

MEDICAL GENETICS: ADVANCES IN BRIEF

Maternal inheritance of atopic IgE responsiveness on chromosome 11q

Cookson WOCM, Young RP, Sandford AJ, *et al.* *Lancet* 1992;340:381-4

Following on the data, from the same group, which assigned a gene for respiratory atopy to chromosome 11q13, this study investigated the epidemiological observation that children of atopic mothers are at higher risk of atopy than those of atopic fathers. Data were evaluated by affected sib pair analysis. Although atopy free sibs showed the expected 50/50 distribution in allele inheritance at the 11q13 locus, affected sibs showed a significant ($p=0.001$) deviation from random allele inheritance at this locus. Paternal alleles at this locus were randomly inherited by affected sib pairs and unaffected sibs alike. Having ruled out increased recombination in males at this chromosomal region, the authors feel that "the inheritance of atopy at this locus has occurred through the maternal line". Since the corresponding area of the murine genome is known to be imprinted, the article speculates on this as a possible explanation. While the excess sharing of maternal alleles among affected sibs is independent of the mothers' own atopic state, atopy is also seen in children of atopic fathers and non-atopic mothers, in which patient group 11q13 maternal and paternal alleles are randomly distributed. Given the independent observation that the risk of atopy is increased if both parents are atopic, this patient subgroup could possibly represent a genetically distinct form of atopy. The results await comparison with and corroboration by other patient datasets. Meanwhile their precise significance must remain uncertain. However, they do suggest that the earlier linkage reports in this patient cohort between respiratory atopy and chromosome 11q13 were not misplaced, although confirmation by other researchers using other patient datasets has been slow to emerge. Finally, given the generality of 'atopy' as a descriptive term and as a clinical response, one wonders if the authors should not continually emphasise the predominantly respiratory nature of the symptomatology in this patient cohort.

WILLIAM REARDON

Integration of human α -satellite DNA into simian chromosomes: centromere protein binding and disruption of normal chromosome segregation

Haaf T, Warburton PE, Willard HF. *Cell* 1992;70:681-96.

The mammalian centromere is characterised by the presence of varying amounts of non-transcribed repetitive sequences (satellite DNAs) with α -satellite DNA predominating in primates. Circumstantial evidence suggests that satellite DNA and several different centromere associated proteins (CENPs) are involved in centromere function. This paper reports findings that provide direct evidence for a role for α -satellite DNA in centromere function. Human α -satellite DNA was transfected into African green monkey (AGM) cells. Immunocytochemistry with antisera against CENPs showed co-localisation of CENPs with α -satellite DNA indicating that α -satellite DNA binds directly to the CENPs. Furthermore, presence of both the AGM and human α -satellite sequences on

the same chromosome resulted in disruption of chromosome segregation. This suggests that the α -satellite DNA contributes to the formation of de novo centromeres and that the disruption of segregation is the result of the di- or multicentricity of the transfected chromosomes. Chromosomes bearing only the human α -satellite DNA segregated normally at anaphase. Although the data indicate a role for α -satellite DNA in centromere function, it is unclear whether it is involved in kinetochore formation or apposition of sister chromatids or both. These data are also interesting because there is a lack of sequence conservation among centromere specific satellite DNAs in mammals. It is possible that repeated DNA sequences other than the α -satellite DNA may be able to execute similar functions.

N S THAKKER

Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis

Handyside AH, Lesko JG, Tarin JJ, Winston RML, Hughes MR. *N Engl J Med* 1992;327:905-9.

Preimplantation diagnosis of cystic fibrosis was attempted in three couples, both members of each couple being carriers of the Δ F508 deletion. In vitro fertilisation techniques were used to recover oocytes from each woman and fertilise them with her husband's sperm. Three days after insemination, embryos in cleavage stage underwent biopsy and removal of one or two cells for DNA amplification and analysis. Two oocytes from one woman were fertilised; DNA analysis of one of the embryos failed and cystic fibrosis was diagnosed in the other so neither was transferred. The oocytes of each of the other two women produced non-carrier, carrier, and affected embryos. Both couples chose to have one non-carrier and one carrier embryo transferred. One woman became pregnant and gave birth to a girl free of the deletion. This case received wide publicity in the lay press recently and genetics centres have received many requests for preimplantation diagnosis for this and other autosomal recessive disorders. However, before this demand can be met the disadvantages of this approach need to be thoroughly assessed. In particular, we need to know how likely a normally fertile couple are to achieve a pregnancy by this approach, and so far this information is not available.

ANDREW NORMAN

Mice deficient for Rb are nonviable and show defects in neurogenesis and haematopoiesis

Lee EYHP, Chang CY, Hu N, *et al.* *Nature* 1992;359:288-94.

The era of the targeted mouse mutant is moving into full swing. The past few months have seen models for Gaucher's disease, p53 mutation, and cystic fibrosis described in *Nature*. In this issue, knockout mutants of the RB-1 gene in mice are described by three independent groups (in the above paper and others by Jacks *et al* and Clarke *et al*), using the positive/negative selection system pioneered by Capecchi. Briefly, a

construct comprising part of the target gene, interrupted by a neomycin resistance gene and flanked by thymidine kinase (TK) genes, is electroporated into mouse embryonic stem (ES) cells; G418 treatment selects for cells containing inserts, while gancyclovir causes the suicide of cells retaining TK activity because of non-homologous integration. ES cells are injected into blastocysts and transferred to pseudopregnant mice, producing chimeric mice that can transmit the mutation in the germline in the next generation. The phenotype of the RB⁻ mice produced by the three groups is very similar: homozygotes appear normal until embryonic day 12, then die by day 16 with severe erythropoietic and nervous system abnormalities. This supports the notion that RB-1 serves a critical function in normal development. Heterozygous mice are predisposed to pituitary tumours, but otherwise appear healthy; they do not develop the retinoblastomas or sarcomas that characterise the human mutation. This reminds us that although mice provide valuable disease models, they do not fully mimic the situation in humans.

ANDREW WILKIE

A large deletion in the LDL receptor gene - the cause of familial hypercholesterolemia in three Italian families: a study that dates back to the 17th century (FH-Pavia)

Bertolini S, Lelli N, Coviello DA, *et al.* *Am J Hum Genet* 1992;51:123-34.

Time and space clusters of the French-Canadian M1V phenylketonuria mutation in France

Lyonnet S, Melle D, de Braekeleer M, *et al.* *Am J Hum Genet* 1992;51:191-6.

Bertolini and colleagues found three apparently unrelated families from different parts of northern Italy who had the same mutation, a 25 kb deletion of the LDL receptor gene eliminating exons 2 to 12, causing familial hypercholesterolaemia. They traced these three families back using family history, local council records, and parish archives through 13 generations to a common ancestor living in a small town called Gravellona in Lombardy in 1615. The phenylketonuria M1V mutation was thought to be exclusive to French-Canadians. Lyonnet and colleagues carried out mutation and RFLP haplotype analysis in contemporary French families. They found the M1V mutation in 4/152 independent French chromosomes. The people carrying these mutations all live in southern Brittany. A genealogical reconstruction of the Quebec families identified shared ancestors in the Perche area to the east of Brittany. Assuming that this is where the mutation first arose, either people moved from Perche to both Quebec and Brittany or an individual person or group returned from Quebec to Brittany. These two articles show again how a combination of genealogy and molecular biology can be used for historical reconstruction. Conversely, when new mutations causing disease are identified, information from local historians may be of use in predicting where, geographically, the mutation is most likely to be found.

JUDITH GOODSHIP