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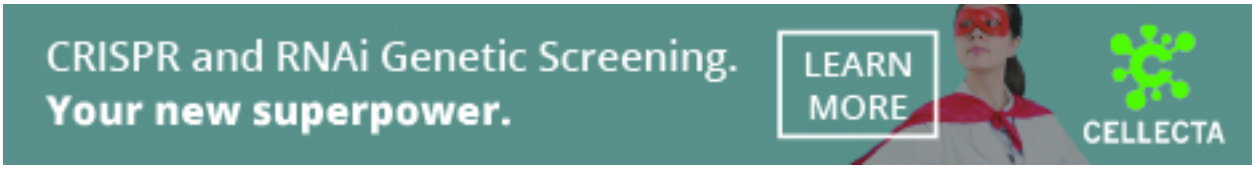

Review

Genomic Approaches to Understanding Asthma

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Asthma is the most common chronic childhood disease in developed nations, and it is a complex disease that has high social and economic costs. Asthma and its associated intermediate phenotypes are under a substantial degree of genetic control. The genetic aetiology of asthma offers a means of better understanding its pathogenesis and, thus, improving preventive strategies, diagnostic tools, and therapies. Considerable effort and expense have been expended in attempts to detect genetic loci contributing to asthma susceptibility, and extensive candidate gene studies and a number of whole-genome screens have been undertaken. This article reviews the current state of knowledge of the genetics of asthma, with a focus on genomic approaches to understanding allergic diseases.

Asthma and eczema are the most serious of the atopic (allergic) diseases. Asthma is the most common chronic childhood disease in developed nations (Asher et al. 1995) and carries a very substantial direct and indirect economic cost worldwide (Lenney 1997). Asthma has become an epidemic, affecting more than 155 million individuals in the developed world. The cost of treating the disease in the United States is approximately US$6 billion per annum (Smith et al. 1997). The worldwide market for asthma medication is currently worth US$5.5 billion per annum to the pharmaceutical industry (Cookson 1999).

It has been widely observed that the prevalence of asthma and other allergic diseases has risen over the past 2 decades in developed nations (Woolcock 1991; McNally et al. 1998). During the same period, the genetic etiology of asthma has been increasingly emphasized as a means of better understanding its pathogenesis, with the ultimate goal of improving preventive strategies, diagnostic tools, and therapies. Considerable effort and expense are currently being expended in attempts to detect genetic loci contributing to asthma susceptibility (Daniels et al. 1996; CSGA 1997; Ober et al. 1998; Wjst et al. 1999). However, many of the questions relating to the genetic epidemiology of asthma and associated factors remain unanswered.

The Genetic Epidemology of Asthma and Associated Traits

Asthma is associated with a number of intermediate phenotypes, including elevation of the total serum IgE and nonspecific airway responsiveness to inhaled spasmogens such as histamine or methacholine. The atopic state underlies most childhood asthma and infantile eczema and is detectable by elevations of the serum IgE and prick-skin-test responses to common allergens (Burrows et al. 1989). A positive family history of asthma and other atopic disorder is one of the strongest risk factors for asthma, increased airways responsiveness, lower respiratory symptoms, and atopy (Sibbald et al. 1980; Dold et al. 1992; Laprise and Boulet 1996; Sears et al. 1996; Jenkins et al. 1997). The age-dependent distribution of atopic disease and associated quantitative traits suggests a reduced penetrance of genetic susceptibility in early and later life. Twin studies have generally shown that concordance rates for asthma are significantly higher in MZ twins than in DZ twins (Hopp et al. 1984; Duffy et al. 1990; Nieminen et al. 1991; Sarafino and Goldfedder 1995), whether reared apart or together (Hanson et al. 1991). Broad-sense heritability estimates derived from twin studies range from 36% (Nieminen et al. 1991) to 75% (Duffy et al. 1990).

The asthma-associated quantitative phenotypes of atopy, elevated blood eosinophil counts, and increased airways responsiveness are also highly heritable. Total serum IgE levels have a heritability of ~ 50%–80% (Grundbacher 1975; Hopp et al. 1984; Blumenthal and Bonini 1990; Hanson et al. 1991; Lawrence et al. 1994). Blood eosinophil counts also exhibit a high degree of familial aggregation (Moro-Furlani and Krieger 1992; Holberg et al. 1999). The aggregation of increased airways responsiveness to cholinergic agents within families has been well documented, suggesting a heritability of 22%–66% (Hopp et al. 1984, 1988; Lawrence et al. 1994; Postma et al. 1995).

Asthma and all of its associated quantitative phenotypes are characterized by heterogeneity. Although the evidence suggests that the commonly measured asthma-associated pathophysiological factors are under some genetic control, the degree of genetic control and the extent to which most of these traits are geneti-

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cally distinct from each other and from asthma is still unclear. Recent studies suggest that serum IgE levels and airways responsiveness to methacholine are genetically distinct (Palmer et al. 2000), with implications for gene discovery programs.

Asthma is a Genetically Complex Disease

Complex genetic diseases do not exhibit classical Mendelian patterns of inheritance and characteristically involve multiple genes that interact in complex ways with multiple environmental factors (Elston 1995). While monogenic cases of atopic disease have been documented (McKusick 1992), such cases are rare, and the majority of atopic asthma is likely to be the result of numerous interacting genetic and environmental factors.

Environmental Modifiers

Environmental factors also play a key role in the pathogenesis of atopic asthma (Ownby 1990), and it is likely that asthma reflects exposure to environmental trigger factors in genetically susceptible individuals. Three primary environmental exposures that lead to airway inflammation and allergic symptoms have been identified (Sporik et al. 1992; Weiss 1994; Martinez 1995; Becker and Chan-Yeung 1998): exposure to common aeroallergens such as the house dust mite, environmental tobacco smoke exposure, and exposure to viral respiratory infections. In susceptible individuals, these exposures may result in disease from early childhood. The strong association with environmental factors that are themselves clustered within families complicates gene discovery in asthma.

Maternal Effects

A further complication of gene discovery in asthma is that many epidemiological studies have suggested that maternal phenotype influences the inheritance of asthma and atopy (Moffatt and Cookson 1998b). The presence of asthma, eczema, elevated serum IgE levels, and skin-prick-test positivity in children have all been accompanied by an increased prevalence of asthma or atopy in mothers (Moffatt and Cookson 1998b). The differential risk of transmission between parents may be fourfold. The mechanism or mechanisms for these parent-of-origin effects are unknown, but possibilities include genomic imprinting or maternal modification of the developing infant's immune system by transmission of immune factors across the placenta or through breast milk. Parent-of-origin effects have been noted in other immunological disorders, most notably type I diabetes (Warram et al. 1984), rheumatoid arthritis (Akolkar et al. 1997), inflammatory bowel disease (Koumantaki et al. 1997), and selective IgA deficiency (Vorehovsky et al. 1999), suggesting that parental effects on the developing infant's immune system may be an important common process modifying genetic diseases that are immunological in origin.

Gene Discovery in Asthma

Two general approaches have been used to investigate the molecular genetics of asthma: candidate gene approaches and whole-genome screens followed by positional cloning attempts. The mapping of human susceptibility loci for asthma is made difficult by a high population frequency, incomplete penetration, phenocopies and genetic heterogeneity, and phenotypic pleiotropy.

The evidence from epidemiological studies of asthma phenotypes strongly suggests substantial genetic heterogeneity, which is likely to operate at the levels of both the genes and the alleles of these genes. Strategies to minimize the effects of genetic heterogeneity in studies of asthma genetics have included the use of large pedigrees (Ober et al. 1998), genetically isolated populations likely to exhibit founder effects (Zamel et al. 1996; Palmer et al. 1997; Ober et al. 1998), and phenotypically homogenous subgroups such as childhood-onset asthma (Hill and Cookson 1996). Importantly, the issue of variability in age of onset has seldom been addressed in genetic studies using a dichotomous asthma phenotype.

The use of intermediate, quantitative phenotypes such as serum IgE levels and measures of airways responsiveness has become widespread in asthma genetics research. Complex variance-components modeling of asthma-associated phenotypic traits has suggested that traits such as serum IgE and airways responsiveness are genetically distinct and should, therefore, be examined separately in genetic studies of asthma (Cookson and Palmer 1998; Palmer et al. 2000). It is also likely that intermediate, asthma-associated quantitative traits will offer more power than will a dichotomous trait reflecting clinical asthma (Risch and Zhang 1995; Cookson and Palmer 1998).

Animal Models

The genetics of asthma- and atopy-associated physiological traits have been studied extensively in inbred strains of experimental animals (Levitt and Mitzner 1988; deWeck et al. 1997). Most studies of inbred strains and backcrosses have suggested strong genetic control of serum IgE levels (Biozzi et al. 1979; Sapin et al. 1984), eosinophil levels (Lammas et al. 1988; Dawkins et al. 1989), and airways responsiveness to cholinergic agents (Levitt and Mitzner 1988; De Sanctis et al. 1995).

Although it is uncertain to what extent these traits and their underlying genetic control correspond to their human counterparts, it seems likely that animal models hold considerable potential for understanding the genetics of asthma and associated disease. Animal

models offer controlled exposure, limited and consistent genetic variation, and unlimited size of sib-ships. A whole-genome screen for airways responsiveness (De Sanctis et al. 1995) in A/J-C57BL/6J-crossed mice identified three potentially linked loci, each mapping near candidate loci implicated in the pathobiology of asthma. In particular, linkage was seen to mouse chromosome 17, near the MHC complex and the TNF genes. A whole-genome screen for several asthma-associated quantitative traits in BP2-BALB/c-crossed mice (Zhang et al. 1999) identified five potentially linked loci. Several loci corresponded to human regions of syntenic homology that previously have shown linkage to asthma-associated traits. These included the cytokine cluster on human chromosome 5, the MHC and TNF genes on human chromosome 6, and the exotaxin and chemokine cluster on human chromosome 17.

Candidate Gene Approaches

The number of biologically plausible candidate genes that might be involved in the determination of asthma and associated traits is very large (Sandford et al. 1996). There is now an extensive and growing list of candidate genes investigated for linkage and association with asthma- and atopy-associated traits in non-genome-screen studies.

A region with extensive evidence of linkage and association is the cytokine cluster within the 5q31 region (Marsh et al. 1994; Meyers et al. 1994; Hay et al. 1995; Rossenwasser et al. 1995; Xu et al. 1995; Palmer et al. 1998). Several associations have been noted between measures of atopy and genes of the cluster, including IL4, IL13, and CD14 (Rosenwasser 1997; Baldini et al. 1999; Graves et al. 2000; Heinzmann et al. 2000). The congregation of cytokine genes in the region may have evolved for their coregulation, and claims for the importance of particular polymorphisms within the cluster should be interpreted in the context of possible linkage disequilibrium with other known or unknown genes. An effect on atopy and serum IgE levels of IL4-Receptor (on chromosome 16) has been recognized (Hershey et al. 1997; Rosa-Rosa et al. 1999; Shirakawa et al. 2000; Takabayashi et al. 2000) and may be stronger than the effects of polymorphism in IL4 itself.

Coding variants within the β-adrenergic receptor have been shown in vitro to be functionally important (Green et al. 1994) and associated with airways responsiveness, although associations with clinical asthma are inconsistent (Reihsaus et al. 1993; Liggett 1995; Martinez et al. 1997; D'Amato et al. 1998; Weir et al. 1998). It remains to be seen if these polymorphisms are important regulators of the response to the commonly prescribed asthma treatment of β-adrenergic agonists. A variant within the 5-lipoxygenase gene has been suggested recently to predict the response to the antileukotriene ABT-761 (Drazen et al. 1999). Confirmation of these findings may mark the beginning of the clinical use of genotyping as an adjunct to pharmacotherapy for asthma and many other disorders.

Polymorphism within the *Fc$_\varepsilon$R1*-β gene on chromosome 11q13 has been related in different studies to atopy (Hill and Cookson 1996), asthma (Shirakawa et al. 1996), bronchial hyperresponsiveness (vanHerwerden et al. 1995), and severe atopic dermatitis (Cox et al. 1998a). Polymorphic markers within this gene have also been associated with levels of IgE in heavily parasitized Australian aborigines, implying a protective role for the gene in helminth infestation (Palmer et al. 1997). Although a few coding changes have been identified within *Fc$_\varepsilon$R1*-β (Shirakawa et al. 1994; Hill and Cookson 1996), they are conservative and do not seem to alter gene function. The functional mechanism for the influence of the gene or nearby gene(s) on atopic disorders has yet to be described.

The human MHC on chromosome 6p, particularly HLA (Freidhoff et al. 1988; Marsh and Huang 1991; Young et al. 1994; Aron et al. 1996) and tumor necrosis factor (TNF) locus polymorphism (Campbell et al. 1995; Moffatt and Cookson 1997), has also been investigated extensively, as has polymorphism in the 12q15-24 region (Barnes et al. 1996; Wilkinson et al. 1996). Other candidate genes investigated include, but are not limited to, the α region of the T-Cell Receptor (TCR) α/δ locus (Moffatt et al. 1994); the α_1-Antitrypsin gene (α_1-AT; Katz et al. 1976; Hyde et al. 1979; Liebermann and Colp 1990); histo-blood-group genetic systems (Kauffmann et al. 1996); the cystic fibrosis gene (ΔF508; Mennie et al. 1995; Schroeder et al. 1995); Gm allotypes of IgG genes (Oxelius 1990); the Ig heavy-chain γ 4 locus (IGHG4; Amoroso et al. 1996); the Clara cell-secretory-protein (CC16) locus (Laing et al. 1998; Mao et al. 1998); the chemokine receptor loci on chromosome 3 (Hall et al. 1999; Syed et al. 1999); and angiotensin-converting enzyme (ACE) gene (Benessiano et al. 1997). A number of these studies have not yet been replicated in independent populations.

Whole-Genome Approaches

A number of whole-genome screens for asthma and atopy phenotypes have now been published (Daniels et al. 1996; CSGA 1997; Cox et al. 1998b; Ober et al. 1998, 1999; Bleecker et al. 1999; Dizier et al. 1999; Wjst 1999; Wjst et al. 1999). All of these studies have used microsatellite markers and have investigated a number of asthma-associated phenotypes. Most have utilized nonparametric sib-pair linkage strategies, with the exception of the studies of Hutterite (Ober et al. 1998) and Dutch (Bleecker et al. 1999) populations, which used semiparametric and parametric methods, respectively. Caucasian populations have generally been

studied (Daniels et al. 1996; Ober et al. 1998; Bleecker et al. 1999; Dizier et al. 1999; Wjst et al. 1999), although the U.S. Collaborative Studies on the Genetics of Asthma (CSGA) study has investigated ethnically diverse populations (Caucasian, Hispanic, African American; CSGA 1997). Three studies have used samples of highly selected affected sib-pairs (CSGA 1997; Dizier et al. 1999; Wjst et al. 1999), one study has been of a sample subselected on the basis of nonconcordant sibships from a population-based sample of families (Daniels et al. 1996), one of a sample selected on the basis of an adult proband with asthma (Bleecker et al. 1999), and one study has been of a genetically isolated founder population (the Hutterites; Ober et al. 1998).

Strategies aimed at minimizing type I (false positive) and type II (false negative) errors in these whole-genome screens for asthma have included the adoption of stringent criteria for significance (including calculation of empirical *P* values; Daniels et al. 1996; Dizier et al. 1999), replication in multiple independent data sets (Daniels et al. 1996; Ober et al. 1998; Dizier et al. 1999), adjustment either analytically or via subject selection for known potential confounders (CSGA 1997), and the use of stringent selection criteria for affected subjects (CSGA 1997; Ober et al. 1998; Dizier et al. 1999; Wjst et al. 1999).

While there are some inconsistencies between the locations of the important linkages found in the genome screens undertaken to date (Daniels et al. 1996; CSGA 1997; Cox et al. 1998b; Ober et al. 1998; Bleecker et al. 1999; Dizier et al. 1999; Wjst et al. 1999), there are also so-called consensus areas of linkage to asthma, atopy, or a related phenotype such as serum IgE levels. These include chromosome 5q (CSGA 1997; Ober et al. 1998; Bleecker et al. 1999; Dizier et al. 1999), chromosome 6p (Daniels et al. 1996; Wjst et al. 1999), chromosome 11q (Daniels et al. 1996; Cox et al. 1998b), and chromosome 12q (CSGA 1997; Ober et al. 1998; Dizier et al. 1999; Wjst et al. 1999). These regions all contain biologically plausible candidate genes, and most have been linked previously to asthma phenotypes in candidate gene studies.

There are a number of limitations and problems with the genome screens for asthma and atopy phenotypes published to date. Sample sizes have generally been modest, and the precise number of sib-pairs analyzed has not always been explicitly stated (CSGA 1997). The relatively small numbers studied would have both tended to limit the power of these genome screens to detect linkage to dichotomous phenotypes ('asthma'; Cookson and Palmer 1998) and to increase the possibility of type I experimental error. The use of an appropriate genome-wide threshold for statistical significance is a contentious area (Lander and Schork 1994; Suarez and Hampe 1994). The use of widely differing thresholds for significance and the use of differing statistical methods in these studies makes it somewhat difficult to compare them. Multipoint linkage is generally likely to be more informative than single-point analysis (Goldgar 1990), although it is also more sensitive to genotyping errors, and only three studies utilized multipoint analysis (CSGA 1997; Bleecker et al. 1999; Wjst et al. 1999). In several of the studies, no replication of putative novel linkages was attempted in independent population samples of similar ethnicity (CSGA 1997; Bleecker et al. 1999; Wjst et al. 1999). Finally, the calculation of empirical *P* values by simulation in order to provide some impression of the plausibility of the results does not appear to have been attempted in several of the studies (CSGA 1997; Ober et al. 1998; Wjst et al. 1999). In one study, only the first 40% of the sample was presented in the initial paper (CSGA 1997). However, when further sib-pairs were analyzed (Cox et al. 1998b), substantially different results were found.

Another problem in interpreting all of the whole-genome screens published to date is that the phenotypic traits examined are highly correlated and many of the markers in each genome screen show evidence of linkage to several traits (Daniels et al. 1996; CSGA 1997; Ober et al. 1998; Wjst et al. 1999); it is thus unclear to what extent the different linkages might reflect differing, trait-specific genes. Further, the assumption that the susceptibility genes for quantitative traits associated with asthma and atopy will be equivalent to the susceptibility genes for asthma and atopy may not necessarily be valid.

There are some interesting overlaps between genome-screen linkages found in whole-genome screens and recent findings regarding monogenic disorders. Both Netherton's syndrome (Chavanas et al. 2000), which involves atopic manifestations, and familial hypereosinophilia (Rioux et al. 1998) localize to chromosome 5q32. Hyper-IgE syndrome has recently been localized to chromosome 4q (Grimbacher et al. 1999). Because single-gene disorders are generally far easier to clone positionally than complex human diseases, it is encouraging that these Mendelian syndromes are associated with phenotypes closely related to asthma. The human major histocompatibility complex (MHC) on chromosome 6p21 is also of particular interest, as many other immune disorders such as rheumatoid arthritis and insulin-dependent diabetes mellitus also exhibit linkage to this region (Charron 1990). While candidate gene studies indicate that it is unlikely that variation in HLA-DR molecules explain these linkages (Moffatt and Cookson 1996), it is likely that one or more susceptibility loci for asthma exist among the many other known genes (>150) in the MHC.

Positional Cloning

The ultimate goal of positional cloning is to identify

sequence variants within the coding or controlling regions of a gene associated with the phenotype of interest. Following genome-wide linkage studies, positional cloning attempts are under way in several groups to isolate susceptibility loci for asthma (Moffatt and Cookson 1998a). The involvement of commercial enterprises in the cloning of such genes has put a premium on secrecy, and it is not clear which loci are currently being chased in industry. However, the chromosome 13 atopy locus and a locus on chromosome 2 near the IL1 cluster are being physically mapped at the moment by our group at the Wellcome Trust Centre for Human Genetics.

New Genomic Approaches to Gene Identification in Asthma

Technological advances such as the generation of single-nucleotide polymorphism (SNP) maps from high-throughput sequencing projects (Schena et al. 1995; Velculescu et al. 1995; Wang et al. 1998; Marth et al. 1999) and the identification of differentially expressed transcripts in normal versus affected tissues (using serial analysis of gene expression [SAGE] or chip-based expression analyses; Johnston 1998; Ryo et al. 1999) may add to the process of gene discovery in asthma research. However, the real efficacy of such non-hypotheses-driven trawling exercises has not yet been established, despite claims to the contrary (Landegren et al. 1998; Cargill et al. 1999).

The growing availability of SNP maps together with the identification of genes associated with the ongoing Human Genome Project (Fields 1997) might make genome-wide association analyses feasible in the future (Risch and Merikangas 1996; Kruglyak 1999). However, tradeoffs in power to detect genetic effects through association rather than linkage (Risch and Merikangas 1996; Kruglyak 1999) are likely to be offset by the need for very large sample sizes and a substantial penalty necessary to correct for multiple comparisons. Further limitations come from the cost of typing the very large number of markers (suggested to be around 500,000 in the general outbred population) required for a genome-wide analysis (Kruglyak 1999) and the uncertain properties of linkage disequilibrium between alleles of tightly linked SNPs across the genome (Terwilliger and Weiss 1998; Moffatt et al. 2000).

Although the pace of technological development in SNP analysis is rapid (Landegren et al. 1998; Kurian et al. 1999), there are many problems with these systems that limit their utility at present, such as the cost and the inherent lack of flexibility in hardwiring markers on a chip. Concomitant statistical advances in the LD mapping of complex traits will also be required (Terwilliger and Weiss 1998; Zhao et al. 1998; Long and Langley 1999).

Although gene expression and SNP mapping pose multiple and serious problems if used in genome-wide strategies, the problems become much more manageable when applied to limited chromosomal regions, such as those already defined by genome-wide screens for genetic linkage. It is therefore quite possible that these new technologies will form a bridge between genetic linkage and gene identification.

Conclusions

Asthma clearly aggregates within families, and many studies have demonstrated evidence of a genetic component to the familial aggregation. The recurrence of asthma in families is suggestive of a multifactorial etiology. The evidence suggests that some of the intermediate phenotypes associated with asthma (in particular the serum IgE) are caused by an oligogenic background modified by strong environmental factors.

Despite much progress in defining the genetic basis of asthma and atopy in the last decade, further research is required. In particular, flexible general methods for handling phenotypic complexity have yet to be developed, and genetic localization of most asthma susceptibility loci is still insufficiently precise for the positional cloning of new genes influencing the disease. However, a number of groups are currently active in addressing methodological problems in phenotypic assessment and technological advances in positional cloning attempts using fine mapping techniques.

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