Conference report

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Report on meeting on molecular studies of inherited cancer syndromes

As part of their regular programme of meetings the UK Cancer Families Study Group held a two day meeting on molecular aspects of familial cancer in the Paterson Laboratories, Christie Hospital, Manchester on 10 and 11 February 1986.

The opening consideration of the occurrence of cancer in families emphasised the critical importance of accurate diagnosis and complete ascertainment as a basis for molecular studies. In particular, mildly affected subjects must be recognised and included in the affected group. The need for sub-classification was also stressed, in some instances at least, strong familial association involved a specific type of pathology or a specific clinical presentation. Dr Ray Cartwright (Leeds) pointed out the need to consider genetic environmental interactions, since it appeared that a susceptible genotype might lead to the occurrence of the disease in only a minority of cases.

The following section dealt with the methodologies. Dr Julia Bodmer (London) outlined classical linkage studies using the multiple alleles at the HLA loci. She also pointed out the power of sib pair analysis in such systems. Professor Bob Williamson (London) gave an optimistic forecast of the coverage of the human genome using restriction fragment length polymorphisms, though problems may arise from the fact that there may be only two alleles in many instances. Dr Steve Harris (Leicester) described the application of the minisatellite probes in general and in particular to some families with neurofibromatosis. In effect this was equivalent to scoring 25 to 35 loci in a single experiment. Sir Walter Bodmer (London) suggested, in discussion, that the same effect might be achieved by simply mixing known probes. Several speakers who have been using such technologies to investigate genetically determined disease not associated with cancer then outlined their experience. It became clear that while enormous advances had been made in locating known genes or DNA probes close to the locus of interest, there still remained formidable problems in actually isolating the gene in question. Dr Susan Kenrick (Oxford) presented elegant work on Duchenne muscular dystrophy, but even here with an X linked gene and many closely linked probes, the results are still puzzling and could suggest rearrangements near the DMD locus at least in some cases.

The introduction of new techniques, such as pulsed field electrophoresis and new multiple point methods of analysis, are, however, holding out hope for rapid progress.

On the second day, discussion moved on to specific chromosome regions or specific loci associated with cancer. Dr Nick Hastie (Edinburgh) described recent progress on the analysis of the region near 11p13 which is associated with the Wilms'-aniridia-genitourinary syndrome and other childhood cancers such as rhabdomyosarcoma. In particular, chromosome mediated gene transfer is proving to be a powerful technique for the analysis of chromosome regions rather than specific loci. Dr Peter Little (London), again focusing on chromosome 11, gave a lucid and detailed account of the possibilities of molecular analyses of such regions of interest.

He emphasised that while much of the technology is already available it will certainly take some time and a bit of luck to come up with meaningful answers. Techniques such as the overlapping cosmids technique for 'walking' are, however, adding to the power of these methodologies. Similar problems face those attempting to analyse the retinoblastoma region on chromosome 13q14. Dr John Cowell (London) outlined progress in this field and mentioned one instance of the kind of luck that is required for quick progress, namely a translocation t(1;13) which may have its breakpoint in the retinoblastoma locus. Malcolm Taylor (Birmingham) outlined some exciting new results which place the breakpoints for the specific rearrangements seen in ataxia telangiectasia lymphocytes outside, and proximal to, the immunglobulin heavy chain locus (and therefore different from the 14q32 breakpoint in Burkitt's lymphoma) and close to α chain locus of the T cell receptor at 14q11.

Consideration of other diseases where attempts at genetic analysis are being made emphasised the need for close liaison between clinicians, cell biologists, and molecular geneticists. The chromosomal locations of neurofibromatosis, polyposis coli, and MEN 2 are still not clear. Dr Bruce Ponder (London) pointed out
that in the latter case, in spite of a possible cytogenetic indication that MEN 2 is on chromosome 20, the molecular techniques had so far failed to detect linkage. Dr Doug Easton (London) in a cautious appraisal of "which families to start with" suggested that as many as 40 sib pairs might be required to give a meaningful association and in the common cancers where 'non-genetic' sib pairs would occur by chance the figure could be closer to 100.

The meeting was useful not so much because of any detailed discussion but because it brought together people from many different fields and pinpointed the complexities of the problems and the difficulties of the application of molecular techniques in this field.

The ability to recognise cancer susceptible subjects at or even before birth using molecular genetic techniques raises many practical and ethical problems. It is likely that counselling decisions will vary with the particular type of cancer and even with the individual patient. If a DNA probe reveals a retinoblastoma gene in utero is this a reason for termination? Should the parents of a child be told that she carries a gene which will make her unduly susceptible to breast cancer 40 years later?

There was a strong consensus that as the technology advances the new information should be made available to the patients at the earliest possible opportunity but bearing in mind the needs and sensitivities of the individual cases.

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