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EDITORIAL

Do genetic factors determine atopy or allergy?

Evaluation of the genetic influences of a disease is usually based on the study of the familial grouping of cases, and particularly on the study of monozygotic (univitelline) twins. When genetic influence is maximum, the observed case coincidence is 100%, although when genetic influence is minimum and the disease is dependent only on environmental factors, the percentage coincidence is approximately similar to that seen in the unrelated general population.

There have been many observations over the years of the familial incidence of allergy, although agreement is lacking on the type of inheritance involved. Atopy and allergic disorders are multifactorial and heterogeneous conditions, and although a hereditary component is clearly present, no classical Mendelian pattern is observed. In such cases the hereditary mechanism is considered to be complex, representing the result of the interaction of multiple genetic regions with each other and with a range of environmental factors.

Although extensive research has been done on the genetics of allergic disease, the findings to date indicate that those principles presumed to be solid are in fact only very good hypotheses. The concepts thought to be scientifically confirmed in relation to allergic asthma are the following: a) Asthma tends to group in families. b) The concordance of asthma in monozygous twins is greater than in non-identical twins. c) The disease does not follow the pattern observed in monogenic disorders. d) Certain chromosomal regions are suspected to contain genes associated to the pathogenesis of asthma. e) Some genes present variants that are statistically associated to asthma, and which could participate in its pathogenesis.

In the current issue of *Allergologia et Immunopathologia*, Yilmaz-Demirdag et al.¹ present a study in which they ponder whether hereditary factors determine allergic manifestations or sensitisation to a specific allergen. The study was carried out in 58 pairs of twins—25 monozygous and 33 dizygous—all with a family history of atopy, and inheritance was seen to influence the development of atopy.

Thus, monozygotic twins showed increased atopy, the IgE levels were higher, and the allergic manifestations appeared at an earlier age, and were moreover more extensive. However, hereditary factors are not seen to condition sensitisation to a given allergen.

Monozygotic twins have the same genetic composition, with the exception of minor replication errors that may occur during embryonic development.² In contrast, dizygotic twins have only 50% of their genetic configuration in common. However, in coincidence with the observations of the aforementioned study, phenotypic differences have been described in genetically identical individuals, and historically have been attributed to environmental factors.

In this sense, it must be mentioned that patients with multiple mutations predisposing to allergic diseases require less exposure to environmental factors in order to develop symptoms than patients with few mutations.³ The ideal situation would be to identify an allergy marker capable of establishing those factors which predispose certain individuals to develop sensitisation to certain allergens.

The genetic factors capable of influencing the development of diseases such as allergy can be studied using different methodological approaches. Certain DNA sequences can be inherited along with the gene or genes responsible for such diseases, and it is possible to study their underlying linkage. After establishing such linkage, studies can be made to specify the location and thus identify the relevant candidate gene or genes. The genes that encode for proteins presumably implicated in allergic responses are distributed in the different chromosomes. Some regions have drawn special attention on the part of investigators, since they are believed to be more probably implicated in the development of atopy and/or asthma. These regions are referred to as “candidate regions”. The implicated chromosomes would be 1, 2, 5, 6, 7, 8, 11, 12, 14, 16, 19 and 22.^{4–8} Chromosome 5, for example, includes genes related to certain cytokines: IL-3, IL-4, IL-5, IL-9, IL-12 and IL-13.

Other studies are designed to identify associations of known variations in DNA sequences known as mutations.

Such association studies make it possible to identify relationships between certain genes and the disease, and to identify the genetic variations associated in this case to allergy. At present, most studies combine different strategies, and this has made it possible to implicate over 20 genes in the case of asthma.

One research strategy which has become widespread is the study of the gene polymorphisms that may be associated to allergic diseases, since it seems that the great majority of the genetic variations that contribute to genetically complex disorders such as atopy and allergy probably reflect the contribution of such polymorphisms – specifically, single-nucleotide polymorphisms (SNPs). These polymorphisms can be found in the encoding regions, and as such could modify the structure of the proteins synthesised by such regions. Alternatively, they may be found in the promoter regions, and thus alter the level of protein expression, or may be silent – in which case no changes occur in the synthesised amino acid, although modifications may be produced in the end protein product through mechanisms that are still not fully clear.⁹

Some studies in this field have been designed mainly to determine the polymorphisms located in the genes that encode for proteins of physiopathological importance, such as for example the prostaglandin pathway^{10–12} (e.g., the PTGDR gene), or the leukotriene pathway.^{13–15} In this context, our group for example has detected an association between polymorphism –444 A>C in the promoter region of LTC4S and the asthma phenotype, as well as between polymorphism 927T>C – implicated in the region encoding for leukotriene receptor-1 (*CYSLTR1*) – and asthma in children.^{13–15}

Other studies in relation to polymorphisms have examined the implication of the latter in the modification of drug responses among allergic patients – this representing an important field known as the “pharmacogenetics” of allergic disease. In fact, many polymorphisms have been found in genes that may affect the response to drugs used for the treatment of allergic diseases, such as the beta-2-agonists, glucocorticoids, theophylline, the muscarinic agonists, and the antileukotrienes.^{16,17}

Despite the above comments, genetic studies of atopy are meeting greater difficulties than expected. The problem of immunological pathogenesis reaches levels of great complexity. In a more or less direct manner, many cells, cytokines, receptors and intracellular messengers may facilitate atopic reactions.

The main and fundamental limitation of genetic studies is that much is still unknown about atopic disorders, and the rapid increase over the last 30–40 years¹⁸ in the incidence of allergic diseases cannot be explained only by an increase in the number of diagnoses made, or by environmental changes. In turn, the time elapsed is not considered sufficient to induce changes in the genetic markers. An explanation is required that can integrate the genetic effects and the environmental factors in a timeframe consistent with the current epidemiological data.

Given the difficulty of controlling environmental factors in humans, and the bias seen in epidemiological studies, a new factor must be introduced as a linking element between them. In this sense, experimental studies in animals under controlled environmental conditions have shown that

monozygous mice developing in one same controlled environment occasionally present phenotypic differences. In fact, it is believed that only 30% of the observed variability can be explained by environmental factors, and that the remaining 70% must be due to such a “third factor”¹⁹, currently attributed to epigenetics. In this context, epigenetics is defined as those “inheritable changes occurring in gene expression, without actual modification in the DNA sequence”. Genetic information is encoded by DNA, which is compacted within the cell nucleus, associated to proteins, forming chromatin. From the cellular perspective, heterochromatin is dense, inaccessible to enzyme action and presents few active genes, while in contrast euchromatin is an open structure, accessible to enzymes and with transcriptionally active genes. A number of epigenetic mechanisms control and regulate modifications in chromatin, making it more or less accessible to transcription factors, and thus contributing to determine the level of expression of different genes.

Epigenetics could help identify the molecular effects of environmental factors. In the case of allergic disease, epigenetics could help explain not only the discordances observed between monozygous twins – and which in the case of asthma reach 25% – but also phenomena such as incomplete penetrance, variable expression, age at onset or presentation, gender and progenitor effects, and sporadic cases^{20–22}.

This is a fundamental issue, particularly in paediatrics, where children who are not atopic or asthmatic today, may become so years later.

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