Editorial

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DNA prediction in cystic fibrosis

The localisation of the cystic fibrosis gene by linkage to markers on the long arm of chromosome 7, documented in a series of papers late in 1985,1–5 marked the end of a long period of search and opened up the possibility of applying these markers in carrier detection and prenatal diagnosis. Since that time, events have moved rapidly in terms of both additional information and public awareness. Already clinical geneticists and paediatricians are facing requests from families and are having to confront both the risk estimations in individual cases and the logistics of trying to integrate the new developments into overstretched (or non-existent) molecular genetics services.

Several important facts are already reasonably clear: two probes at least (Met and 3.11) are extremely close to the CF locus, with recombination unlikely to exceed 1%. We are thus not dealing with an area of genetic instability, such as appears to exist around the Duchenne muscular dystrophy locus. Secondly, the probes are also extremely informative, with polymorphisms demonstrable using several different enzymes. Thus, the chance of a favourable combination of genotypes is high, probably at least 80%. Thirdly, there is currently no evidence of multiple loci, even from families of diverse geographical and ethnic origin.

The scene thus seems set for clinical applications, which may well contain complexities and pitfalls for the unwary. The paper by Farrall and colleagues on page 295 of this issue gives some examples of carrier prediction and shows how exclusion of the carrier state can be helpful to sibs at high risk. Unfortunately, neither DNA nor other tests are currently able to test the partners of those who are carriers. Prenatal diagnosis at present perhaps gives greater practical applications, but is also not without its difficulties. The DNA markers are readily detectable by first trimester chorion villus sampling, making this approach much more acceptable than the mid-trimester methods used until now. but there is no possibility of confirming a pregnancy to have been affected, while availability of DNA from a previous affected child is usually essential if a prediction is to be possible. Despite these reservations, first trimester prenatal diagnoses based on DNA have now been undertaken6 and it is likely that demand will become widespread as families become aware of this.

Should a first trimester prediction, either positive or negative, be backed up by amniocentesis using alkaline phosphatase?7 It is tempting to suggest that it should, at least until we are more certain that error due to recombination is minimal. However, this may create new uncertainties, as outlined by Brock in the correspondence section of this issue (p 376) and in a recent Prenatal Diagnosis Group Newsletter,8 since the discrimination of normal from abnormal given by amniotic fluid alkaline phosphatase is less great than that provided by linked markers. Brock points out that where DNA prediction is maximally informative, an alkaline phosphatase result disagreeing with the DNA prediction would leave the situation indeterminate, while a concordant result (whether positive or negative) would only serve to strengthen an already strong prediction. Where DNA prediction is impossible, either because of family structure or lack of probe informativeness, then amniotic fluid alkaline phosphatase will be the only possible option, but there is one situation, not always predictable in advance, where the two approaches may help each other. This is the ‘partially informative’ situation, in which certain genotypes give a definite prediction, while others are essentially neutral, in which case a later amniocentesis may be helpful. It is important that families are warned that this situation may arise, as a late termination may not always be acceptable.

Some of these complexities should be resolved when the CF gene itself is isolated and when a
screening test for heterozygotes (probably based on the gene product) is feasible. Meanwhile, those involved in providing genetic services, both clinical and laboratory, and those responsible for specialist CF clinics need to work closely together to ensure that the new techniques actually reach the families that need them, and that they are applied accurately and efficiently. Rather than wait for pregnancies at risk to occur and then type and counsel families as an emergency, it will be preferable to type in advance all those families likely to require prediction. Such a systematic approach is certainly more work initially, but is likely to be more efficient in the long run. Like any comprehensive service it will have significant financial implications for both clinical and laboratory time, so careful planning at a regional level will be essential to avoid duplication of efforts. The present time is none too early for this planning to begin.

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References


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