MEDICAL GENETICS: ADVANCES IN BRIEF

Editorial: our educational challenge

The current rate of progress in research into medical genetics is unprecedented. Advances in cytogenetics, molecular and biochemical genetics are producing information relevant to all fields of clinical medicine, which will therefore involve most physicians. Human geneticists face a considerable challenge in constantly updating themselves, and they are also involved in the education of other health care providers, medical students, and the patients themselves. One study has already examined the ability of non-geneticist physicians to deal with the expanded knowledge of genetic tests which they will have to offer, and found that pediatricians and obstetricians/gynaecologists scored significantly higher than other doctors on factual genetic knowledge. This is not surprising as these specialties have had greatest exposure to genetics in the past. Other specialties may have predictive tests to offer soon, including, perhaps, presymptomatic tests for breast cancer, colon cancer, coronary artery disease, adult polycystic kidney disease, and Alzheimer’s disease. As many patients may be unaware of the implications of predictive testing, physicians must be prepared to explain the benefits and risks of testing, and it is suggested that the diffusion of genetic testing should not proceed more rapidly than the time it takes providers to gain adequate understanding. Subsequent papers include a report of the successful use of a PCR based cystic fibrosis carrier screening test in a first year medical student biochemistry laboratory, and a study of genetic knowledge among obstetricians and gynaecologists. Steiner-Grossman and David surveyed the involvement of rabbis in New York in counselling: they found that 96% of rabbis discussed health issues generally, as a routine part of premarital counselling, and 54% discussed Tay-Sachs disease carrier testing, while 22% had counselled a couple after prenatal diagnosis of an affected fetus. Even though 90% of the sample viewed genetic counselling as part of their rabbinical role, most felt poorly prepared to give it. The challenge facing the limited number of human geneticists in educating the much greater number of other health care professionals, and patients, cannot be underestimated. The Human Genetics Education section of the American Journal of Human Genetics is one forum where ideas about ways of implementing educational efforts may be exchanged.

FRANCES FLINTER

Replication structure of the human β-globin gene domain

Given the wealth of knowledge about human molecular biology, remarkably little is understood about how DNA is replicated before cell division. Specifically, does replication start at particular sites, and if so, what determines their location, and what controls them? This paper may represent a landmark towards answering these questions: not for the first time, the β-globin complex provides the paradigm. Two elegant and independent methods were used to assay for replication origins. In the first, cells are cultured in bromodeoxyuridine (BrdU) and emetine. The BrdU is preferentially incorporated into the leading DNA strand, because lagging strand DNA synthesis is decreased by emetine (a protein synthesis inhibitor). The DNA is denatured, the heavy BrdU labelled DNA strand separated by centrifugation, and hybridised to labelled single stranded RNA probes specific to each strand. In the second experiment, the second strand replication follows univalently, and hybridisation of the second strand allows the first strand site to be observed. This has enabled the DNA replication origin to be localised to a 2 kilobase segment, and this contains a sequence motif previously implicated in other eukaryotic origins.

ANDREW WILKIE

Diagnosis of human genetic disease using recombinant DNA; fourth edition

These authors present what will be their last hard copy update of this useful database. Its major feature is a tabular list of genetic conditions giving disease, McKusick number, gene name code, probe, distance between probe and genetic locus, method of detection, nature of the mutation, and recent references up to and including 1992. Over the two years since the last edition, the number of conditions for which analysis is possible has increased. This is an ever-evolving field, and the vast majority of identified gene defects remain point mutations and deletions with only a relatively minor contribution from insertions, duplications or other gene rearrangements. Despite the tremendous progress in identifying the specific cause of many of the major genetic diseases, there is a growing number of conditions which can be approached only through linkage analysis (113 from the current list). This series has fulfilled its aim in providing genetic counselors, clinical geneticists, and others with a quick reference to relevant publications and thereby to groups working on a specific disease; for future advances we refer to the electronics of Online Mendelian Inheritance in Man available through all good Human Genome Database terminals.

JOHN C K BARBER

Denys-Draunc syndrome: relating a clinical disorder to genetic alterations in the tumor-suppressor gene WT1

Denys-Draunc syndrome (DDS) was initially described in three males with ambiguous genitalia, nephropathy, and Wilms’ tumour. Subsequently, the criteria for diagnosis were widened to include patients of either sex with nephropathy owing to diffuse or focal mesangial sclerosis and either Wilms’ tumour or ambiguous genitalia. The genital abnormalities are variable and are usually only seen in males. The nephropathy is of early onset in the majority of cases and progresses to end stage renal failure in childhood. The Wilms’ tumours show similar histological changes to those in patients without DDS but are more likely to be bilateral. The WT1 locus at 11p13 was analysed using molecular genetic techniques in 36 patients with DDS. Thirty-four were found to have point mutations and one a deletion of this locus. Not all regions of the gene were screened. All but two mutations were missense mutations and the majority were clustered in exons 9 with 19 patients sharing the same mutation. The authors speculate on the role of the WT1 gene, a tumour suppressor, in producing the various features of DDS. The development of Wilms’ tumour is presumably related to the loss of function of the gene and a critical role for WT1 in developing kidney is suggested as glomerular epithelial cells have high levels of WT1 messenger RNA in the embryo. WT1 is expressed in the genital ridge and fetal gonads in the human and mouse embryo, suggesting that it may be responsible for genitourinary malformations although the male preponderance of these has still to be explained, and that the coexistence of point mutations in females without genital abnormalities confirms that these are not an essential part of the syndrome. It seems surprising that after such convincing molecular genetic results the authors are somewhat dismissive of their usefulness, concluding that the renal biopsy findings remain the hallmark of DDS. They do agree that analysis of WT1 is indicated in children with mesangial sclerosis and may influence the management of the patient, for example, by earlier nephrectomy. An inherited WT1 mutation has been described in a DDS patient with a phenotypically normal father and examination of the WT1 locus in parents is therefore indicated. This finding is puzzling. It may indicate incomplete penetrance or other modifying factors and suggests that the use of WT1 analysis as a prenatal diagnostic test is clearly limited. Future studies of the WT1 protein may help to answer some of the questions raised in this paper and confirm the role of WT1 in embryonic development.

JILL CLAYTON-SMITH