Medical genetics: advances in brief

Molecular biology and genetics of allergy and asthma

Anderson GG, Morrison JFJ. *Arch Dis Child* 1998;78:488-94.

This article reviews recent progress made in understanding the pathogenesis of allergy at the cellular and subcellular level. The discovery of several genes that predispose to the development of asthma (one example of an allergic condition) represents the first insight into why some people suffer from the disease and others do not. Asthma is a syndrome characterised by acute diffuse narrowing of the bronchi relieved by bronchodilators or anti-inflammatory drugs. Gaining insights into the molecular mechanisms of asthma is important because it affects 10% of the child and 5% of the adult population in this country and carries significant mortality and morbidity despite modern therapeutic interventions. One theme in research of asthma is that it occurs in people with genetic susceptibility after exposure to certain irritant environmental agents. The risk ratio increases from the general population figure of 4-8% to 20-25% in those with affected first degree relatives, especially in maternal-child transmission. The problem in how to approach finding these susceptibility genes is the complexity of the asthma pathway itself, including antigen expression, B cell response, IgE production, mast cell reaction, and eosinophil response. The interpretation of genetic studies has been made more difficult by the use of different examples of these criteria to define the phenotype. Despite these difficulties, by a combination of genome wide searches, positional cloning, genetic linkage studies, and candidate gene approaches, several asthma genes have now been identified. Genetic linkage of asthma to 11q13 in apparent autosomal dominant pedigrees has been shown by several studies and disputed by others. One candidate gene in this region is the β subunit of the high affinity IgE receptor and some authors have reported an association between a specific polymorphism in this receptor and antigen specific atopic responses. Other studies have refuted this finding, excluded the CC10 gene, and suggested that another locus on 11q may predispose to atopy. Loci on chromosome 14 which have been linked include 14q23, 14q32.1, and 14q11.2. The T cell receptor TCR $\alpha\delta$, nuclear factor κ inhibitor, and TGF- β 3 map to 14q and are considered candidate genes. Other loci which are reviewed in the article include tumour necrosis factor (TNF), the cytokine gene cluster on

5q, the MHC locus on 6p, and the chromosomal region 12q15-q24.1 (including the stem cell factor and insulin growth factor I). The article concludes that at the present time the strongest candidate genes for asthma are interleukins 4 and 5 (which map to 5q), TNF, and GM-CSF (granulocyte macrophage colony stimulating factor). Although atopy, and asthma in particular, is the subject of intensive research, this article highlights that many studies are conducted independently of each other. Strict criteria for definition of atopic phenotypes, multicentre studies with large numbers of subjects, and a coordinated approach are likely to be needed in order to address the complexity of the molecular basis of atopic disease. It is hoped that the more precise definition of the molecular determinants of atopy may improve pharmacological and immunological treatment strategies in the future.

SARAH SLANEY

Frequency of somatic and germ-line mosaicism in retinoblastoma: implications for genetic counselling

Sippel KC, Fraioli RE, Smith GD, *et al.* *Am J Hum Genet* 1998;62:610-19.

The existence of mosaicism has been acknowledged for several years, and since the development of molecular methods for detecting specific mutations within genes, it has been possible in some cases to prove mosaicism in some diseases, most notably Duchenne muscular dystrophy. Data regarding the incidence of mosaicism are available for only a few diseases, however, and sometimes genetic counsellors have resorted to using an empirical recurrence risk of 1% when germline mosaicism is a possibility. In this study, 156 families with retinoblastoma (RB) were evaluated, the initial oncogenic mutation in the RB gene having been identified. In 15 (10%) mosaicism for the initial mutation in the RB gene was documented either in the proband or in the proband's parents. In other families mosaicism was suspected but could not be proven because of a lack of DNA from key family members. Germline DNA from two mosaic fathers was analysed: in one the mutation was found in both sperm and leucocyte DNA, in the other the mutation was detected only in sperm DNA. Mosaicism may occur more frequently than has been recognised previously, particularly in conditions which have a high

incidence of new mutations. The analysis of germline DNA can be very useful if the mutation is identified, and some patients with a bilateral RB may actually face an offspring risk of less than 50% if they are somatic mosaics. It will be interesting to see whether any other disorders which were previously thought to show autosomal recessive inheritance (on the basis of recurrences in sibs) turn out to represent new mutations with somatic or germline mosaicism, as has been the case with campomelic dysplasia, for example.

FRANCES FLINTER

Mutations in the caveolin-3 gene cause autosomal dominant limb-girdle muscular dystrophy

Minetti C, Sotgia F, Bruno C, *et al.* *Nat Genet* 1998;18:4:365-8.

Limb-girdle muscular dystrophy (LGMD) is genetically heterogeneous and includes autosomal dominant and recessive forms. A number of components of the muscle sarcolemma dystrophin associated protein complex are known to cause muscular dystrophies, and the protein caveolin-3, which is immunoprecipitated by antidystrophin antibodies, is thought to be part of this complex. With this knowledge in mind, Minetti *et al* have studied 137 patients with LGMD and immunostaining of muscle biopsies showed reduced cell surface caveolin-3 in eight subjects from two families with dominant inheritance. The gene was then isolated from a human skeletal muscle cDNA library and found to give a single 1.5 kb transcript predominantly expressed in heart and skeletal muscle. YAC screening and FISH analysis localised the gene to chromosome 3p25. In the two families with reduced caveolin-3, two mutations were found, a missense mutation in the membrane spanning region and a deletion in the scaffolding domain, both mutations being in regions highly conserved across species. The authors have therefore identified a further cause of autosomal dominant LGMD in addition to LGMD1A linked to 5q and LGMD1B linked to 1q11-21. The main clinical features of patients with caveolin-3 deficiency were found to be mild calf hypertrophy and mild to moderate proximal muscle weakness. The identification of this gene will be of great importance for the genetic analysis and counselling of affected families.

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