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


X-linked agammaglobulinemia (XLA) is caused by a disorder of B lymphocyte differentiation, which leads to recurrent bacterial infections from infancy. Female carriers are asymptomatic, and their offspring, regardless of sex, always inherit the disease from their affected father. It was not until 1970 that the genetic basis was determined. Certain members of mature B cells lack an essential early step 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 uninformative, and one was uninformative for the HAR polymorphism. In each of the second category of families, there was a sporadic case of XLA among the offspring of 11 of the mothers tested showed skewing, with three showing random inactivation, and one being uninformative. This 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 agammaglobulinemia. 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 this skewing, and one showed X inactivation 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 consultand 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 series), 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 X linked gene has been identified in a particular family. They suggest that extensive screening of the colon 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 has 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 Vetrin, personal communication).

FRANCES FLINTNER

Autosomal dominant transmission of the Pallister-Hall syndrome


Pallister-Hall syndrome (PHS) is a multiple congenital anomaly syndrome first described in 1980, with a pattern of clinical features including hypothalamic hamartoma, polydactyly, perineal perforate anus, and dysmorphic facial features. Most reported patients have died of pulmonary 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 hamartoma 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 rather than variant inheritance. The evidence seems rather than an environmental cause as has been suggested previously. It also draws attention to the importance of the family history and the fact that this condition may be associated with normal intelligence in patients who survive the perinatal period. Although 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


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. There have been recent reports providing 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 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


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 techniques have been limited in their 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 recently 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 region of unknown function, factor VIIIa and its two more telomeric exons 1-12. This extragenic FVIII gene that exons 1-12 are associated from exons 23-26. Almost 50% of these cases have underlying rearrangement. The Southern blot analysis showed that one copy 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 this technique. We conclude that this is a substantive finding or a statistical quirk as suggested in the accompanying editorial.

W REARDON

A healthy male with compound and double heterozygositites for ΔF508, F508C and M470V in exon 10 of the cystic fibrosis gene


Most males with cystic fibrosis are infertile with no evidence secondary to absence of the vas deferens. Congenital bilateral absence of the vas deferens (CBADV) may also be found in 1-2% of healthy infertile males who have no evidence of cystic fibrosis (CF). The existence of seven reported familial cases of CBADV in otherwise healthy males led to the suggestion that the inheritance could be autosomal recessive, and in 1992 Anguiano et al suggested that CBADV could, sometimes, represent a very mild, primarly hormonal 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 CBADV 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 this might be the general situation, rather than a unique situation. In this group, in 1993 Meschede et al described a patient with CBADV who was heterozygous for ΔF508, and a compound heterozygote for the ΔF508 and C501G mutations, and postulated that the M470V allele would contribute to the clinical phenotype of CBADV if it was inherited together with another mutation. Meanwhile, 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 ΔF508. The authors conclude that, contrary to the suggestion by Meschede et al it is unlikely that the compound and double heterozygositites for ΔF508, F508C, and M470V in exon 10 of the CF gene could contribute to the CBADV phenotype. The possibility of non-paternity has not been excluded, however. Meanwhile, there are several genetic implications to be addressed. Patients with CBADV 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 in vitro fertilisation programmes (sperma- genesis in men with CBADV is normal). In both partners are CF carriers, prenatal diagnosis can be offered, but it may be difficult to predict the outcome of pregnancy if one of the parents is a carrier of the ΔF508 mutation in the fetus when rarer mutations are involved.

FRANCES FLINTNER