EDITORIALES

Inherited renal diseases: Genetic aspects

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The wide clinical spectrum of inherited kidney diseases[1], the inheritance of glomerular diseases[2] and the involvement of genetic factors in human renal disease[3] have been emphasized in previous reviews. In the present paper, we will focus on the strategies used in molecular genetics and on some recent advances in autosomal dominant polycystic kidney disease (ADPKD) and Alport's syndrome, the two most frequent inherited renal diseases.

Classical versus reverse genetics

Until recently, molecular genetics has proceeded largely through identification and characterization of specific proteins and their corresponding genes. This approach (or «classical genetics») is exemplified in thalassemia syndrome, familial hypercholesterolemia, and in inherited metabolic diseases, such as Fabry's disease[4]. The first step was based on recognition of the affected proteins (globins, LDL receptor and α-galactosidase) prior to gene location and analysis of the molecular gene defect.

In contrast, in reverse genetics, the aim is to isolate a gene without reference to a specific protein or without any functional assays useful in its detection. The first step, using restriction fragment length polymorphisms (RFLPs) and cytogenetic methods in affected families, is to establish the map position of the gene, and then to identify a specific gene within this region in which mutations are strictly correlated with the disease[5]. This approach has recently been very successful in inherited diseases for which adequate biochemical explanations were lacking. The gene product was subsequently identified, thus opening new avenues in the understanding of the disease process. In Duchenne muscular dystrophy, in chronic granulomatous disease, in retinoblastoma, in cystic fibrosis and in neurofibromatosis, decisive progress has been achieved in recent years through reverse genetics.

In inherited kidney diseases, both approaches, classical and reverse, have been applied. In ADPKD, Reeders et al. have located the mutant gene on the short arm of chromosome 16 by using reverse genetics[6]. In the last five years, great efforts have been made by several groups to identify the gene itself. The gene region has been localized by finding flanking markers, situated on both sides of the ADPKD locus. This region contains approximately 25 genes, and the main challenge for the future is to identify among them the ADPKD gene (in the absence of knowledge of the gene product, i.e., the protein specifically involved in cyst formation). This shows well both the power and the difficulties of reverse genetics. Both classical and reverse genetics have been used in Alport's syndrome, and this approach has very recently been successful[7]. Several steps have been involved in this regard: identification of the specific ultrastructural lesion in the glomerular basement membrane; identification of an antigenicity defect involving the Goodpasture antigen; biochemical characterization of this antigen in the globular domain of the type IV collagen molecule, but not in α1 and α2 chains; localization of the mutant gene of X-linked Alport's syndrome on the long arm, near the Xq 22 region (for review see 8); identification of the α5 chain of type IV collagen, α5(IV)[9]; and finally mapping of the COL4A5 collagen gene to the same chromosomal region as Alport's syndrome[7].

Genetic or environmental factors in inherited diseases?

Environmental factors (such as sex) may influence the expression of genetic diseases. The progression of renal failure seems to be more rapid in males than in females with ADPKD (see ref. in 10). It is not easy to delineate the respective roles of genetic and environmental factors. The study of twin pairs may be valuable in this regard. Two of us (ML and JPG) have initiated a cooperative study supported by a Concerted Action of the European Economic Community, aimed at collecting data on twins with ADPKD. The ages at first appearance of hypertension and renal failure, and the rate of renal progression will be analyzed and compared in both affected identical (or not) twins. The part of nongenetic influence could thus be estimated.

Intracranial aneurysms (ICA) are significantly associated with ADPKD. The prevalence of occult ICA is not well known, ranging from 10 to 40 % in various series; the overall prevalence of ICA rupture ranges from 2 to 3 %[10]. Is the occurrence of ICA genetically determined in ADPKD? Familial clustering of ICA in ADPKD has already

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been emphasized. No large epidemiological study, however, is so far available. With Dr. Y. Pirson (Brussels), a cooperative European study has been initiated. In a preliminary survey made in France, Belgium and Switzerland, we collected data on 46 patients with ruptured ICA and ADPKD. The study is still in progress and is open to all European nephrologists. A positive family history of ICA was documented in 27 % of these families. It remains to be determined whether these kindreds with both ADPKD and ICA represent or not a specific subset, whether a specific DNA molecular defect is involved, and what is the molecular status of the remaining 73 % of the families.

In any case, familial clustering of ICA should be recognized by nephrologists since in these ADPKD families, routine screening for occult ICA is recommended by using high resolution computed tomography or magnetic resonance imaging[11].

Genetic heterogeneity

Genetic heterogeneity is well established in Alport's syndrome. In approximately 80 % of the families, inheritance is compatible with X-linked dominant transmission. In 20 % of the kindreds, there is clearly autosomal dominant inheritance, with father-to-son transmission. In very rare families (< 5 %), the transmission is compatible with autosomal recessive inheritance, the disease appearing first in several siblings just after a consanguineous marriage[12].

Genetic heterogeneity has also been documented in ADPKD. In approximately 5 % of the families, the disease is not linked to the PKD_1 locus, located on the short arm of chromosome 16. At least two morbid loci must therefore be considered, PKD_1 and the other(s) so far unlocated. It has been suggested that the renal disease in families unlinked to PKD_1 might have a less rapid rate of progression (see 10).

Molecular heterogeneity is found in many inherited metabolic diseases. Beta-thalassemia, an autosomal recessive disease, is a good example of such heterogeneity. The β-globin gene was one of the first human genes to be cloned in bacteria, in 1978. The gene is unusually small and simple for a human gene. A total of 51 point mutations in this gene and three deletions that produce «simple» β-thalassemia are known[13]. In Fabry's disease (an X-linked recessive disorder), Bernstein et al. have identified 7 different DNA lesions in the α-galactosidase gene, in 7 of 130 affected families[4]. The study of molecular heterogeneity has just started in X-linked Alport's syndrome since the structure of the COL4A5 gene has just been in part identified[7]. Three structural aberrations were found, an intragenic deletion, a point mutation, and an as yet uncharacterized abnormality. These lesions have been shown in 3 of 18 unrelated Alport kindreds[7]. Other DNA lesions will be identified in the future and might be correlated with the clinical and histopathological findings[14]. Obviously, molecular heterogeneity cannot be investigated in ADPKD since the PKD_1 gene is not identified and thus its molecular structure cannot be studied.

Gene testing in inherited diseases with late onset

Many physicians believe that genetic diseases manifest early in life, in childhood, leading to more or less debilitating consequences. In their minds, the field of clinical genetics is mainly restricted to pediatrics. In fact, many genetic disorders, such as ADPKD, Huntington's disease, Alzheimer's disease, etc. do not lead to clinical manifestations in childhood and have only a late symptomatic onset in adulthood, in the fourth decade or later. The prevalence of the latter diseases (usually with an autosomal dominant inheritance) is even higher than that of most hereditary disorders (often recessive) whose first symptoms appear in children.

Clinical needs differ in early- and late-onset inherited disorders. Schematically the first aim of investigators in early-onset diseases is to provide prenatal diagnosis with the hope of eradicating these very devastating diseases from affected families.

The issue is more complex in late-onset diseases. Presymptomatic testing may raise difficult ethical and psychological problems, for example in Huntington's disease[15, 16]. The need for caution has also been pointed out in ADPKD[1, 17]. It should be recalled that approximately 50 % of ADPKD patients are *not* in end-stage renal failure at 70 years of age, and that the rate of progression cannot so far be predicted from gene analysis. The limitations, requirements and drawbacks of gene testing have been emphasized in previous papers[3, 10, 12]. Nephrologists should avoid indiscriminate use of prenatal diagnosis in ADPKD. In well informed families, only 4 % of ADPKD patients and 8 % of at-risk individuals would terminate a pregnancy for ADPKD in Denver, Colorado, USA[18]. Such data suggest that presymptomatic testing will not substantially modify the incidence of ADPKD since it may only occasionally alter reproductive plans. These attitudes of the patients should be kept in mind by nephrologists. They will need to be reevaluated in the future, in the light of progress achieved.

In late-onset inherited diseases, we can look forward to obtaining information on gene defects and gene products, to better understanding the mechanisms of the diseases, to positively altering their courses and finally to better coping with the needs of the families.

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