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 Pseudomo-
aeus aeruginosa later on. 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 to study the DNA extracted from the patient and her family, we detected the first two mutations. One of these mutations was a homozygous patient's mutation to the affected child. This mutation is associated with haplotype 1121221 on the paternal chromosome, and with haplo-
type 1221221 on the maternal chromosome, as defined by the markers D/TaqI, M/TaqI, G2/XbaI, XV2C/TaqI, KM19/ Ptrl, D9/MpiI, and J3/11/MpiI.

The XX chromosome is predicted to result in decreased levels of mutant mes-

genger mRNA as well as a truncated cystic fibrosis protein from NBD-1, suppressing 63% of the mRNA and 22% of the protein. The homozygous patients for G542X previously reported had mild pulmonary disease, which would imply alternative splicing mechanisms suppressing the effect of the stop mutation in some tissues. Contrasting with these results, 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 neonat-
al period by Bienvenu et al. Such contradic-
tions in genotype/phenotype correlations might be resolved in the future by mRNA and protein expression studies in target tissues.

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FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

We read with interest the article by Connor et al.1 'A three generation family with fibrodyplasia ossificans progressiva' (J Med Genet 1993;30:807–9). In the article, the hip synovial osteochondromatosis was described and was said never to have been reported previously in FOP. In fact, Kalila et al.2 described this finding in Pediatric Radiology (1995;23:91–3) and in an article entitled 'Fibrodyplasia ossificans progressiva and synovial chondromatosis in 10 and 15 year old patients'. Given these reports perhaps synovial chondromatosis de-
ers 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 Young3 on possible causes for low segregation ratios in autosomal recessive disorders, and I believe it would be good to add some further thoughts and possibilities to the beha-

vioural, methodological, and biological factors that were described in their paper.

Parents may segregate away from 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) Pregnancies which have been termi-
nated, either prenatally or postnatally 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. In contrast to Maître,4 Sulisalo and et al.5 found no evidence of reduced penetrance in Finnish CHH patients. However, their conclusion was based on 14 small families seen for linkage analysis, where the observed portion 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.,6 in their original paper, put forward environmental factors as a hypothesised 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 another factor only in combination with some environmental factor. Although they refer to two X linked disorders to illustrate this possibility (GDP deficiency and vitamin D resistant rickets),7 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.8 But, in addi-
tion, 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 statured CHH patients have been checked for immunode-

ficiency,9,10 with the exception of one in which sibs were used as controls.11 Therefore CHH patients with only mild immunode-

ficiency could have been missed, thereby skewing the number of affected sibs.

In this well known increased risk of intra-
uterine 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 inheritance ratio of cystic fibrosis, perhaps because of other modifying loci, makes it plausible that
Cutis laxa: a feature of Costello syndrome.

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