ing from Murcia, Spain. She was born in 1987, without meconium ileus, and was diag-
osed as having cystic fibrosis at the age of 5 months.

The patient’s sputum was examined and a mutation G542X in the CFTR gene was trans-
mitted to the affected child. This mutation is associated with haplotype 11212111 on the pata-
ernal chromosome, and with haplo-
type 12212111 on the maternal chromosome, as defined by the markers D/TaqI, M/TaqI, G2/XbaI, XV2C/TaqI, KM19, P-ul, D9/Mpi, and J311/Mpi.

The G542X mutation is predicted to result in decreased levels of mutant messen-
ger RNA

and in a truncated CFTR protein from NBD-1, suppressing 63% of the lipase activity after protein. Patients for G542X previously reported had mild pulmonary disease,\(^1\) which would imply alternative splicing mechanisms sup-
pressing the effect of the stop mutation in some tissues. Contrasting with these reports, we present the second case of a child homozy-
gous for G542X with severe pancreatic and lung disease. Another similar finding has just been reported in a Turkish boy in the neon-
al period by Bienvenu et al.\(^2\) Such contradic-
tions in genotype/phenotype correlations might be resolved in the future by mRNA and protein expression studies in target tissues.

We wish to express our gratitude to the Association Française de Lutte contre la Mucoviscidose (AFLM). The manuscript was typed by T. Bous-
quet.

**Cutis laxa: a feature of Costello syndrome**

We were extremely interested to read the letter 'Cutis laxa and the Costello syn-
drome' in \(3\) in which the authors reviewed some of their previous paper describing children with cutis laxa\(^\text{2}\) and make a diagnosis of Costello syndrome. Recently, and indepen-
dently, we have reviewed the same 7 from the same paper and on both history and clinical examination made an unequivocal diagnosis of Costello syndrome.\(^1\)

Now that two separate cases within this subgroup of congenital cutis laxa with ret-

eration 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 pres-
ce of postnatal growth retardation and delayed development.

**Fibrodysplasia ossificans progressiva**

I read with interest the article by Connor et al.\(^3\) ‘A three generation family with fibrodysplasia ossificans progressiva’ (\(J\) Med Genet 1993;30:807–9). 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 de-
serves to be considered a feature of FOP.

**Low segregation ratios in autosomal recessive disorders**

I read with interest the article by Bundey and Young\(^4\) on possible causes for low segregation ratios in autosomal recessive disorders. They hypothesise on possible mechanisms and explanations concerning the low segre-
gation ratio in cartilage-hair hypoplasia (CHH) found in Finland.\(^5\) I would like to add some further thoughts and possibilities to the beha-

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

Parental consanguinity 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 par-
tent’s behaviour instead of bona fide biological mechanisms. It will then be difficult to

unbiased, that is, uncounseled, populations.

(2) Pregnancies which have been termi-

nated and pathological 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.\(^2\) In contrast to M captivating,\(^6\) Sulli et al.\(^7\) found no evidence of reduced penetrance in Finnish CHH families. However, their conclusion was based on 14 small families. The linkage analysis, where the 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) McKusik et al.\(^8\) in their original paper, put forward environmental factors as a hypothe-
cal 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 evident only in combination with some environmen-
tal factor. Although they refer to two X linked disorders to illustrate this possibility (GOFD deficiency and vitamin D resistant rickets),\(^9\) 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.\(^10\) 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.\(^11\) However, in most studies only short statured CHH patients have been checked for immunodeficiency,\(^12\) with the exception of one in which sibs were used as controls.\(^13\) Therefore CHH patients with only mild immunode-
ficiency could have been missed, thereby skewing the number of affected sibs.

The well known increase in risk of intra-

uterine lethality in several AR disorders, though not in CHH,\(^1\) can be considered to be the most severe of this spectrum of variability. Also the penetrance of cys-
tic fibrosis, perhaps because of other modifying loci,\(^1\) makes it plausible that