Autosomal Dominant Polycystic Kidney Disease

ST REEDERS

From Yale University School of Medicine, Department of Internal Medicine, Nephrology/208 LCI Building, New Haven, CT, USA

The lack of reliable data on frequency, age of onset, survival, spontaneous mutation rate and prognosis in autosomal dominant polycystic kidney disease is a continual source of frustration to physicians involved in counselling patients and their relatives. The only major study to address all of these issues in a defined population was presented by Dalgaard as a 251-page doctoral thesis in 1957 [1]. Although Dalgaard's work is a perfect example of careful characterization of a genetic disease, the development of more sensitive, non-invasive cyst imaging methods and the advent of chronic dialysis and transplantation have weakened many of his conclusions.

Fortunately, Davies et al. [2] have begun to obtain the data required to satisfy the urgent need for answers to the above questions by studying the families of all affected individuals in a Welsh population of 2.1 million. The first report of this study deals with prevalence, de novo mutation rate and trends in dialysis acceptance and survival [2].

Davies et al. estimate the prevalence of autosomal dominant polycystic kidney disease in Wales to be 1:2459, a figure which is substantially lower than the previous estimates of between 1:400 and 1:1000 in other Caucasian populations [1, 3]. There are several possible explanations for this discrepancy. First, all the probands in the Welsh study had symptomatic renal disease or hypertension. If a substantial number of all patients are asymptomatic, and if asymptomatic disease runs true in families, the selection of symptomatic probands would be expected to lead to low estimates of frequency. The fact that higher frequencies of polycystic kidney disease have been observed at autopsy than have been estimated clinically lend credence to this possibility. Hatfield and Pfister [4], for example, found that less than half of patients with polycystic kidney disease diagnosed at autopsy had symptoms, and only one of 32 asymptomatic cases had a family history. The increasing use of ultrasonography in the screening of undiagnosed abdominal illness is also bringing many additional cases of asymptomatic polycystic kidney disease to light. Therefore, whereas symptomatic disease was previously considered to be the predominant form, it now appears that it may be just the tip of the iceberg. The difference between symptomatic and asymptomatic disease has not been explained at the molecular level but Parfrey et al. [5] have recently shown that a form of autosomal dominant polycystic kidney diseases that is not linked to chromosome 16 markers has a significantly better prognosis than the linked form. Once the genes coding for autosomal dominant polycystic kidney disease have been cloned, direct analysis of their mutations may allow a better understanding of the genetic influences on prognosis.

One of the most difficult problems in differential diagnosis of autosomal dominant polycystic kidney disease is the patient in whom de novo mutation appears to have occurred: since family history is such a strong pointer to the diagnosis, the lack of it is always a cause of
concern. This difficulty has been exacerbated by the lack, until now, of a good estimate of the frequency of *de novo* mutation, which is needed so that the Bayesian physician can compute a meaningful prior probability of fresh mutation.

In Dalgaard's population, 80 of the 241 propositi had no family history and yet only one case could be confidently ascribed to *de novo* mutation; in the other 79, there was insufficient evidence to exclude the possibility of asymptomatic disease in the parents. In a study of the population of the Oxford region of England, one new mutation in about 250,000 individuals was found [6]; however, the Oxford study was biased by the desire to identify large pedigrees. One of the most useful features of the Welsh study is that it contains the first good estimate of spontaneous mutations: they found five new mutations in a population of 2.1 million. This estimate is probably a minimum because a number of spontaneous cases with trivial symptoms may be missed because of a low index of suspicion in the absence of a family history. Nevertheless, this study represents the first systematic attempt to measure the mutation rate in a defined population and indicates that new mutations do indeed occur.

The most frequent question asked by newly diagnosed patients is whether autosomal dominant polycystic kidney disease 'runs true' in families. Frequently they are concerned not only about the renal prognosis but about extra-renal manifestations, particularly subarachnoid haemorrhage. Dalgaard showed a modest intrafamilial correlation of age at diagnosis but rate of progression to end-stage renal failure is the variable which is of most concern to patients and their physicians. The extensive register of affected families assembled by Davies *et al.* should now permit the important question of intrafamilial variation to be resolved.

REFERENCES