Medical genetics: advances in brief

Contribution of *BRCA1* mutations to ovarian cancer

Stratton JF, Gayther SA, Russell P, *et al.* *N Engl J Med* 1997;336:1125-30.

Women carrying germline mutations in the *BRCA1* gene are estimated to have lifetime risks of breast and ovarian cancer of 85% and 45% respectively, but the contribution of *BRCA1* mutations to these cancers in the general population is not yet established. This article describes the results of screening for germline *BRCA1* mutations by heteroduplex analysis of the entire coding sequence in 374 women with epithelial ovarian cancer attending a London oncology centre. The patients were younger than 70 at the time of diagnosis, but were otherwise unselected for tumour type and past medical or family history, and included those with borderline tumours. Heterozygous mutations were found in 13 patients (3%), distributed throughout the gene, of which 12 were predicted to result in a truncated *BRCA1* protein and one in a single amino acid deletion. The prevalence of *BRCA1* mutations in those diagnosed before the age of 50 years was 5% (95% confidence interval 2-11%) compared with just under 3% (95% confidence interval 1-6%) at 50 or older. Based on an assumed mutation detection sensitivity of 70% they estimate that the overall proportion of ovarian cancers attributable to *BRCA1* mutations in British women under 70 is 5% (95% confidence interval 3-8%), which is in line with previous indirect estimates. Of the 13 women with *BRCA1* mutations nine had a family history of breast or ovarian cancer or both, all except one in a first degree or paternally related second degree relative. There was no statistically significant difference in the mean age at diagnosis of the women with *BRCA1* mutations and their relatives compared with the non-carriers for either breast or ovarian cancer. Twelve of the 13 patients with *BRCA1* mutations had serous cystadenocarcinomas (compared with 58% of the total study population) suggesting an eightfold increased chance of underlying *BRCA1* mutation in patients with this tumour type. At present screening for germline *BRCA1* mutations in all patients with breast or ovarian cancer is unrealistic.

Furthermore, germline *BRCA2*, *hMSH2*, and *hMLH1* mutations also contribute to familial cases. The authors note that restricting *BRCA1* testing to families with three or more cases of breast or ovarian cancer would not have detected 10 of the 13 mutation patients, whereas including the 20% of index patients who had one relative with either breast cancer before the age of 60 or ovarian cancer would have detected nine of the 13 mutations. Further selection for serous cystadenocarcinoma would not have provided an advantage in their study group.

LOUISE WILSON

Somatic inactivation of the *VHL* gene in von Hippel-Lindau disease tumours

Prowse AH, Webster AR, Richards FM, *et al.* *Am J Hum Genet* 1997;60:765-71.

Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder which predisposes to renal cell carcinomas (RCC), retinal and CNS haemangioblastomas, pheochromocytomas, and pancreatic tumours. Pheochromocytomas are known to occur more commonly in families with missense mutations. In this paper the mechanism of tumourigenesis in VHL tumours was studied. Fifty-three tumours (30 RCCs, 15 haemangioblastomas, five pheochromocytomas, and three pancreatic tumours) from 33 patients (27 kindreds) were analysed. Fifty-one percent of the 45 informative tumours showed loss of heterozygosity (LOH) at the *VHL* locus, and in the 11 cases in which it was possible to distinguish between loss of wild type and mutant alleles, it was the wild type which was lost. LOH was found in all types of tumours and occurred in the presence of a variety of different mutations. Homozygous inactivation of the *VHL* gene is obviously a crucial step in the development of a tumour by the same mechanism as found in retinoblastoma. The mutational events typically involve a "first hit" which is a localised intragenic mutation (for example, point mutations, microdeletion) and then a "second hit" which is a large deletion or mitotic recombination event resulting in LOH at polymorphic markers within or close to the tumour

suppressing gene. Hypermethylation is also important, however, and was detected in 33% (6/18) of tumours without LOH. Although hypermethylation of the *VHL* gene has been reported previously in non-familial RCC, and although methylation of tumour suppressor genes has been implicated in the pathogenesis of other sporadic cancers, this is the first report of somatic methylation in a familial cancer syndrome.

FRANCES FLINTER

Functional screening of 2 Mb of human chromosome 21q22.2 in transgenic mice implicates *minibrain* in learning defects associated with Down syndrome

Smith DJ, Stevens ME, Sudanagunta SP, *et al.* *Nat Genet* 1997;16.1:28-36.

This paper describes the identification of a candidate gene which may influence learning ability in people with Down syndrome. Transgenic mice were constructed containing overlapping YACs covering about 2 Mb of contiguous DNA from human chromosome 21q22.2. Independent low copy number mouse lines containing each of four different overlapping YACs from this region were subjected to behavioural and learning assays. Two YACs were found to be associated with defects in learning and memory. A further mouse line with similar learning defects was then identified containing a 180 kb fragment of one of these YACs. This fragment contains the human homologue of the *Drosophila* gene *minibrain* which is therefore strongly implicated as a cause of learning defects in Down syndrome. The importance of this work is not only the identification of a gene likely to be associated with the Down syndrome phenotype. It also describes a novel approach to the dissection of genes responsible for the individual features of any complex phenotype caused by a trisomy or increased dosage of a chromosomal region. Genotype/phenotype relationships can be analysed using panels of transgenic mice containing overlapping YACs from defined regions of the genome.

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