Commentary

Genetic basis of asthma

Asthma is a chronic, inflammatory disease which affects individuals of all age groups. Most commonly, it is seen in children and young adults. The prevalence of asthma in India has been variably reported in the past. The two recent studies report the prevalence of about two per cent in the general population. The Indian Study on Epidemiology of Asthma, Respiratory symptoms and Chronic bronchitis (INSEARCH) employed a cross-sectional survey design using a standardized, validated questionnaire for interviewing a population sample of 169575 individuals selected in a randomized fashion at 12 different centres across India. In the second study, the investigators used the data from India’s third National Family Health Survey (NFHS-3; 2005-2006) and reported the prevalence of self-reported asthma. The prevalence in children is generally reported to be higher.

Multiple risk factors, both genetic and environmental are important in the aetiology of asthma. Exposure to different allergens (such as the pollens, house-dust mites), micro-organisms, chemicals, vapours, fumes and dusts can precipitate asthma, but cannot alone be blamed to cause asthma. On the other hand, asthma is not a pure genetic disorder. It arises de novo in a large number of patients without the presence of any family history. Presumably, the environmental exposures produce asthma in the genetically susceptible individuals.

Genetic susceptibility

About half of the patients of asthma have genetic susceptibility. Presence of a family history of asthma and/or other atopies in a large population of patients accounts for an important evidence in favour of genetic basis of asthma. As an example, there was an odds ratio of 8.82 (95% confidence intervals of 8.11-9.59) for the family history in the INSEARCH study. Similarly, the presence of other atopies in the family members of asthmatic individuals was higher. In spite of the evidence for genetic susceptibility, it has not been possible to clearly define the genetic abnormalities. Asthma is a heterogenous disorder which manifests with different manifestations and types, often referred to as asthma-phenotypes. It has been difficult to have a single definition of asthma which accounts for its varied aetiology, pathophysiology, and clinical types such as atopy, bronchial hyper-responsiveness, asymptomatic asthma, brittle and near-fatal asthma, etc. It is also likely that the genetic basis of asthma is different for different phenotypes.

Different methods which include familial aggregation and twin studies, segregation analysis, linkage studies, candidate-gene association studies and functional genomics have been used to study the genetic susceptibility. With the help of positional cloning in various studies, several asthma genes or gene complexes have been identified. Some of the identified gene complexes include the ADAM 33, PHF11, DPP10, GRPA and SPINK5. Linkage to multiple chromosomal regions, especially the ‘replicated’ regions which include chromosome 5q, 6p, 11q, 12q and 13q has been reported in different studies.

Genetic studies have also been helpful to know of the increased risk of disease from the presence of a susceptible allele or a ‘severity’ allele through candidate gene association studies. For example, the homozygous individuals for Gly16 are shown to have more severe corticosteroid dependent asthma. On the other hand, the genetic polymorphisms can also be used for disease classification and prospective therapies. A large number of polymorphisms have
been described for asthma, but these are not helpful for clinical classification. Several of the studies have described different single nucleotide polymorphisms (SNP) or other genetic abnormalities.\textsuperscript{10-12}

**Single nucleotide polymorphisms**

Single nucleotide polymorphisms (SNPs) constitute the most common type of genetic variations which occur normally throughout an individual’s DNA. There are about 10 million SNPs in the human genome.\textsuperscript{13} SNPs have been used as high resolution markers in genome-wide association studies. A particular SNP may be associated with a specific phenotype of a disease, such as asthma. In this issue Davoodi and colleagues\textsuperscript{14} report a possible association of genetic distribution of C-589T and C-33T SNPs of \textit{IL-4} with asthma in Indian adults. This is an important addition in the scarce literature on the subject from India. One has to be however, cautious in the interpretation of isolated reports. It is important to have larger, population based studies for any meaningful conclusions on the presence of asthma polymorphisms in India. Even more difficult is to assign the susceptibility role and clinical associations to these results.

One finds a large number of cytokine and other polymorphisms described in asthma with the help of genome-wide linkage and candidate gene studies with the purpose to identify asthma-susceptibility genes.\textsuperscript{15,16} There are a large number of consortia which provide a huge amount of data from large, genome-wide association studies.\textsuperscript{16} In spite of all the information which has become available, it is yet not possible to identify the inheritability or genetic mechanisms of pathogenesis of asthma.

Most of earlier studies emanated from the Western hemisphere which described the genetic polymorphism in the Western populations. Data have now become available from different Asian countries including India.\textsuperscript{17-20} Most of these studies focus on polymorphisms of interleukin-4 (IL-4) which is one of the most important cytokines involved in various allergic disorders and asthma. Polymorphisms of \textit{IL-4} and \textit{IL-13} are commonly described in association with asthma in these reports.\textsuperscript{15-20} We described a protective role against asthma for \textit{IL-8} – 137G/C polymorphisms.\textsuperscript{21} Some of these reports have also described polymorphisms of several other genes such as tumour necrosis factor alpha (\textit{TNF-\alpha}), transforming growth factor beta1 (\textit{TGF-\beta1}), \textit{ADAM33}, \textit{IL12B}, \textit{IL17A} and \textit{IL17F}.\textsuperscript{22-25}

The genome-wide association studies are important to identify genetic risk factors for a greater insight in our understanding of disease mechanisms and predisposition to a particular asthma phenotype. More importantly, these may throw light on the role of genetic development \textit{vis-a-vis} environmental exposures which influence the disease manifestation.\textsuperscript{27-29} These studies may unfold the foetal programming which determines the relative contribution of maternal environmental exposures such as \textit{in-utero} tobacco smoke, vitamin D and folate, etc.\textsuperscript{29}

**SNP based treatment**

Another significant role which is being increasingly assigned to SNPs is to determine the type of response to a particular therapy (\textit{i.e.} personalized medicine). Such an approach is widely used for treatment protocols for several types of cancers, such as the lung adenocarcinoma.\textsuperscript{30} In asthma, the polymorphisms may predict the response to oral and/or inhalational treatments especially the inhaled beta agonist bronchodilators and corticosteroids. As an example, the common arginine-16 variants in the beta-adrenergic receptor gene are shown to have a positive relationship with response to treatment with beta-adrenergic agonists.\textsuperscript{31} A recent study from a Korean asthmatic cohort identified SNPs of the allantoicase (\textit{ALLC}) gene which showed significant association with the mean %\textit{ΔFEV1} (change in the percentage of forced expiratory volume in one second) in response to inhaled corticosteroids.\textsuperscript{32} In view of the wide heterogeneity of asthma, it has been also suggested to employ genetic-scores to determine “drug responders and non-responders, and patients most susceptible to adverse effects.”\textsuperscript{33}

In spite of a significant role of genetic factors in asthma pathogenesis and treatment, it is highly unlikely that gene therapy will be useful to treat asthma. First, the gene therapy can be more appropriately used for single gene disease (such as cystic fibrosis). Secondly, it is also associated with some serious side effects, such as leukaemia.

In summary, there is a long road to travel to unravel the role of genetics in the pathogenesis, phenotypic manifestations and treatment of asthma. The genetic polymorphisms which may have a role...
to play in asthma development need to be studied in various populations. Further, we need to identify the SNPs which interact with environmental exposures for the development of strategies for prevention of asthma. Some of the asthma susceptibility genes may also prove to be potential targets for specific asthma therapies.

Surinder K. Jindal
Jindal Clinics, SCO 21, Dakshin Marg, Sector 20D, Near Guru Ravi Das Bhawan, Chandigarh 160 020, India
dr.skjindal@gmail.com

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