Review

Using single nucleotide polymorphisms as a means to understanding the pathophysiology of asthma

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Abstract

Asthma is the most common chronic childhood disease in the developed nations, and is a complex disease that has high social and economic costs. Studies of the genetic etiology of asthma offer a way of improving our understanding of its pathogenesis, with the goal of improving preventive strategies, diagnostic tools, and therapies. Considerable effort and expense have been expended in attempts to detect specific polymorphisms in genetic loci contributing to asthma susceptibility. Concomitantly, the technology for detecting single nucleotide polymorphisms (SNPs) has undergone rapid development, extensive catalogues of SNPs across the genome have been constructed, and SNPs have been increasingly used as a method of investigating the genetic etiology of complex human diseases. This paper reviews both current and potential future contributions of SNPs to our understanding of asthma pathophysiology.

Keywords: association studies, asthma, genetics, review, SNP

Introduction

Asthma is the most serious of the atopic diseases. It is the most common chronic childhood disease in developed nations [1] and carries a very substantial direct and indirect economic cost worldwide [2]. Asthma has become an epidemic, affecting more than 155 million individuals in the developed world. The cost of treating the disease in the USA approximates US$6 billion dollars a year [3]. The worldwide market for asthma medication is currently worth US$5.5 billion a year to the pharmaceutical industry [4].

Asthma is a genetically complex disease that is associated with the familial syndrome of atopy and increased levels of total serum IgE [5,6]. Asthma and atopy are also closely associated with increased nonspecific responsiveness of airways to spasmogens [7,8] and elevated blood eosinophil counts [9,10]. These intermediate physiological phenotypes are themselves highly heritable and are the subject of much research into the genetics of asthma [11,12].

The prevalence of asthma and other allergic diseases has risen over the past two decades in developed nations [13,14]. During the same period, the genetic etiology of asthma has been increasingly emphasized as a method of improving our understanding of its pathogenesis, with the ultimate goal of improving preventive strategies, diagnostic tools, and therapies [12,15]. Considerable effort and expense are currently being expended in attempts to detect genetic loci contributing to asthma susceptibility [16–19]. Concomitant technical developments in molecular genetics and in the use of polymorphisms derived

IL = interleukin; OR = odds ratio; RFLP = restriction fragment length polymorphism; SNPs = single nucleotide polymorphisms.

directly from DNA sequence have occurred, and extensive catalogues of DNA sequence variants across the human genome have begun to be constructed. This review summarizes current and potential future contributions of one type of DNA sequence variant, single nucleotide polymorphisms (SNPs), to our understanding of asthma pathophysiology.

Gene discovery with SNPs: the state of the art

Two types of study have been widely employed in an attempt to identify genetic determinants of complex diseases: positional cloning and candidate gene association studies. Positional cloning begins with the identification of a chromosomal region that is transmitted within families along with the disease phenotype of interest. This phenomenon is described as genetic linkage. Positional cloning has been extremely useful in the identification of genes responsible for diseases with simple Mendelian inheritance, such as cystic fibrosis [20]. The application of linkage analysis to complex disorders without obvious Mendelian inheritance such as asthma has been much less successful so far, because complex diseases tend to be influenced by genetic heterogeneity, environmental phenocopies, incomplete penetrance, genotype–environment interactions, and multilocus effects [12,21].

Association studies rely on the detection of polymorphisms in candidate genes and on the demonstration that particular alleles are associated with one or more phenotypic traits. However, analyses of specific alleles suggesting a statistical association between an allele and a phenotypic trait are due to one of three situations [22]: first, the finding could be due to chance or artefact, such as confounding or selection bias; second, the allele might be in linkage disequilibrium with an allele at another locus that directly affects the expression of the phenotype; third, the allele itself might be functional and directly affect the expression of the phenotype.

The biological principle underlying the association analysis of polymorphisms not directly involved in disease pathogenesis is that of linkage disequilibrium (the second situation above). Linkage disequilibrium arises from the co-inheritance of alleles at loci that are in close physical proximity on an individual chromosome. Alleles at different loci that are in linkage disequilibrium on a particular chromosome form distinct haplotypes. Haplotypes with a greater frequency than would be expected from random association can arise by population admixture, natural selection, genetic drift, or new mutation combined with population 'bottlenecks' [23].

Genetic polymorphism

Initial studies of polymorphism in human genetics relied on the study of physiological and biochemical variation (eg blood group antigens) that follow indirectly from variation in DNA sequence. The widespread availability of human DNA sequence data now means that DNA variants can be detected directly and related to disease phenotype. Importantly, most polymorphism is likely not to alter gene structure or function in any way and might therefore not be directly associated with any change in phenotype [24]. Tests of genetic association using SNPs are therefore based largely on linkage disequilibrium. Problems arise from the now well-described general limitations of investigating genotype–phenotype associations in complex human diseases involving multiple interacting genetic and environmental factors [25,26].

Genetic polymorphism arises from mutation. Different classes of polymorphism are generally named on the basis of the type of mutation from which they result. The simplest class of polymorphism derives from a single base mutation that substitutes one nucleotide for another. Recently, such polymorphism has been called a single nucleotide polymorphism, or SNP. It is important to realize that previous nomenclature was based on the method used to detect a particular SNP. For instance, SNPs detected via the identification of restriction enzyme sites were called 'restriction fragment length polymorphisms' (RFLPs) [27].

In addition to RFLPs, other types of SNP that do not create or destroy a restriction site are detectable by creating restriction sites via primer design in the polymerase chain reaction, by oligonucleotide probing, or by direct sequencing [28]. The frequency of SNPs across the human genome is higher than for any other type of polymorphism (such as repeat sequences or insertion/deletion polymorphisms) [29]. Precise estimates of SNP frequency are difficult to determine and often vary across different populations and genomic regions.

Although linkage analysis can in theory use SNPs, almost all linkage analyses undertaken so far for asthma and other complex human diseases have used variable numbers of tandem repeat polymorphisms ('microsatellites') with a large number of alleles (that is, repeat lengths). SNPs have not yet been used more extensively in linkage analyses because they contain a relatively low level of information in comparison with microsatellite markers. In addition, the expense of genotyping the larger number of SNPs required to give equivalent or better genome-wide statistical power as a panel of microsatellite markers is high, and there remain unresolved issues relating to appropriate statistical analysis.

Unfortunately, linkage analysis and the use of maps designed for linkage analysis studies have not proved powerful enough to detect genes influencing many common multifactorial diseases. This is largely because linkage analysis lacks the power to detect genes with

small to moderate effects [25,30]. One of the limitations of linkage analysis is the difficulty of fine mapping the location of a gene influencing a complex disorder. There are not usually sufficient meioses within 1–2 megabases of the disease gene to detect recombination events; moreover, with the effects of phenocopies and genetic heterogeneity in complex diseases, critical recombination events might not be identified with certainty. The growing recognition of the limitations of linkage analysis in complex human diseases has seen a shift in emphasis away from linkage analysis and microsatellite markers towards SNP genotyping and different analytical strategies based on association and haplotype analysis [31–34]. Association analyses are now recognized as being essential for localizing susceptibility loci, and they are intrinsically more powerful than linkage analyses in detecting weak genetic effects [35].

Discovery and genotyping of SNPs

The past decade has seen an increase in molecular genetic technologies that can potentially be used to understand the biological basis of asthma. The generation of SNP maps from high-throughput sequencing projects [28,29,36,37] might add to the process of gene discovery in asthma research. The process of SNP discovery in the human genome has been the subject of considerable interest in recent years and is increasing exponentially [32,33,38–41]. In addition to large government-sponsored projects in the UK (such as http://www.sanger.ac.uk/), the USA [42], and Japan [43], there are now several major industrial group efforts [44,45], a large academic–industry consortium effort [46], and a number of smaller academic programs (such as http://pga.bwh.harvard.edu/) devoted to large-scale SNP discovery. The current focus is thus on SNP discovery, leading to the creation of SNP catalogues, and on improving technologies for SNP genotyping. However, the exact applications and ultimate utility of SNP catalogues and technologies to complex disease genetics remain unclear. The real efficacy of non-hypothesis-driven trawling exercises such as these has not been established, despite claims to the contrary [47,48].

Although the pace of technological development in SNP analysis is rapid [48,49], using microarray and other technologies [50], there are many technical problems with these systems that limit their utility at present, such as cost and the inherent lack of flexibility in hardwiring markers on a chip. The detection of Mendelian genotyping inconsistencies with biallelic markers might also be an issue [51].

SNP analysis and complex human disease

There are several potential advantages to using SNPs to investigate the genetic determinants of complex human diseases in comparison with other types of genetic polymorphism [42,52]. First, SNPs are plentiful throughout the human genome, being found in exons, introns, promotors, enhancers, and intergenic regions, allowing them to be used as markers in dense positional cloning investigations with the use of both randomly distributed markers and markers clustered within genes [52,53]. Furthermore, the abundance of SNPs makes it likely that alleles at some of these polymorphisms are themselves functional [54,55]. Second, groups of adjacent SNPs might exhibit patterns of linkage disequilibrium and haplotypic diversity that could be used to enhance gene mapping [56] and that might highlight recombination 'hot-spots' [57]. Third, inter-population differences in SNP frequencies might be used in population-based genetic studies [58,59]. Last, there is good evidence that SNPs are less mutable than other types of polymorphism [60,61]. The resultant greater stability might permit more consistent estimates of linkage disequilibrium and genotype–phenotype associations. There is mounting evidence that biallelic SNPs are more powerful and more accurate than microsatellite markers in association-based analysis [62].

However, there remain several serious limitations to the use of SNPs in investigations of complex disease genetics. Some of these relate to technical issues in SNP genotyping referred to above. More fundamentally, the growing focus on SNP genotyping has made it clear that concomitant statistical advances in the linkage disequilibrium mapping of complex traits will also be required [63–65]. The SNP genotyping effort has caused a broad re-examination of mapping methodologies and study designs in complex human disease [21,23,25]. The testing of large numbers of SNPs for association with one or more traits raises important statistical issues about the appropriate false positive rate of the tests and the level of statistical significance to be adopted given the multiple testing involved [25]. The required methodological development in genetic statistics is non-trivial given the complexity of common diseases such as asthma. Current areas of methodological development include haplotyping [66–68], distance-based mapping measures [69,70], combined linkage and association analyses [71], techniques for modelling linkage disequilibrium and population history [66], and approaches based on Monte Carlo Markov Chains [72].

SNPs and asthma susceptibility

There are six primary areas of potential application for SNP technologies in improving our understanding of asthma pathophysiology: gene discovery and mapping; association-based candidate polymorphism testing; pharmacogenetics; diagnostics and risk profiling; prediction of response to non-pharmacological environmental factors; and homogeneity testing and design of epidemiological studies [32]. Although only a few of these areas are currently areas of active research in asthma genetics, it is likely that some of them might become relevant to investigations of the genetic susceptibility to asthma.

Gene discovery and mapping: animal models

The genetics of physiological traits associated with asthma and atopy have been studied extensively in inbred strains of experimental animals [73,74]. Most studies of inbred strains and backcrosses have suggested strong genetic control of serum IgE levels [75,76], eosinophil levels [77,78], and the responsiveness of airways to cholinergic agents [74,79].

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 sibships. SNPs are more informative in animal models than in humans because biallelic markers are fully informative in analysing crosses between inbred strains. So far, genetic research with animal models of asthma has focused on linkage analysis with microsatellite markers [79,80]; only recently have SNPs begun to be genotyped within candidate loci [81]. However, large-scale SNP discovery projects in the mouse are under way [82], and it can be expected that SNP-based projects in experimental animal models will have a larger role in asthma genetics.

Gene discovery and mapping: whole-genome screens in humans

After genome-wide linkage studies, positional cloning attempts are under way in several groups to isolate susceptibility loci for asthma [83]. 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 sought by industry. The chromosome 13 atopy locus and a locus on chromosome 2 near the interleukin (IL)-1 cluster are being physically mapped at present by our group at the Wellcome Trust Centre for Human Genetics. However, whole-genome screens have yet to result in the discovery of a functional mutation affecting asthma susceptibility and will not be considered further in this review.

The growing density of SNP maps, together with the identification of genes associated with the Human Genome Project [84], might make genome-wide association analyses feasible in future [25,85]. However, trade-offs in power to detect genetic effects through association rather than linkage [25,85] 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 association analysis [85] and the uncertain properties of linkage disequilibrium between alleles of tightly linked SNPs across the genome [63,86].

Although SNP mapping poses multiple and serious problems if used in genome-wide strategies, these problems become much more tractable 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.

Candidate gene polymorphism testing in humans

Linkage disequilibrium mapping relies on genotype–phenotype associations at the level of population [87] and requires a dense map of markers [25]. Linkage disequilibrium mapping can also be enhanced by haplotype analysis; although haplotype analysis in practice has proved difficult [67], it is likely to be more powerful than focusing on a single SNP locus.

Several useful SNP databases are available on the World Wide Web (see Table 1); these databases are constantly updated and are growing rapidly. However, the data contained in them are far from infallible and as yet there has been no systematic review of the accuracy of the results, an indeterminate proportion of which will be due to sequencing errors. Limitations related to cost and the current incomplete status of SNP databases has meant that the association analysis of SNPs in asthma genetics has so far been limited to polymorphisms within biologically plausible candidate loci.

The number of biologically plausible candidate genes that might be involved in the determination of asthma and associated traits is very large [11,12]. There is now an extensive and growing list of candidate genes investigated with regard to traits associated with asthma and atopy.

The most investigated candidate location for atopy and asthma susceptibility loci has been the 5q31–33 region [88–90], because it contains a large number of important candidate genes [91] including the genes for the cytokines IL-4, IL-5, IL-9, IL-13, and their receptors. Other candidate genes in this region include those encoding granulocyte/macrophage colony-stimulating factor (GM-CSF), fibroblast growth factor acidic (FGFA), and β_2-adrenergic receptor. Coding variants within the β-adrenergic receptor have been shown *in vitro* to be functionally important [92,93] and associated with the responsiveness of airways, although associations with clinical asthma are inconsistent [94–98]. SNPs within the β-adrenergic receptors are the subject of growing interest in pharmacogenetic studies of asthma (see 'Pharmacogenetics' below). Several other associations have been noted between measures of atopy and genes of the cluster, including IL-4, IL-13, and CD14 [99–102]. The congregation of cytokine genes in the region might have evolved for their co-regulation, and claims for the importance of particular polymorphisms within the cluster should be interpreted in the context of possible linkage disequilib-

Table 1

Selected web sites

Title	Web address
dbSNP Polymorphism Repository	http://www.ncbi.nlm.nih.gov/SNP/
GeneSNPs	http://www.genome.utah.edu/genesnps/
Genetic Annotation Initiative	http://cgap.nci.nih.gov/GAI/
HGBase	http://hgbase.cgr.ki.se/
HUGO Mutation Database Initiative	http://ariel.ucs.unimelb.edu.au:80/~cotton/mdi.htm
Human SNP Database	http://www-genome.wi.mit.edu/SNP/human/index.html
SNP Consortium Database	http://snp.cshl.org/
The Sanger Centre	http://www.sanger.ac.uk/

rium with other known or unknown genes. Polymorphism of the IL-4 receptor (whose gene is found on chromosome 16) has a recognized effect on both atopy and serum IgE levels [103–106], and this might be stronger than the effects of polymorphism in the IL-4 gene itself.

SNPs within the FcεR1-β gene on chromosome 11q13 have been related in different studies to atopy [107], asthma [108], bronchial hyperresponsiveness [109], and severe atopic dermatitis [110]. SNPs within this gene have also been associated with levels of total IgE in heavily parasitized Australian aborigines, implying a protective role for the gene in infestation with helminths [111]. Although a few coding changes have been identified within FcεR1-β [107,112], 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 [113–116] and tumour necrosis factor (TNF) locus polymorphism [117,118], has also been extensively investigated, as has polymorphism in the 12q15–24 region [119,120]. SNPs in other candidate genes that have been investigated include, but are not limited to, the following: the α region of the T-cell receptor (TCR) α/δ locus [121], the α_1-antitrypsin gene (α_1-AT) [122–124], histo-blood-group genetic systems [125], the cystic fibrosis gene (ΔF508) [126,127], Gm allotypes of IgG genes [128], the Ig heavy chain γ 4 locus (IGHG4) [129], the Clara cell secretory protein (CC16) locus [130,131], the chemokine receptor loci on chromosome 3 [132,133], and the gene encoding angiotensin-converting enzyme (ACE) [134]. A number of these SNP association studies have not yet been replicated in independent populations.

Pharmacogenetics

An expanding area of interest in the application of SNPs to investigations of asthma pathophysiology is the stratification of populations by their genetically determined response to therapeutic drugs ('pharmacogenetics'). Ideally, we would be able to stratify a population into responders, nonresponders, and those with adverse side effects [135]. The ultimate goal of such stratification would be to improve the efficacy of drug-based interventions and to expedite targeted drug discovery and development. Pharmacogenetic initiatives are currently an area of very active research in complex human diseases [136–140]. However, the frequency and penetrance of a gene affecting responsiveness to a particular drug and potential interactions with other genetic and environmental factors must ultimately be assessed in multiple population-based samples. This is particularly important for extrapolation from specific clinical trials to general clinical use in the highly admixed, heterogeneous industrialized populations where asthma is most common [141,142].

Current research in asthma pharmacogenetics has highlighted associations between SNPs in the genes of β-adrenergic receptors and modified response to regular inhaled β-agonist treatments (such as albuterol) [93,140,143, 144]. A variant within the gene encoding 5-lipoxygenase has been suggested to predict the response to the anti-leukotriene ABT-761 in asthmatic subjects [55]. Other work has found associations between a SNP in the histamine *N*-methyltransferase (HNMT) gene and asthma, and speculated that genetically determined differences in histamine metabolism might contribute to the response to therapy in asthma [145]. Confirmation of these findings could mark the beginning of the clinical use of genotyping at an individual level as an adjunct to pharmacotherapy for asthma and many other disorders.

Statistical power

Growing experience with complex disease genetics has made clear the need to restrict the type I error in genetic studies [31,65,146]. Power is especially an issue for SNP-based association studies of susceptibility loci for

Table 2

Sample size requirements for case–control analyses of single nucleotide polymorphisms

	Dominant model			Recessive model		
	Exposure (%)	No. of cases required		Exposure (%)	No. of cases required	
Allele frequency (%)		α=0.05	α=0.005		α=0.05	α=0.005
10	19	430	711	1	6113	10,070
20	36	311	516	4	1,600	2,637
30	51	308	512	9	769	1,269
40	64	354	590	16	485	802
50	75	456	762	25	363	602
60	84	661	1,107	36	311	516

There were two controls per case; a detectable difference of OR is 1.5 or more; power = 80%. The allele frequencies shown are those in controls. Exposure (that is, prevalence) is that in controls assuming a diallelic locus with a dominant or recessive allele at Hardy–Weinberg equilibrium. In the dominant model, estimates are for an OR of 1.5 between cases and controls for the possession of at least one copy of disease-associated SNP by case; in the recessive model, estimates are for an OR of 1.5 between cases and controls for the possession of two copies of disease-associated SNP by case.

phenomena such as the response to pharmacological therapy, which are extremely heterogeneous and are likely to involve genes with a small individual effect.

Table 2 shows some simple estimates of required sample sizes of cases needed to detect a true odds ratio (OR) of 1.5 with 80% power and type I error probability (α) of either 0.05 or 0.005. Power calculations assumed that there were two controls for each case and a SNP that operated as though it were a simple binary factor to which a proportion of the population was exposed in a manner directly related to the genotypic frequency (eg for 19% exposure, equivalent to a dominant allele at Hardy–Weinberg equilibrium with a prevalence of 10%).

Table 2 shows that even for the best case, a common SNP acting in a dominant fashion, a relatively large sample size of more than 300 cases (a total sample size of more than 900 subjects) is required at an α of 0.05. Multiple testing issues are likely to be an issue in many genetic association studies of candidate loci where either multiple SNPs in one gene, multiple SNPs in several loci, or both, are tested [147], suggesting that an α of 0.005 is probably more realistic than an α of 0.05. Use of the more realistic α of 0.005, or assuming an uncommon SNP that acts in a recessive fashion, leads to the need for very large (in some cases logistically improbable) sample sizes.

Finally, Table 2 assumes an effect size (OR = 1.5) that, in the context of a common, multifactorial disease such as asthma, might be quite large. Assuming a smaller effect might be more realistic for many genes and would lead to concomitantly higher required sample sizes. Simulation studies have also suggested that genes of small effect are not likely to be detectable by association studies in sample sizes of less than 500 [65].

These power calculations are simple, because true power to detect functional association and linkage disequilibrium might depend on the prevalence of the mutant allele, the recombination fraction between mutant allele and marker, the size of the effect of the mutant allele on the phenotype, the type of study population, and the penetrances of the functional locus genotypes [23]. Furthermore, the power calculations are based only on a single SNP–disease association analysis of a binary outcome; both multilocus SNP analysis (including haplotype analysis) and the analysis of quantitative traits should be uniformly more powerful [69,70]. However, even these simple calculations make it clear that the sample sizes used in many small-scale case–control studies of the association of candidate genes may well have had insufficient power to detect even quite a large effect of a SNP. This suggests that larger-scale studies than those currently being performed by many groups will be needed in future.

Future directions

Diagnostics and risk profiling

After the identification of a SNP or SNP-based haplotype that is closely associated with a disease or associated trait, it might be possible to use this information to develop diagnostic tests. The ability to determine the risk of disease before the onset of symptoms would be potentially of great benefit in asthma. The understanding of asthma pathophysiology might then enter the realm of clinical and population genetics. As for all diagnostic genetic tests, the utility and ultimate success of diagnostic testing for asthma susceptibility by using SNPs in a particular

population would depend on the following: the extent and nature of disease heterogeneity; the frequency of the high-risk allele and the concomitant attributable risk; the penetrance of a specific allele; and the ability to define a useful risk model including other genetic factors, important environmental risk factors, and interactions between the SNP and factors such as age and gender [32,148]. In addition, there are both technical problems with routine genetic testing, largely related to false negatives, and important ethical and psychosocial concerns that remain unresolved [148–150]. However, it is clear that very large, longitudinal, well-characterized cohort studies originally established for epidemiological purposes, such as the Nurses' Health Study [151] and the Busselton Health Study [152], will be critical to the future success of any diagnostic SNP-based tests.

Gene–environment interaction

In addition to pharmacogenetic applications, the identification of groups of individuals likely to be affected by other environmental exposures owing to their genetic susceptibility might also be beneficial to our future understanding and treatment of asthma. Examples of potentially important environmental factors that might interact with underlying genetic susceptibilities include exposure to cigarette smoke, exposure and sensitization to common inhalant aero-allergens, exposure to viral infections, housing and lifestyle factors, *in utero* factors acting during pregnancy, and diet [4,153–158]. Prediction of response to these environmental factors in individuals genetically predisposed to asthma is potentially of major significance to public health and health economics [4]. The incorporation of genotype, probably based on SNPs, into initiatives in public health could become an increasingly important factor in preventive medicine.

Homogeneity testing and study design

Genetic heterogeneity is a major issue complicating gene discovery in asthma [12]. Strategies to minimize genetic heterogeneity in studies of asthma genetics have included the use of large pedigrees, genetically isolated populations likely to exhibit founder effects, and the division of study populations into phenotypically homogenous subgroups. A further strategy for maximizing homogeneity, at present not feasible for asthma or most other complex diseases, is the division of a study population into genetically homogenous groups on the basis of previously defined susceptibility loci [159]. Random panels of SNPs could be used to partition study populations into genetically homogenous groups. Heterogeneity testing can be used to test explicitly for population stratification in association analyses [160] and to assess the potential generalizability of SNP–phenotype associations. In addition to variation in allele frequencies, there is also a high degree of variation in linkage disequilibrium strength between populations of different origins [161] and also between different genomic regions [162,163].

As SNP-associated pharmacogenetic, diagnostic, and gene–environment effects are discovered and used to further our understanding of asthma pathophysiology, the study of genetic heterogeneity will become increasingly important. This is particularly so as the current major markets for asthma therapeutics are industrialized nations such as the USA, western Europe, and Australia [2], all of which have substantially and increasingly admixed populations.

Conclusions

The technology for SNPs has undergone rapid development, extensive catalogues of SNPs across the genome have been constructed, and SNPs have been used increasingly as a method of investigating the genetic etiology of complex human diseases. The potential areas of application for SNP technology in improving our understanding of asthma pathophysiology include gene discovery and mapping, association-based candidate polymorphism testing, pharmacogenetics, diagnostics and risk profiling, the prediction of response to non-pharmacological environmental stimuli, and homogeneity testing and epidemiological study design. Although only the first three of these are currently areas of active research in asthma genetics, it is likely that they will all become increasingly important in investigations of genetic susceptibility to asthma. There are technical, statistical, ethical, and psychosocial issues that remain unresolved in the use of SNP technology to investigate these aspects of asthma pathophysiology.

Genetic approaches to asthma offer great potential to improve our understanding of the pathophysiology of this disorder, but they also offer significant challenges. Despite much progress in defining the genetic basis of asthma and atopy in the last decade, accompanied by rapid technical progress in SNP genotyping technologies, further research is required. In particular, genetic localization of most asthma susceptibility loci is still insufficiently precise for the positional cloning of new genes influencing the disease. However, many groups are currently active in addressing methodological problems in SNP genotyping and genetic statistics, and technological advances in positional cloning and candidate loci linkage-disequilibrium mapping techniques with the use of SNPs will probably accelerate our understanding of the pathophysiology of asthma.

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