Severe cystic fibrosis phenotype in a ΔF508/3272-26A→G compound heterozygote

In the May 1995 issue of the Journal, Kanavakis et al described three cystic fibrosis (CF) compound heterozygotes for the mutation 3272-26A→G. The patients had a mild clinical phenotype as indicated by advanced age of diagnosis, absence of pancreatic insufficiency, and absence of or mild obstructive lung disease. However, we found during the investigation of 100 French adult CF patients, one compound heterozygous ΔF508/3272-26A→G male patient with a severe type of CF. This mutation 3272-26A→G in intron 17α was detected by denaturing gradient gel electrophoresis and was identified by direct sequencing.1 In this CF patient, pneumothorax appeared in the neonatal period and bronchitis and sinusitis were frequent from the age of 10 months. CF was diagnosed only at the age of 8 years by a positive sweat test associated with pulmonary function abnormalities. There was no evidence of pancreatic insufficiency or other gastrointestinal symptoms, but the patient developed severe nasal polyposis. At the age of 16 years, ten, prominent CF problems included chronic airways infection with Staphylococcus aureus and Pseudomonas aeruginosa. Forced vital capacity was 32% of theoretical values and forced expiratory volume in one second was 28% of theoretical values. He was admitted to hospital at the age of 21 years because of pulmonary decompensation and died a few months later.

This case shows that, in contrast to earlier reports, the 3272-26A→G mutation, which creates an alternative cryptic acceptor splice site that competes with the normal acceptor splice site during RNA processing and probably reduces splicing from the correct site, may lead to severe cystic fibrosis.1,3 The explanation for these conflicting results may be resolved by RNA studies. Environmental, genetic, and medical factors can influence the clinical course and it is very difficult to predict the severity of the damage in the different tissues. This case illustrates again that the presence of any specific CFTR mutation offers little in the way of a prognostic indicator in the individual patient.4

MURCS in a male

I read with interest the article in the Journal reporting on a man with Klippel-Feil deformity, unilateral renal agenesis, and azoospermia.1 The authors suggest that Wolflann duct hypoplasia was responsible for the azoospermia and therefore would be analogous to the Müllerian duct hypoplasia found in female patients with MURCS. We saw a similar patient affected with Klippel-Feil anomaly and azoospermia with normal genitalia and of the vas deferens was diagnosed. The patient was sent for further investigations, in particular to determine the condition of the kidneys. However he did not return for follow up. This observation led us to wonder whether Wolflann anomalies in males is the phenotype corresponding to the Müllerian anomalies in females.2 Such a relationship was found in analysis of the phenotypes of males with associations and syndromes in which Müllerian duct anomalies are frequent and of females in families in which anomalies of the Wolflann ducts are found. The only relationship between the Müllerian and Wolflann defects seems to be a developmental one: in the case of early insult, anomalies are found both in males and females. One example is the association of renal agenesis with Müllerian or Wolflann defects. An early insult in the region of the 7th to 14th somite, in which the cervical spine develops, may cause fetal development of the spine as well as the genitalourinary structures because of the intimate spacial relationship to the pronephros and the pronephric ducts. This might explain the relatively high frequency of renal abnormalities in the Klippel-Feil anomaly and the presence in females of Müllerian duct anomalies (MURCS association). Since, as expected, renal anomalies are also frequent in males with the Klippel-Feil anomaly, Wolflann defects should be searched for in those males, as suggested by Wellesley and Slaney.1

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The present volume comprises 15 chapters. Five are exclusively on plants, and might be deemed irrelevant to this readership, but the article "Plant genetic engineering and future agriculture" (S Riazuddin) is of importance to all of us. The author is based in Pakistan, and it was particularly refreshing to read an exploration of this subject in relation to the world's burgeoning population problem from the perspective of a developing country, with gene therapy applied to humans, the technical and ethical hurdles are formidable and, although much is promised, the impact on agricultural production as yet appears to have been small.

Space does not permit all the other 10 articles to be mentioned individually, but I have picked out six which will be of particular interest to those in the human genetics community and help to convey a flavour of the subject matter of the volume. "Transfer of YACs to mammalian cells and transgenic mice" (C Huxley) provides a timely overview of this subject. The advantage of yeast artificial chromosomes (YACs) in transgenesis is that the problem of dissecting all the cis-acting control elements required for normal in vivo expression of the gene of interest can be neatly bypassed by introducing a large genomic DNA segment that contains all the necessary flanking sequences. Furthermore, the process of yeast to mouse recombination facilitates genetic manipulation of the transgene, for example, the introduction of selectable markers or particular mutations. There are useful tables summarising the confusing diversity of YAC vectors available and published transgenic