

# Allergic rhinitis and association with the O blood group

Clara Carpeggiani

Institute of Clinical Physiology, National  
Research Council – CNR, Pisa, Italy

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## Corresponding author:

Clara Carpeggiani  
Institute of Clinical Physiology  
National Research Council –CNR  
Via Moruzzi 1  
56124 Pisa, Italy  
Phone: 39 050 315 2005  
clara@ifc.cnr.it

[www.rbhh.org](http://www.rbhh.org) or [www.scielo.br/rbhh](http://www.scielo.br/rbhh)

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Affecting about 600 million people worldwide, allergic rhinitis (AR) is an atopic disease that has a significant impact on the quality of life. The prevalence has increased abruptly in recent years in most Western countries. The disease, also known as hay fever or pollinosis, occurs in individuals with a sensitized immune system. The allergen triggers the production of IgE antibodies, which bind to mast cells and basophiles containing inflammatory mediators such as histamine, which are then released into the bloodstream.

This is a complex multifactorial allergic disease with environmental and genetic components. One hypothesis to explain the steep rise in allergic diseases in recent years is the 'hygiene hypothesis': the excessive 'cleanliness' of the environment has led to a decline in the infectious stimuli that are necessary in the development of the immune system. Many other factors have been suggested to play a role in the development and expression of atopic diseases including changes in lifestyle, pollution, dietary changes with diminished nutritive value and stress. The strongest risk factors in the development of allergic symptoms are a family history of allergies, secondhand cigarette smoke exposure and male gender.

The mechanism of inheritance is still unclear. Familial aggregation has been described for many years. It is commonly believed that allergies are caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis with each gene being influenced by the environment in a different way. Twin studies have provided key evidence for a genetic effect as there was a greater concordance of allergic manifestations observed in monozygotic compared to dizygotic twins; the heritability for atopy is estimated to range between 50 and 84% of these twins. Many candidate genes have been suggested in atopy and allergic diseases. The most important linkages include the genes for IL-4, IL-13, HLA-DRB, TNF, LTA, FCER1B, IL-4RA, ADAM33, TCR  $\alpha/\delta$ , PHF11, GPRA, TIM, p40, CD14, DPP10, T-bet, GATA-3, and

FOXP3.<sup>(1)</sup> However, no genome wide association study has been performed specifically for allergic rhinitis.

ABO is the major human blood group system, the distribution of which varies between countries. ABO blood groups are genetically transmitted through locus 9q34 of chromosome 9. The ABO, H, and Lewis histo-blood group antigens are determined by the action of glycosyltransferases that attach sugar molecules to disaccharide precursors on the red blood cells. The addition of fucose to these disaccharide precursors creates the H antigen and further modifications to the H antigen by glycosyltransferases leads to the synthesis of the blood group antigens encoded by the *ABO* gene. The O allele does not produce an active enzyme and has  $\alpha$ -fucose (1  $\rightarrow$  2) galactose disaccharides [O(H) structures] on its cell surface while in type A or B individuals, the O antigen is capped by the addition of  $\alpha$ -N-acetylgalactosamine or  $\alpha$ -galactose residues, respectively. The A and B genes differ in a few single-base substitutions that change four amino-acid residues which may cause differences in A and B transferase specificity. A critical single-base deletion was found in the O gene, which results in an entirely different, inactive protein incapable of modifying the H antigen.

The Lewis blood group is a minor blood group that is related to saliva secretor status. Saliva ABH secretor determination is based on testing for blood group antibodies in saliva. ABH secretors are identified by the secretion of ABO antigens in fluids such as saliva, sweat, tears and breast milk. Almost 15% of people are ABH non-secretors. The secretor gene that encodes for 2-alpha-L-fucosyltransferase and the ABO blood grouping system that encodes for glycosyltransferases, act in concert to build-up oligosaccharide structures in exocrine secretion systems, including the respiratory tract, playing a role in the adhesion of environmental factors to epithelial cells.

Studies evaluating the relationship between ABO blood group status and atopic diseases have appeared in the literature since the late sixties. Apparent discordant results have been reported. In 1964, the observation that ABO agglutinins are present in a wide variety of pollens from grasses, flowers and trees, raised the possibility that these agglutinins might interact with cells containing blood group antigens in the respiratory epithelium, an effect that would be neutralized in secretor patients. In 1968, Denborough was the first to study secretor status in allergic diseases of the respiratory tract comparing 435 subjects with hay fever and asthma and 411 controls. No significant differences in ABO blood group distribution, secretor status and salivary isoagglutinins were detected between patients and controls.<sup>(2)</sup> A recent study by Bijanzadeh of 200 Indian children and adults confirmed these results with no association being found between asthma and any blood group.<sup>(3)</sup>

On the contrary, many other publications reported associations between blood groups and atopic diseases. The major difference in the studies is related to the ABO allele responsible for susceptibility to atopic diseases. Two studies found an association between blood group A and/or B antigens and atopic conditions such as rhinitis, hay fever

and asthma, and the shift appeared to be largely due to a contribution from female patients with pollinosis.<sup>(4)</sup> The majority of the studies reported an association between atopic diseases such as rhinitis and the O group, while resistance was associated to A phenotypes.<sup>(5)</sup> In particular, a higher susceptibility was found for the O group in Lewis-negative or non-secretor children and adults. The results of the paper by Falsarella et al. published in this edition of the *Revista Brasileira de Hematologia e Hemoterapia* are in agreement with previous conclusions and underlines the male gender impact on the association.<sup>(6)</sup>

Glycosyltransferases are controlled by the ABO system to build oligosaccharide structures on the cell surface of erythrocytes and vascular endothelium, as well as in the exocrine secretion system including the respiratory tract. Alpha-2-fucosyltransferases *FUT1* (H) of red blood cells and vascular endothelium, and *FUT2* (Secretor positive) of the exocrine secretion system, are structural genes that collaborate with glycosyltransferases. Studies based on separate analysis of the ABO and Secretor systems have led to discordant results, probably because of the complexity of the interactions between these genes. When a combined analysis of ABO blood groups and secretor phenotypes was performed, a cooperative interaction between the two systems was described. Blood group O/non-secretor subjects had lower lung function values and higher prevalence of atopy. The product of ABO and secretor genes seems also to influence the adhesion of infectious agents, thus having a modulator effect on viral and bacterial respiratory tract infection. Since the oligosaccharide composition of the cell membrane and mucosal secretions change with age and influence the adhesion of infectious agents, the age pattern of atopic diseases could reflect the interaction between cell maturation and oligosaccharide structure and its effect on susceptibility to viral and bacterial agents.

The limited number of patients enrolled in the studies is the biggest limitation of the literature on this issue. More studies with large populations could be helpful to determine the exact function of the involved genes and the gene-environment interaction which could help to better understand the pathology, prevention and treatment of this disease.

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