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 diarrhoea and steatorrhoea), and repeated bronchitis. *Staphylococcus aureus* then *Pseudomonas aeruginosa* have been found in 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 the patient is classified as severely affected by the clinicians.

Using the SSCP technique[11] 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 1221221 on the maternal chromosome, as defined by the markers met D/*Taq*I, met H/*Taq*I, G2/*Xba*I, XV2C/*Taq*I, KM19/*Pst*I, D9/*Msp*I, and J3.11/*Msp*I.

The stop mutation G542X is predicted to result in decreased levels of mutant messenger RNA[12] and in a truncated CFTR protein from NBD-1,[1] suppressing 63% of the molecule. However, the homozygous patients for G542X previously reported had mild pulmonary disease,[3-5 10] which would imply alternative splicing mechanisms suppressing 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 just been reported in a Turkish boy in the neonatal period by Bienvenu *et al.*[13] Such contradictions in genotype/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 syndrome',[1] in which the authors review case 5 of their previous paper describing children with cutis laxa[2] and make a diagnosis of Costello syndrome. Recently, and independently, we have reviewed case 7 from the same paper and on both history and clinical examination made an unequivocal diagnosis of Costello syndrome.[3]

Now that two separate cases within this subgroup of congenital cutis laxa with retardation of growth and development have been independently diagnosed as Costello syndrome, it is obviously time for a review of this heterogeneous group and recognition of this syndrome as a differential diagnosis in congenital cutis laxa, especially in the presence 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;30:687–9). In the article, hip synovial osteochondromatosis was described and was said never to have been reported previously in FOP. In fact, Kalifa *et al* described this finding in *Pediatric Radiology* (1993;23:91–3) in an article entitled 'Fibrodysplasia ossificans progressiva and synovial chondromatosis in 10 and 15 year old patients'. Given these reports perhaps synovial chondromatosis deserves to be considered a feature of FOP.

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## Low segregation ratios in autosomal recessive disorders

I read with interest the article by Bundey and Young[1] on possible causes for low segregation ratios in autosomal recessive (AR) disorders. They hypothesise on possible mechanisms and explanations concerning the low segregation ratio in cartilage-hair hypoplasia (CHH) found in Finland.[2] I would like to add some further thoughts and possibilities to the behavioural, methodological, and biological factors that were described in their paper.[1]

(1) Parents may decide to refrain from having further children, "even in the absence of genetic counselling".[1] 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 parents' behaviour instead of bona fide biological mechanisms. It will then be difficult to find unbiased, that is, uncounselled, populations.

(2) Pregnancies which have been terminated after prenatal diagnosis will also have to be taken into account for the purpose of accurate ascertainment.

(3) Reduced penetrance in CHH has been found in both of the published population studies.[2 3] In contrast to Mäkitie,[2] Sulisalo *et al*[4] 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 proportion of affected sibs (after exclusion of the probands) was 0·38. The chance of finding even more (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) McKusick *et al*,[3] 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 becomes evident 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[3]), 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.[2-6] But, in addition, variable expression, although uncommon in most AR disorders, may also cause a low segregation ratio. The occurrence of mild immunodeficiency without dwarfism has been described in CHH.[7] However, in most studies only short statured CHH patients have been checked for immunodeficiency,[2-6] with the exception of one in which sibs were used as controls.[8] Therefore CHH patients with only mild immunodeficiency could have been missed, thereby skewing the number of affected sibs.

The well known increased risk of intrauterine lethality in several AR disorders, though not in CHH,[1] can be considered to be the most severe end of this spectrum of variability. Also the intrafamilial heterogeneity of cystic fibrosis, perhaps because of other modifying loci,[9] makes it plausible that