Medical genetics: advances in brief

Proceed with care: direct predictive testing for Huntington disease

Benjamin CM, Adam S, Wiggins S, *et al.*
Am J Hum Genet 1994;55:606-17.

This paper describes protocols for direct predictive testing for adult and prenatal assessment devised on the basis of the experience of the Canadian Collaborative Study on Predictive Testing (CCSPT). The results provided during the last eight years include >400 tests using DNA linkage analysis, and 416 using direct measurement of the CAG expansion in the HD gene. Eighty-six percent of requests for direct predictive testing came from persons who had not previously received results using linkage studies. (Of the 29 patients previously tested using linkage who subsequently requested a direct test, only one received a contradictory result, when a prior risk estimate of 85% was reduced to <1% on direct testing). In devising their current protocol, a questionnaire was sent to patients who had participated in the predictive testing programme previously. Patients indicated that the self-assessment questionnaires were of great value, but there is no objective evaluation of this. Patients also indicated that a minimum of two counselling sessions should be offered before the results, with follow up counselling available at "regular intervals". The protocol which the Canadians use is very similar in format to that in general use in the UK, but over a considerably compressed time scale. Counselling is done by two professionals, typically a geneticist working with a genetic counsellor, psychologist, or social worker, and patients are encouraged to bring a support person to counselling sessions. If a patient has never been seen before, they are offered an introductory session before formal enrolment in predictive testing. At the first session, the patient fills in the questionnaire, undergoes a neurological examination (having stated beforehand whether or not they wish to be informed of any abnormal signs), receives information about HD and the predictive test, and then signs the consent form. Presumably (although this is not stated explicitly in the test) the blood sample is also taken at this session, as the second session is scheduled for only three weeks later, that session being just one to two weeks before the results session. The professionals counselling the patients have no knowledge of the DNA results during the second session, as they are held in the laboratory until the results session. At the second session the patient is counselled again about the test and prepared for the results session. After the results session (which is one month after the first session), all patients are offered a further appointment two weeks later, but subsequent follow up depends on the result, implying that the result influences the follow up required, contrary to other studies. For patients who inherited the HD gene, personal interviews at six months and one year are recommended. For patients who have not inherited the gene, follow up telephone contact occurs at six months and a personal interview at one year. This protocol raises many questions. There are several published studies indicating that the way in which

people are offered tests influences their participation in a testing programme. If there is a time interval between receiving the information and having the blood sample taken, participation rates fall. It is important that the Canadians can show that their policy of taking the blood sample early in the testing programme is not influencing patients' decisions to ask for their results. It would also be helpful to establish that patients feel that a three week interval between the first and second counselling sessions is long enough to consider all the emotional and practical issues involved (including enough time to arrange insurance policies, etc). The authors state that they inform people that they may withdraw from the testing programme at any time, but it might be harder to pull out if your result is already known to others in the laboratory. The authors also state that their results can only be disclosed to other parties with the express written consent of the patient, but what would happen if the patient had decided against receiving the result, and a relative subsequently requested it before entering into a predictive testing programme himself or herself? The original patient might feel under pressure to change his or her mind and release the result. The paper does not include a figure for the dropout rate from the testing programme, but this is very important, as it could be compared with that seen in other studies. Follow up by the geneticists appears to cease after one year, so studies to evaluate how the patients who have been tested cope in the longer term will be difficult. Other interesting points emerge as well. Patients at 25% risk may be offered exclusion testing in the first instance, if the intervening parent does not wish to be tested, and only if that does not exclude HD do they consider proceeding to direct testing. The authors found one unaffected, unrelated spouse with a CAG repeat length of 39, with no history of HD over two generations. Why this sample was tested in the first place is unclear, but the authors quote an incidence rate of 1 in 1595 chromosomes of this happening. Presumably this person has a significant chance of developing HD, but counselling in these circumstances would be very difficult. The Canadian protocol is not to report the size of the CAG expansion, despite the inverse correlation between age at onset and repeat length, because the confidence intervals for prediction are very broad. Patients with suspected HD who do not have a confirmed clinical family history of the illness are not rare, and this study suggested that at least 3% of families may represent new mutations. However, among symptomatic persons with a negative family history, 17/56 (30%) did not have a CAG repeat length in the affected range. Some of these may turn out to have dentatorubropallidolysian atrophy (DRPLA), another triplet repeat disease which can mimic HD, and for which direct testing is now possible. Overall there is an urgent need to collect data from all the various testing protocols in use worldwide, so that programmes can be modified as appropriate. The rate at which quite large numbers of people are being tested already makes this work particularly urgent, and the title of this

report is certainly appropriate: proceed with care.

FRANCES FLINTER

A molecular approach to the stratification of cardiovascular risk in families with Marfan's syndrome

Pereira L, Levrin O, Ramirez F, *et al.*
N Engl J Med 1994;331:148-53.

All families with classic Marfan's syndrome that have been studied so far have shown a consistent linkage between fibrillin (FBN1) and the disease phenotype. However, it is not uncommon for persons to have a Marfanoid phenotype, sometimes inherited as a family characteristic, without any of the major manifestations that commonly occur in the condition. This paper is of considerable clinical interest as it reports three newly characterised intragenic microsatellite polymorphisms within the FBN1 gene that will further improve linkage analysis for this condition. Not only does this report come at a time when FBN1 mutations have been proving elusive, but it goes on to show the usefulness of the polymorphic markers for presymptomatic diagnosis. Among the families studied were two in whom some family members showed either classic Marfan's syndrome or a milder but closely related phenotype. In one family, the copy of the fibrillin gene that cosegregated with classic Marfan's syndrome was not inherited by family members with the milder phenotype. A new frameshift mutation in the fibrillin gene, present in the proband of the second family, was not found among other family members with a milder phenotype. Associated limited linkage analysis in the family showed cosegregation of the milder phenotype with a fibrillin intragenic haplotype which the proband had not inherited. Interestingly, these milder phenotypes, previously diagnosed clinically as Marfan's syndrome, were not associated with aortic involvement. They are also consistent with an earlier report of a large French kindred with incomplete, atypical, and variable manifestations of Marfan's syndrome which does not show linkage to FBN1. The report highlights the need for a review of the current diagnostic criteria for Marfan's syndrome. While the study supports the use of a linkage method for presymptomatic diagnosis of Marfan's syndrome, an associated editorial points out the question of heterogeneity has not been fully resolved.

DAVID RAVINE

Ultrasound measurement of placental thickness to detect pregnancies affected by homozygous α -thalassaemia-1

Ghosh A, Tang MHY, Lam YH, Fung E, Chan V. *Lancet* 1994;344:988-9.

In south east Asia homozygous α -thalassaemia 1 is the commonest cause of hydrops fetalis. The infants do not survive beyond the early neonatal period and many are stillborn. The placenta becomes large and oedematous in