MEDICAL GENETICS: ADVANCES IN BRIEF

Application of carrier testing to genetic counseling for X-linked agammaglobulinemia

Allen RC, Nachtmann RG, Rosenblatt HM, Belmont JW. *Am J Hum Genet* 1994;54:25-35.

Bruton X linked agammaglobulinaemia (XLA) is caused by a disorder of β lymphocyte differentiation, which leads to recurrent bacterial infections from infancy. Female carriers are asymptomatic, and have normal numbers of mature B cells in their peripheral circulation, but they show a characteristic B cell lineage specific skewing of the pattern of X inactivation. Allen *et al* report patterns of X inactivation at the human androgen receptor (HAR) locus in 58 women from 22 families referred with XLA. The first category studied consisted of 20 females from five families with well established X linked inheritance, in which they found > 95% skewing in six out of seven obligate carriers (one was uninformative), and in five further at risk females. Of the remaining eight at risk females, six showed random inactivation, one was indeterminate, and one was uninformative for the HAR polymorphism. In each of the second category of families tested, there was a single, isolated case of XLA and seven of the 11 mothers tested showed skewing, with three showing random inactivation, and one being uninformative. These data would fit with expectations for the occurrence of new mutations in an X linked lethal disease, although the absence of skewing in the peripheral blood would not exclude the possibility of gonadal mosaicism, or autosomal recessive agammaglobulinaemia. The six families in the third category tested had no living affected males, but the mother of a dead child was found to be a carrier in three of the five cases tested. Of the remaining two mothers, one showed random X inactivation, and one showed X inactivation skewing in the T and B cells, suggesting that the primary diagnosis may have been incorrect. While the results were of clinical benefit in several cases (in 10 families the consultant was pregnant), the problems of interpretation in cases with partially skewed inactivation cannot be resolved by this method. There is a paucity of data generally relating to X inactivation patterns in normal controls (only 24 controls were used in this study), and it has been shown that other diseases can also be associated (?coincidentally) with non-random X inactivation. The authors underemphasise the potential of molecular studies which can provide definitive information regarding carrier status once a mutation in the *btg* gene has been defined in a particular family. They suggest that extensive scanning of the coding sequence may fail to detect a substantial percentage of mutations at some loci, on the basis of temporary problems experienced with one gene (haemophilia A), which have now been resolved. In fact, a range of mutations has now been defined in XLA families, and the mutation detection rate in the subgroup with a positive family history is at least 80% (D Vetrie, personal communication).

FRANCES FLINTER

Autosomal dominant transmission of the Pallister-Hall syndrome

Topf KF, Kletter GB, Kelch RP, *et al*. *J Pediatr* 1993;123:943-6.

Pallister-Hall syndrome (PHS) is a multiple congenital anomaly syndrome first described in 1980, with a pattern of clinical features including hypothalamic hamartoblastoma, polydactyly, imperforate anus, and dysmorphic facial features. Most reported patients have died of pituitary failure in the first year of life. Around 25 patients have been reported and these have all been sporadic, with the exception of one family in whom autosomal dominant inheritance was suggested,

but the evidence was not entirely convincing. This group from Michigan report a 9 year old boy and his 34 year old father who both have a hypothalamic hamartoblastoma and other features suggestive of PHS. Both had normal intellectual development and the child presented with precocious puberty, rather than pituitary failure. Although the report lacks useful illustrations, this is the most convincing evidence to date that this condition is the result of a single gene disorder with autosomal dominant inheritance, rather than an environmental cause as has been suggested previously. It also draws attention to the intrafamilial variability and the fact that this condition may be associated with normal intellect in patients who survive the perinatal period. Hypothalamic hamartomas are notoriously difficult to visualise on CT scans, but were detected with great ease on MRI scanning in this family, proving that this is the method of choice for screening for these tumours in those suspected of having PHS and perhaps in their parents.

JILL CLAYTON-SMITH

Association of the APC tumour suppressor protein with catenins

Su L-K, Vogelstein B, Kinzler KW. *Science* 1993;262:1734-7.

Association of the APC gene product with β -catenin

Rubinfeld B, Souza B, Albert I, *et al*. *Science* 1993;262:1731-4.

Mutations in the APC gene confer the dominantly inherited predisposition to colon cancer seen in familial adenomatous polyposis and are also involved in the early stages of sporadic cancer of the colon. These two teams have now provided the first indication of the possible function of APC by raising antibodies to APC and using them to immunoprecipitate proteins from wild type and mutant APC cell lines. Not only were APC gene products detected but so too were proteins which seemed to be identical to both α - and β -catenin. The association between the APC gene product and catenins is potentially important as catenins are essential components of the transmembrane complexes in which E-cadherin is the cell surface end and the catenins the cytoplasmic partners which connect with the cytoskeleton. These complexes are thought to play a vital role in maintaining the integrity of epithelial cell layers. Both teams propose that mutant APC has a reduced affinity for catenins and that this could result in impaired cell adhesion or communication. An extra twist is provided by the protein sequence homology between β -catenin and the *Drosophila* segment polarity protein Armadillo which has in turn been shown to play a key role in cell adhesion.

JOHN C K BARBER

Factor VIII gene rearrangements in patients with severe haemophilia

Goodeve AC, Preston FE, Peake IR. *Lancet* 1994;343:329-30.

Although the factor VIII gene, responsible for haemophilia A, has been cloned for 10 years and mutations in the gene identified since 1985, mutation detection has proven to be of limited value in clinical counselling application. The reason for this was thought to be the large size of the gene, 26 exons spanning 189 kb, and thus not readily amenable to the cumbersome techniques of mutation detection used in the mid 1980s. Surprisingly, PCR based techniques only increased the rate of mutation detection to a little over 50% and in almost half of all severely affected patients no mutation could be found. Recent data have shown

that this is because of homologous recombination involving an intragenic gene of unknown function, factor VIIIa and its two more telomeric copies. This disables the FVIII gene so that exons 1-22 are dissociated from exons 23-26. Almost 50% of severe cases have this underlying rearrangement. The Southern blot technique allows rapid recognition of this rearrangement and may be used as an aid to counselling females where there is no surviving affected member, as shown by Goodeve *et al*. There are also implications for management in that FVIII inhibitor did not develop in any of the 10 cases identified with the intragenic rearrangement, in contrast to seven of 12 cases resulting from other mutations. Larger numbers of cases will help to determine whether this is a substantive finding or a statistical quirk as suggested in the accompanying editorial.

W REARDON

A healthy male with compound and double heterozygosity for $\Delta F508$, F508C and M470V in exon 10 of the cystic fibrosis gene

Desgeorges M, Kjellberg P, Demaille J, Claustre SM. *Am J Hum Genet* 1994;54:384-5.

Most males with cystic fibrosis are infertile with aspermia secondary to absence of the vas deferens. Congenital bilateral absence of the vas deferens (CBAVD) may also be found in 1 to 2% of healthy infertile males who have no evidence of cystic fibrosis (CF). The existence of seven reported familial cases of CBAVD in otherwise healthy males led to the suggestion that the inheritance could be autosomal recessive, and in 1992 Anguiano *et al* suggested that CBAVD could, sometimes, represent a very mild, primarily genital form of CF, as more than half of affected subjects which he studied carried at least one CF mutation. In 1992 data from two groups were combined to show that, of 44 men with CBAVD who had been screened for mutations in the CF gene, 24 had at least one abnormal CF gene, including three who were compound heterozygotes. Only a limited range of mutations had been screened for, and so it seemed possible that other, rare mutations remained undiscovered in this group. In 1993 Meschede *et al* described a patient with CBAVD who was heterozygous for $\Delta F508$, and a compound heterozygote for the variants F508C and M470V, and the authors postulated that the M470V allele would contribute to the clinical phenotype of CBAVD if it was inherited together with $\Delta F508$ and F508C. Now Desgeorges *et al* have described the same genotype in a healthy man who presented for CF carrier testing as his wife was pregnant and he had a nephew with CF who was homozygous for $\Delta F508$. The authors conclude that, contrary to the suggestion by Meschede *et al*, it is unlikely that the compound and double heterozygosity for $\Delta F508$, F508C, and M470V in exon 10 of the CF gene could contribute to the CBAVD phenotype. The possibility of non-paternity has not been excluded, however. Meanwhile, there are several genetic implications to be addressed. Patients with CBAVD may have a mild form of CF and DNA from such patients can be analysed for mutations in the CF gene. Any patients found to carry one or more CF mutations will need careful genetic counselling, together with their partners, who may also be offered screening, particularly if the couple is considering microsurgical aspiration of sperm from the epididymis for use in vitro fertilisation programmes (spermatogenesis in men with CBAVD is normal). If both partners are CF carriers, prenatal diagnosis can be offered, but it may be difficult to predict the likely severity of CF in the fetus when rarer mutations are involved.

FRANCES FLINTER