gene–gene interaction and in how linkage disequilibrium blocks and haplotypes can be used as functional units to pinpoint mutations and capture the relative risk of mutated genes in complex diseases such as

asthma [22•]. Moreover, asthma is a phenotypically heterogeneous disorder, and the phenotypes of adult-onset asthma are still poorly understood [23•]. In this respect, occupational asthma offers the advantage of defining an accurate phenotype of the disease.

A number of studies have examined the role of genes coding for class II HLA and the development of occupational asthma. HLA class II molecules are highly polymorphic, are encoded by the major histocompatibility complex genes on 6p, and are plausible candidate genes that influence the development of a specific immunological response. Associations of occupational asthma with class II molecules have been demonstrated for isocyanates [24], complex platinum salts, western red cedar, acid anhydrides, laboratory animal proteins and natural rubber latex. Apparent discrepancies between studies on HLA associations with isocyanate-induced asthma may be due to differences in study design and in selection of subjects. In a recent study [25•], it was shown that *DQB1\*501* is particularly frequent in subjects sensitized to organic acid anhydrides, indicating that the *DQB1\*05* gene confers susceptibility to develop specific IgE antibodies against organic acid anhydrides. It is of interest that the *DQB1\*0501* is protective for other LMWAs such as isocyanates and plicatic acid, suggesting that different affinities for the corresponding specific class II molecules may exist [25•]. A recent study [26•] of the association of HLA class II genes with sensitization to and symptoms of rat lipocalin allergens showed that approximately 40% of the participants examined could be attributed to an HLA-DRB1\*07 phenotype, whereas the attributable proportions for atopic status and daily exposure in an animal housing facility were 58 and 74% respectively.

Occupational asthma has been reported among aluminium smelter pot-room workers, even if the mechanisms have not been clarified. A case–control study [27] examined whether polymorphisms were associated with the development of pot-room asthma. Genotyping was performed for the  $\beta$ 2-adrenoreceptor, high affinity IgE receptor, and tumour necrosis factor (TNF), but no associations were found between pot-room asthma case status and genotype.

Indeed, the conclusions are that genetic polymorphisms that code for HLA class II genes may predispose to occupational asthma for a number of agents. Moreover, HLA associations indicate a specific immunologic response in asthma induced by LMWAs.

In isocyanate-induced occupational asthma, the role of a gene coding for class I HLA has also been examined, and no significant associations have been found [28].

Occupational sensitizers may cause oxidative stress, and defects in antioxidant defences could contribute to the

susceptibility to occupational asthma. In isocyanate-induced asthma, a role is played by the  $\mu$ -class of the polymorphic glutathione-S transferase (GST) [29]. More recently, it was shown that homozygosity for the *GSTP1*\**Val* allele confers protection against both asthma induced by exposure to toluene diisocyanate (TDI) and airway hyperresponsiveness (AHR) [30]. This view is supported by the finding that the protective effect is more apparent with increasing duration of exposure. Our data also suggest that the *GSTP1 Ile*<sup>105</sup>-*Val*<sup>105</sup>, rather than the *Ala*<sup>114</sup>-*Val*<sup>114</sup>, substitution mediates the protective effect. Moreover, the association between the *GSTP1* genotype and TDI-induced asthma was independent of atopy, sex, age, and smoking history. The ability to handle reactive oxygen species and their products may be an important independent risk factor in determining development of airway inflammation leading to asthma. This study confirms previous data showing a strong association of *GSTP1* genotypes with asthma and AHR in a cohort of English patients with atopic asthma, in whom the association of the *GSTP1* genotype with asthma and AHR appeared independent of atopic status. Recently, in a Turkish sample of asthmatics, a significant association between *GSTP1 Ile105Val* polymorphism and susceptibility to asthma and a protective role for *GSTP1 Val105* genotype were reported, indicating similarities between reactive oxygen species induced by toluene diisocyanate and non-occupational asthma [31]. The idea that GST genes are critical in the protection of cells from reactive oxygen species, key components of inflammation, is supported by two studies published in 2004. The first [32<sup>•</sup>], performed on asthmatic children living in Mexico City in an area with high ozone exposure, demonstrated that asthmatic children with a genetic deficiency of *GSTM1* may be more susceptible to the deleterious effect of ozone on the small airways. The second [33<sup>••</sup>], a randomized, placebo-controlled crossover study, on the basis that particulate pollution may be associated with the occurrence of asthma and allergy, tested the hypothesis that *GSTM1* and *GSTT1* are key regulators of the adjuvant effects of diesel exhaust particles on allergic responses. In patients sensitive to ragweed allergen, challenged intranasally with the allergen alone and with allergen plus diesel exhaust particles, *GSTM1* and *GSTP1* modified the adjuvant effect of particles on allergic inflammation, with greater effects with both the *GSTM1* null and *GSTP1 I/I* genotypes.

In addition to GST, *N*-acetyltransferase genotypes play a role in occupational asthma. The *N*-acetyltransferase slow acetylator genotypes posed a 7.77-fold risk of TDI asthma [34].

TNF- $\alpha$  A-308G is not associated with susceptibility or resistance to the development of TDI asthma [28].

An attempt to develop a systematic approach to investigate how genetic risk factors interact with the environment to induce or prevent disease was recently made by the Working Group 3 (Sensitivity to Organic Dust-Atopy and Gene polymorphisms) [35<sup>•</sup>]. The workgroup specifically focused on individual sensitivity to inhaled agents. The authors emphasized the importance to identify genetic polymorphisms on the toll-like receptors and other innate immune receptors, as well as downstream signal transduction members. They also suggested caution in developing research plans to identify individual susceptibility to inhaled organic dusts because the frequencies of polymorphisms may vary between populations. Second, when present in low frequencies, polymorphisms have little statistical effect on the prevalence of disease at the population level. As expected, their effects may be difficult to identify in population-based cohort studies.

### Animal models

In a mouse model of isocyanate-induced asthma, TNF- $\alpha$  plays a role because its deficiency abrogates TDI-induced Th2 cytokines in airway response, resulting in a significant reduction in the migration of airway dendritic cells to the draining lymph nodes [36]. In a novel model of asthma induced by hexamethylene diisocyanate (HDI), it was shown that, in contrast to contact hypersensitivity, induction of Th2 responses after epicutaneous exposure to HDI is strongly influenced by genetics. Furthermore, the lung inflammatory response to inhaled HDI depends primarily on the effective generation of CD4<sup>+</sup> Th2 responses, as is the case in atopic asthma [37<sup>•</sup>].

In a murine model of ovalbumin-sensitized allergic rhinitis, by using mice deficient in the gene encoding TNF- $\alpha$ , the authors demonstrated that TNF- $\alpha$  was necessary for antigen-specific IgE production and for the induction of Th2-type cytokines and chemokines, and they concluded that the lack of TNF- $\alpha$  inhibited the development of allergic rhinitis [38<sup>•</sup>].

### Conclusion

There have been few studies examining genetic markers in occupational asthma, and further genetic studies are required to identify these markers and to understand their interactions with the environment. It is essential to continue this approach because occupational asthma is an important and frequent clinical condition and because the identification of individuals who are predisposed to develop the disease may increase the likelihood of preventing its development.

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