MEDICAL GENETICS: ADVANCES IN BRIEF

Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A

Mulligan LM, Kwok JBJ, Healey CS, *et al.* *Nature* 1993;363:458–60.

MEN 2A is a dominantly inherited cancer syndrome characterised by medullary thyroid carcinoma and pheochromocytoma. Until now, family screening has relied on laborious biochemical investigation and it has been unclear whether this should be offered to the relatives of isolated cases with single tumours. Mulligan *et al* have now used a 'positional candidate' approach to identify germline mutations in the RET oncogene on chromosome 10q11.2 in 20 out of 23 MEN 2A families. RET was previously known to show gross rearrangements in 25% of papillary thyroid carcinomas, but in striking contrast, the mutations in the MEN 2A families are all amino acid substitutions, and in 19 families the same cysteine residue (codon 380) is involved. Five different mutations of this residue were identified and haplotype analysis suggests that some of the individual mutations may have multiple independent origins. If confirmed by other groups, these results would have important implications for screening, as a high proportion of germline RET mutations could be detected without laborious genome scanning methods. As yet it is unclear whether MEN 2B (additionally associated with mucosal neuromatosis and Marfanoid habitus, and mapping to the same region of 10q) is allelic, but I would bet that the answer will not be long in coming.

ANDREW WILKIE

Identification of the von Hippel-Lindau disease tumour suppressor gene

Latif F, Tory K, Gnarr J, *et al.* *Science* 1993;260:1317–20.

Von Hippel-Lindau (VHL) disease is a rare familial cancer syndrome with an estimated incidence of 1 in 36 000. It is inherited as a dominant conferring a high risk of cancer of the brain, eye, or kidney; average life expectancy is reduced to 49 years. After a six year search, this French, American, and British team has identified the VHL gene by positional cloning. Large deletions of up to around 15 kb have been found in 18/221 VHL families. Furthermore, deletions and insertions at the nucleotide level have been identified in VHL families as well as in sporadic renal cell carcinoma patients. Interestingly, both the two transcripts of the gene are expressed in all adult tissues but only the shorter tran-

script in fetal brain and the longer transcript in fetal kidney. The gene is evolutionarily conserved, but shows no significant homology with any known gene or protein. The authors suggest that the presence of a repeated acidic pentamer indicates the protein product is membrane mounted and may be involved in signal transduction or cell adhesion. Isolation of this gene should be of immediate benefit to known VHL families and also provides a new target for the identification of mutations present in sporadic cancers.

JOHN C K BARBER

Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia

Moorani S, Roy M, Torres A, *et al.* *Lancet* 1993;341:1303–6.

Familial hypercholesterolaemia (FH) results from mutations involving the low density lipoprotein (LDL) receptor gene causing a highly variable rise in plasma cholesterol levels and premature coronary heart disease (CHD). Moorani *et al* present data on 21 patients, homozygous for FH, and consider their plasma cholesterol levels and clinical course in terms of the underlying mutations. Eleven patients were homozygous for a large (greater than 10 kb) deletion of the promoter region and exon 1, the remaining 10 patients being homozygous for an exon 3 missense mutation. In terms of function, these mutations result respectively in receptor negative and receptor defective forms of FH. The striking observation is the marked rise of plasma cholesterol in the receptor negative group compared to the receptor defective cohort. This is so profound that there is no overlap in level between the two patient groups suggesting that mutation nature has a direct bearing on plasma cholesterol level. This observation would appear to be true for both homozygotes and heterozygotes. The authors further suggest that the expression of the wild type allele in heterozygotes may be modified by the nature of the mutation to account for their observations in regard of plasma cholesterol in such patients. Their final conclusion is that CHD, while equally frequent in both mutation types, arose earlier in the receptor negative cohort, implying that the raised plasma cholesterol in this group is directly linked to the genesis of coronary heart disease, an observation supported by findings in an earlier Japanese

study. This is a most interesting paper, particularly as it makes sense of the 4 to 8-fold variability in cholesterol levels which have been reported in FH subjects. Whether the claims for altered wild type expression by mutant are sustainable or not will call for further and larger scale work, to which we may look forward.

W REARDON

A molecular defect in the vasopressin V2-receptor gene causing nephrogenic diabetes insipidus

Holtzman EJ, Harris HW, Kolakowski LF, Guay-Woodford LM, Botelho B, Ausiello DA. *N Engl J Med* 1993;328:1534–7.

A mutation in the vasopressin V2-receptor gene in a kindred with X-linked nephrogenic diabetes insipidus

Merendino JJ, Spiegel AM, Crawford JD, O'Carroll A, Brownstein MJ, Lolait SJ. *N Engl J Med* 1993;328:1538–41.

The antidiuretic action of arginine vasopressin requires the binding of the hormone to the renal type (V2) vasopressin receptor, which results in the activation of adenylate cyclase, the generation of cAMP, and increased reabsorption of water across the apical membrane of the cells of the renal collecting duct. In congenital nephrogenic diabetes insipidus (NDI) the renal response to arginine vasopressin is impaired. Affected boys present soon after birth with repeated episodes of severe dehydration and hypernatraemia which may damage the CNS. Linkage studies mapped the gene to Xq28 and as the vasopressin V2 receptor gene (ADHR) was also localised to this region it became an obvious candidate gene for NDI, its role being confirmed by two papers in *Nature* last year. Holtzman *et al* sequenced PCR amplified ADHR from a NDI family and showed a C→T transition leading to tryptophan substitution for arginine in the expressed protein. This was found in all the affected subjects and obligate heterozygotes and in none of the unaffected members of the pedigree. Merendino *et al* showed a frame shift mutation causing premature polypeptide termination in their family. The vasopressin V2 receptor belongs to a family of G protein coupled receptors which include rhodopsin and other opsins. Earlier diagnosis and treatment of affected offspring in known families is now possible.

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