MEDICAL GENETICS: ADVANCES IN BRIEF

Cloning of cDNAs for Fanconi's anaemia by functional complementation

Strathdee CA, Gavish H, Shannon WR, Buchwald M. *Nature* 1992;**356**:763–7

Fanconi's anaemia, a DNA repair disorder showing particular sensitivity to DNA cross-linking agents (for example mitomycin C and diepoxybutane), is characterised clinically by progressive pancytopenia, acute myeloid leukaemia, skin pigmentation, and radial defects. Classical cell mixing experiments have shown at least four complementation groups: after a long search these authors have identified the molecular basis of the group C type. The major novelty in their approach was the use of an Epstein–Barr virus based cDNA expression shuttle vector, which could be maintained episomally in the mammalian cell during treatment with cross-linking agents; plasmids conferring resistance were then easily recovered by shuttling back to *Escherichia coli*. Three cDNAs were isolated, corresponding to alternatively spliced and truncated derivatives of the same gene, termed FACC; appropriate mutations within this gene were identified in some Fanconi patients. Comparison with nucleic acid and protein sequence databases showed no homology with any known gene. This work is a first step in elucidating the molecular relationship between the Fanconi complementation groups, and may shed light on why mutation of DNA repair genes should lead to specific developmental abnormalities.

ANDREW WILKIE

Common sequence motifs at the rearrangement sites of a constitutional X/autosome translocation and associated deletion

Giacalone JP, Francke U. *Am J Hum Genet* 1992;**50**:725–41.

This paper investigates the mechanism by which a t(X;4) translocation has occurred. The authors exploit the fact that this de novo translocation has disrupted the dystrophin gene. The results from their series of experiments showed a tetramer present on both the X and the chromosome 4 at the site of the breakpoint and in the same orientation. They also found a 5 kb deletion of DNA from the X chromosome with four bases matching the tetramer inverted at the distal end of the deleted fragment. Thus this is another example of an apparently balanced translocation being more complex, an important message for those cloning translocation breakpoints in order to identify a disease gene. It is surprising that such a short region of homology seems to be implicated at the translocation breakpoints, though this echoes the findings at the t(X;21) translocation breakpoint cloned by Bodrug *et al*, who found the tetramer CGCGC present in one copy on the X and several copies on chromosome 21. This translocation was paternal in origin bringing the numbers of X;autosome translocations that are paternally derived to 13/13. This leads to speculation about whether this is a feature of spermatogenesis or that it is only in male meiosis that a large part of the X chromosome is 'free', as in the female the two X chromosomes will synapse. This question can be addressed by looking at the parent of origin in de novo autosome;autosome translocations.

JUDITH GOODSHIP

Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus

Scambler PJ, Kelly D, Lindsay E, *et al.* *Lancet* 1992;1138–9.

Most patients with DiGeorge syndrome are monosomic for a region of chromosome 22q11. Following the revision of the diagnosis of DiGeorge syndrome to that of velo-cardio-facial syndrome in two patients, Dr Scambler and colleagues analysed DNA from patients with the latter condition to test the hypothesis that the clinical spectrum of velo-cardio-facial syndrome encompasses DiGeorge syndrome, and has a related causation. All five patients with velo-cardio-facial syndrome tested were deleted for at least one 22q11 probe. Additionally, one velo-cardio-facial syndrome patient examined by fluorescent in situ hybridisation (FISH) showed hemizygosity for a 22q11 cosmid clone. Moreover, a further velo-cardio-facial patient with an interstitial deletion has been established to be deleted for 22q11 probes. Based on these three sources of evidence, the authors conclude that hemizygosity at 22q11 may be associated with a wide range of phenotypes and that a proportion of patients with isolated features of DiGeorge or velo-cardio-facial syndrome may have deletions or mutations at 22q11. The authors are seeking such patients to test this hypothesis.

W REARDON

Abnormal regulation of mammalian $p21^{ras}$ contributes to malignant tumour growth in von Recklinghausen (type 1) neurofibromatosis

DeClue JE, Papageorge AG, Fletcher JA, *et al, Cell* 1992;**69**:265–73.

The sequence and functional homology between the catalytic domain of the NF1 gene, yeast IRA, and mammalian GAP genes suggests that the NF1 protein (neurofibromin) may be a regulator of the *ras* oncogene. This paper describes abnormal regulation of the *ras* protein, $p21^{ras}$, in cell lines derived from malignant schwannomas from NF1 patients. The cell lines showed a reduced expression of neurofibromin but normal levels of $p21^{ras}$ were observed. However, there was an increase in the active, GTP bound form of the $p21^{ras}$. Further investigation of one of the cell lines showed a severe reduction in GTPase activity in cell extracts. Since GAP is expressed in this cell line, this also suggests that GAP is less important than neurofibromin in $p21^{ras}$ regulation in Schwann cells. Introduction of GAP catalytic region into these cells induced a reversion of the morphology and a reduction in the GTP bound form of $p21^{ras}$ to control levels. These findings suggest that neurofibromin is a downregulator of $p21^{ras}$ and that reduced neurofibromin levels in NF1 tumour cell lines cause an increase in the active GTP bound form of $p21^{ras}$.

N S THAKKER

Point mutations and polymorphisms in the human dystrophin gene identified in genomic DNA sequences amplified by multiplex PCR

Kilimann MW, Pizzuti A, Grompe M, Caskey CT. *Hum Genet* 1992;**89**:253–8.

Approximately one-third of Duchenne muscular dystrophy patients have mutations undetectable by Southern blotting or multiplex exon amplification. Prenatal diagnosis and the assignment of carrier status in female relatives of such patients therefore still relies upon linkage analysis with its inherent error rate owing to recombination. This paper describes the screening of 60 such DMD patients for point mutations by chemical mismatch cleavage analysis of PCR amplified exons and subsequent sequencing. Two frameshift mutations were found which resulted in a deficiency of dystrophin protein. Four polymorphisms were also detected. Because of the identification of a single base insertion in one of the two frameshift patients it was possible to use allele specific oligonucleotides to show that the patient's mother was a carrier of the mutation. PCR primers covering only one fifth of the dystrophin coding sequence were used and therefore the authors assume that more mutations would be found upon analysis of the whole coding sequence. They suggest that mismatch analysis of PCR amplified dystrophin mRNA would be appropriate for this. In conclusion the authors have described a useful addition to the available techniques for the identification of mutations within the dystrophin gene and of female carriers of such mutations.

D O ROBINSON