ing from Murcia, Spain. She was born in 1987, without meconium ileus, and was diagnosed as having cystic fibrosis at the age of 5 months, on the basis of growth retardation, gastrointestinal problems (especially diarrhea and steatorrhea), and repeated bronchitis.

Staphylococcus aureus then Pseudomonas aeruginosa have been isolated from the patient’s sputum since she was 6 months old. She is treated with pancreatic enzymes and antibiotics, but her obstructive lung disease has increased and her patient is classified as severely affected by the clinicians.

Using the SSCP technique to study the DNA extracted from the patient and her family, we detected then identified the stop mutation G542X in the two CFTR genes transmitted to the affected child. This mutation is associated with haplotype 1121221 on the paternal chromosome, and with haplotype 1221211 on the maternal chromosome, as defined by the markers D/TaqI, met H/TaqI, G2/XbaI, XV2/TaqI, KM19/PrI, D9/MspI, and J31/MspI.

The mutation G542X is predicted to result in decreased levels of mutant messenger RNA and in a truncated protein from NBD-1, suppressing 65% of the CFTR protein. The homozygous patients for G542X previously reported had mild pulmonary disease, which would imply alternative splicing mechanisms suppress- ing the effect of the stop mutation in some tissues. Contrasting with these reports, we present the second case of a child homozygous for G542X with severe pancreatic and lung disease. Another similar finding has been reported in a Turkish boy in the neonatal period by Bienvenu et al. Sometimes, in group phenotype correlations might be resolved in the future by mRNA and protein expression studies in target tissues.

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Cutis laxa: a feature of Costello syndrome

We were extremely interested to read the letter 'Cutis laxa and the Costello syn- drome' in which the authors review 5 of their previous paper describing children with cutis laxa and make a diagnosis of Costello syndrome. Recently, and indepen- dently, we have reviewed the same paper and on both hospital and clinical examination made an unequivocal diagnosis of Costello syndrome.

Now that two separate cases within this subgroup of congenital cutis laxa with rep- erguscular and development have been independently diagnosed as Costello syndrome, it is obvious that review of this heterogeneous group and recognition of this syndrome as a differential diagnosis in congenital cutis laxa, especially in the pres- ence of postnatal growth retardation and delayed development.

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Fibrodysplasia ossificans progressiva

I read with interest the article by Connor et al. 'A three generation family with fibrodysplasia ossificans progressiva' (J Med Genet 1993;30:807-10). In the paper, their description of the clinical features and the pathology is only in broad terms, and it is clear that there are many similarities and differences between this condition and chondrodystrophy syndromes. However, they do not provide any information about the molecular basis of the disease.

In this study, we wished to determine the molecular basis of this condition in order to understand the pathogenesis of the disease.

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Low segregation ratios in autosomal recessive disorders

I read with interest the article by Bundey and Young on possible causes for low segregation ratios in autosomal recessive disorders. They hypothesise on possible mechanisms and explanations concerning the low segrega- tion ratio in cartilage-hair hypoplasia (CHH) found in Finland. I would like to add some further thoughts and possibilities to the beha- vioural, methodological, and biological factors that were described in their paper.

In general, parents may have children with having further children, "even in the absence of genetic counselling". This implies that with improvement of clinical genetic facilities, proper early genetic diagnosis, and adequate, non-directive counselling, segregation ratios in AR disorders will in future be even lower. As a result of this, we may then actually be measuring an effect of counselling upon par- ents' behaviour instead of bona fide biological mechanisms. It will then be difficult to find unbiased, that is, un counselled, populations.

(2) Pregnancy which have been tem- natively diagnosed as having a different diagnosis will also have been taken into account for the purpose of accurate ascertainment.

(3) Reduced penetrance in CHH has been found in both of the published population study. In contrast to Mieschter, Solisio et al. found no evidence of reduced penetrance in Finnish CHH families. However, their conclusion was based on 14 small families selected for linkage analysis, where the fraction of affected sibs (after exclusion of the probands) was 0.38. The chance of finding even more penetrant (non-penetrant) affected sibs is unlikely, given the already high segregation ratio in this sample, and so the question of reduced penetrance is still open.

(4) McKusich et al., in their original paper, put forward environmental factors as a hypothetical cause of reduced penetrance and a low segregation ratio in CHH: either the homozygous phenotype is corrected by some normal dietary constituent or the homozygous phenotype is corrected by an environmental factor only in combination with some environmental factor. Although they refer to two X linked disorders to illustrate this possibility (G6PD deficiency and vitamin D resistant rickets), environmental factors could also hypothetically lower the segregation ratio in AR disorders.

(5) Apparent reduced penetrance may partly be the result of ascertainment bias, since in most of the studies undertaken, short stature and x ray abnormalities were the main criteria for diagnosis. But, in addition, variable expression, although uncom- mon in most AR disorders, may also cause a low segregation ratio. The occurrence of mild immunodeficiency without dwarfism has been described in CHH. However, in most studies only short stature CHH patients have been checked for immuno- deficiency, with the exception of one in which siblings were used as controls. Therefore, CHH patients with only mild immuno- deficiency could have been missed, thereby skewing the number of affected sibs.

The well known increased risk of intra-uterine lethality in several AR disorders, though not in CHH, can be considered to be the most severe of this spectrum of variability. Also the potential lethality of cystic fibrosis, perhaps because of other modifying loci, makes it plausible that