Annotation

National haemophilia B molecular genetic register

Francesco Giannelli and his colleagues in this issue recommend a national molecular database for haemophilia B to strengthen research and to make widely available the clinical benefits of new, economical, and effective forms of mutation analysis.

Giannelli and colleagues describe their experience in screening for sequence variation by mismatch analysis in heteroduplexes formed by wild type and complementary test DNA strands. This method allows sequencing to be limited to the region of the gene containing anomalies and reduces the time to characterise a haemophilia B mutation to four to five person working days. Carrier and prenatal diagnosis is then possible by direct detection of the gene defects in every case. In only one in 170 patients with haemophilia B has the group failed to find a mutation in an essential region of the gene. This makes one confident that screening is capable of detecting all types of mutation.

The importance for genetic counselling is that direct identification of molecular pathology overcomes the disadvantages of linked genetic markers whose use is often thwarted by incomplete families or recombination. Mutation analysis has the extra value of providing a means for exploring the relationship between mutation and disease. Already the plethora of mutations (more than 600 world wide) has been associated with effects ranging from promoter changes leading to relatively minor factor IX deficiency having a clear tendency to improve at puberty, to gross defects predisposing to the development of inhibiting antibodies against therapeutic factor IX, making treatment extremely difficult. One anticipates that a data bank will allow any new mutation to be confirmed as pathological and its likely clinical effects to be predicted. In addition, reference to the database will allow relatives to be alerted to their risk and to the probable clinical effects

of the mutation. Thus the case for carefully documenting this heterogeneity with its important clinical implications becomes overwhelming.

However, clinical geneticists are generally opposed to national genetic registers and advocate regional genetic registers instead because they allow physicians to relate clinically with the patients and their families and to control the use of information so as to maintain confidentiality. In contrast, national registers are held at a site remote from the majority of patients and may be little more than lists of patients. Confidentiality may be difficult to preserve and direct interaction is prevented, thus losing the most clinically beneficial effects.

In the case of the haemophilia registers initial concern is perhaps mitigated by the obvious advantages. Haemophilia centres have already established successful haemophilia A and haemophilia B clinical registers and the proposals for this new one share their built in safeguards. Each centre's physicians control the release of information pertinent to their patients and remain totally in charge of contacts with patients and their relatives. The responsible physicians ensure that informed consent from patients and other persons is obtained and control the use of the database by themselves answering diagnostic enquiries from people aware of their risks. The physicians responsible for the care of the patients exploit the more active register function of contacting relatives to inform them of their risk and availability of accurate carrier and prenatal diagnostic tests.

RODNEY HARRIS

*Department of Medical Genetics,
St Mary's Hospital,
Hathersage Road,
Manchester M13 0JH.*