

Medical genetics: advances in brief

The severe perinatal form of autosomal recessive polycystic kidney disease maps to chromosome 6p21.1-p12: implications for genetic counseling

Guay-Woodford LM, Muecher G, Hopkins SD, *et al.* *Am J Hum Genet* 1995;56:1101-7.

Autosomal recessive polycystic kidney disease affects between 1 in 6000 and 1 in 40 000 neonates, making it one of the commonest cystic renal disorders in childhood. The phenotype can vary quite considerably, but most cases present in infancy. Most congenitally affected babies die shortly after birth. Prenatal diagnosis in the past has been difficult; only antenatal ultrasound scanning could be offered, with a considerable risk (20-50%) of a false negative result, even with the most experienced operators. (Affected fetuses may have enlarged, echogenic kidneys and oligohydramnios secondary to poor renal function in utero, and as a consequence may develop the Potter phenotype.) Historically there has been debate about the genetic basis of ARPKD, with some authors suggesting that there were four discrete phenotypes caused by four distinct genes. Subsequent reviews refuted this argument. Last year, Zerres *et al* mapped the gene for ARPKD in a cohort of families, mostly with the milder phenotype, to a 13 cM region of chromosome 6p21-cen. Now the authors of this paper have been able to study a separate cohort of 22 families with the severe phenotype. Their data confirm linkage to the same region, and refine ARPKD region to a 3.8 cM interval delimited by the markers D6S465, D6S427, D6S436, D6S272, and D6S466. Combining the results from the two studies, the implication is that there is a single ARPKD gene, despite the wide variability of clinical phenotype. Now we must wait for the cloning of the gene before the description of individual mutations can help to explain the broad clinical spectrum of severity. Meanwhile, it is extremely important that DNA is banked from affected subjects, because the linkage results are strong enough to allow first trimester prenatal diagnosis in informative families, and there is likely to be considerable demand for this.

FRANCES FLINTER

KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2

Dong JT, Lamb PW, Rinker-Schaeffer CW, *et al.* *Science* 1995;268:884-6.

Cancer of the prostate is one of the leading causes of cancer death and expected to develop in as many as 1 in 11 males by the end of their lives. The lack of a means of distinguishing those with benign hyperplasia of the prostate from those with a malignancy which can spread by metastasis to other sites is a major problem. This team had already identified a region of chromosome 11 that was capable of suppressing the normal metastatic potential of a rat prostate cancer cell line (AT6.1) when fused to non-metastatic cancer cells. Now they have cloned a gene from this region termed KAI1 from *kang ai*, the Chinese for anti-cancer. When the cDNA of this KAI1 gene was cloned into the same AT6.1 prostate cancer cells, higher levels of suppression of AT6.1 lung induced metastasis in nude mice were correlated with levels of KAI1 mRNA. In addition, northern blotting of human cell lines derived from metastatic prostate tumours also showed reduced expression by comparison with control prostate tissue. The gene is expressed in multiple tissues, is evolutionarily conserved, and belongs to a family of leucocyte surface proteins which all have N-glycosylated extracellular domains consistent with the established connection between N linked oligosaccharide processing and metastasis. The KAI1 sequence also has homology with other transmembrane 4 proteins (which zigzag through the membrane four times) which are thought to maintain cell-cell connections. Reduced KAI1 expression might then release cells from a primary cancer which could be circulated to other sites. The discovery of KAI1 and other metastatic suppressor genes opens up the possibility of differentiating cancers with and without metastatic potential. In addition any factor capable of limiting the spread of cancer could be of enormous therapeutic potential.

JOHN C K BARBER

Rapid antibody test for fragile X syndrome

Willemsen R, Mohkamsing S, De Vries B, *et al.* *Lancet* 1995;345:1147-8.

The issue of screening for fragile X syndrome is a complex one. Although the use of DNA technology could allow for screening to detect those at risk of affected offspring, the optimum timing of testing of the general population has not been established. For neonatal screening the issues raised by the detection of asymptomatic carriers have made routine testing unlikely until the potential benefits and hazards have been evaluated. The phenotype in fragile X is believed to result from deficiency of FMRP, the protein product of the FMR-1 gene. Anomalous methylation associated with the expansion mutation in full mutation carriers results in the absence of mRNA and of the protein product. Detection of the protein product could avoid some of the contentious issues in screening by only detecting those likely to have a clinical phenotype associated with absence of the protein. Willemsen *et al* describe a method to detect FMRP by the use of monoclonal antibodies to FMR-1 that can be used on blood. Microscopy of the lymphocytes is required after incubation with the antibody. The authors have found this method reliable in detecting affected males, with no overlap in levels of expression between mosaic males and normals. In a female full mutation carrier they show that FMRP can be detected in only 60% of her lymphocytes. The numbers of affected subjects tested is still small and the method may be cumbersome in females but is likely to provide an accurate and reliable assay for detecting affected males. The authors suggest that this technique could be used for neonatal screening using a Guthrie type blood spot. The identification of males affected with mental handicap where therapy has little to offer in terms of modifying the outcome needs especially rigorous assessment before implementation. However, this method is important and will provide a valuable tool in further developing understanding of fragile X syndrome.

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