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 technique¹¹ 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/TaqI, met H/TaqI, G2/XbaI, XV2C/TaqI, KM19/PstI, D9/MspI, and J3.11/MspI.

The stop mutation G542X is predicted to result in decreased levels of mutant messenger RNA¹² 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 laxa² 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 Bunday and Young¹ 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.*³ 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 rickets³), 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

variable expression in AR disorders is perhaps less rare than assumed.

(6) Interestingly, de novo AR gene mutations are not mentioned as a possible cause for reduced segregation ratios in AR disorders.¹ As new AR mutations usually have no phenotypic effect, we therefore know very little about mutation rates in this category, but there is no reason to assume they are rarer than de novo autosomal dominant or X linked mutations. The evolving plethora of mutations in the CFTR gene would appear to give credence to this idea. However, as yet, no proven new mutations have been found among more than 700 families analysed in the Netherlands (D Halley, Rotterdam, and H Scheffer, Groningen, personal communications). From the Finnish CHH families, only two out of 83 couples were consanguineous² and here the mutated alleles are very likely to be identical by descent, although DNA analysis sometimes proves there are exceptions to this rule.¹⁰ Twenty families could be linked genealogically and here the unlinked mutation could be different, or even perhaps new, as in the other 61 CHH families. Only when the CHH gene, recently assigned to chromosome 9,⁴ is analysed for mutations will the point be clarified, either by showing the absence of the mutation in the father (with proven paternity) or absence of the mutation in the mother (apparent 'non-maternity'), when isodisomy has been excluded.

(7) Gonadal mosaicism for an AR mutation in one of the parents could theoretically be yet another cause of low segregation ratios in AR phenotypes. However, this will be difficult to distinguish from the above mentioned new AR mutation.

(8) Finally, unstable mutations, as in fragile X syndrome, myotonic dystrophy, or Huntington's disease,¹¹ could play a role in AR disorders. Since damage of gene function only occurs in a certain percentage of gametes in which the gene is segregating, the number of expected affected offspring will be reduced.

In conclusion there are a number of possible explanations for a segregation ratio lower than 0.25, which endorses the conclusion of Bunday and Young.¹ Until we know more about the relative importance of all these factors in several AR disorders, we will have to counsel with caution.

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Del(18p) syndrome with a single central maxillary incisor

In 1991 Aughton *et al*¹ reported a case of del(18p) syndrome and a single central maxillary incisor (SCMI), stating that it was only the second report of a patient with this association. They considered that the only former report was that of Dolan *et al*²; however Boudailliez *et al*³ had already described a similar case in 1983, which deserves attention.

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Prevention of Mediterranean anaemia in Latium, Italy, today

In four previous papers published in this Journal¹⁻⁴ we reported the continuing programme for the prevention of Mediterranean anaemia (thalassaemia major) in Latium, a region of central Italy. This work, supported by the Regional Health Authorities of Latium, has been carried out by the Rome Microcythaemia Institute since October 1975. It consists of the following.

(1) An educational programme among school children in Latium that consists of two steps. The first is detailed information provided class by class with brief lectures and printed and audiovisual material. The second is screening of informed students who have obtained consent to be examined from their parents.

(2) Examination of thalassaemic students' families and identification of carriers of the thalassaemia trait.

(3) The provision of information and screening campaigns to young adult school leavers. In this group, the information is imparted at meetings at the Family Health Services, in explanatory pamphlets at the marital Registry Offices in the towns and villages of the region, by information from the Public Health Offices and family doctors or gynaecologists, and recurrent use of the media.

Screening of school leavers evolved in 1978 through the effect of the school screening and has progressively increased. It is carried out in the outpatients department of

Results of the Latium thalassaemia prevention programme (October 1975 to June 1993)

Population screening	
Secondary school students	828 430
Young adults	164 375
Total	992 805
Non-α thalassaemia carriers	
Secondary school students	15 075
Young adults	20 968
Total	36 043
Identified couples at risk	
Prospective, childbearing age, today	322
Retrospective, childbearing age, today	47
Total	369
Homozygous fetuses aborted from 1982 to 1991	
From prospective couples	59
From retrospective couples	10
Total	69

the Institute and in the Family Health Services of the region.

The results of this continuing work are shown in the table. Young carriers of non-α thalassaemia comprise about 80% of all carriers in Latium (44 000 in a region with 2 000 000 inhabitants of childbearing age and an incidence of non-α thalassaemia of 0.022).⁵

The couples of childbearing age at risk identified (369) comprise 74% of the total (about 500)⁵ in Latium. All these couples are kept under surveillance by our genetic counselling service. In the last 11 years 69 homozygous fetuses have been aborted after prenatal diagnosis. The incidence of newborns affected by Mediterranean anaemia has decreased from 16.04 out of 100 000 live births in 1975/76 to 1.97 in 1989/90. In 1991 and 1992 no affected children have been born in Latium.

This programme offers to young thalassaemic couples the advantage of choosing either postconceptional or preconceptional means of prevention.

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B GRAZIANI
M LERONE
D PONZINI
M C ALIQUO
A AMATO
E FOGLIETTA
M P CAPPABIANCA
E GRECO
P DI BIAGIO
N D'ARCANGELI
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