



Family and twin studies on methacholine hypersensitivity

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Essentially all asthmatics demonstrate a marked sensitivity to inhaled methacholine and histamine, termed non-specific bronchial (airway) hyperresponsiveness (BHR). Airway hyperresponsiveness is a characteristic not only of asthmatics, but can be found in many persons with allergic rhinitis as well as in members of asthmatics' families. The presence of BHR usually precedes the development of clinically identifiable asthma. In recent years there has been an emphasis on inflammation, inducing hyperresponsiveness. However, these factors increase airway hyperresponsiveness by a magnitude of only three-fold compared with normal subjects. The important question is not why asthmatics respond, but why normal subjects do not. The normal subjects are quite able to maintain normal airway function in the presence of high concentrations of methacholine or histamine in vivo but not in vitro, suggesting the presence of protective mechanisms in vivo that are either lacking in, or are less effective in, the asthmatic subjects. There is a strong correlation between the degree of airway hyperresponsiveness and the severity of asthma. In order to determine whether methacholine sensitivity could be used as a potential genetic marker, we studied 750 subjects from 53 asthma families and 26 control families. The best sensitivity and specificity is at 200 breath units. Only 6% of the allergic rhinitis subjects showed a high positive response, but 30% overlapped with asthmatics in that they reacted with 200 breath units or less. There was a group of non-atopic subjects from asthma families who responded by 200 breath units, but there was a significantly lower percentage from normal families. Being from an asthma family is a risk factor in terms of subsequent development of asthma and increased airway reactivity. The parent data suggest that airway reactivity is transmitted to succeeding generations. Studies of twins have revealed that the concordance of asthma is higher in monozygotic than in dizygotic twins, but environmental factors are at least as important as genetic factors. Animal models of asthma comparing genetic strains can provide an important link between airway hyperresponsiveness and the allergic response. The inheritance of asthma fits a polygenetic pattern rather than a single-gene pattern.

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