affected mother had had a cleft lip and palate repaired as an infant. One child had a diaphragmatic hernia. All were of normal intelligence.

Our cases confirm the female bias noted previously in craniofrontonasal dysplasia.

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Ectrodactyly in sisters and half sisters

SIR,

In the April 1987 issue of your Journal (1987;24: 220-4), Mufti and Wood reported on two sisters and two half sisters with ectrodactyly. In addition, two of them had aplasia of the tibia. They suggested an autosomal recessive mode of inheritance in this family.

We think the reported family is probably an example of the aplasia of tibia-ectrodactyly syndrome, as was recently described by Majewski *et al.*¹ These authors described six new families with 35

affected persons, reviewed published reports on 27 sporadic cases and 99 familial cases, and showed that this disorder has great variability and markedly reduced penetrance.

Recently, we were able to investigate two cousins with this disorder. The first case had peromelia of the right ulna with agenesis of the radius, ectrodactyly of the left hand, a hypoplastic right femur and tibia with synostosis between the femur and fibula, and a hypoplastic left femur and aplasia of the left tibia (fig 1). The second case had postaxial hexadactyly of the right hand, syndactyly of the left third and fourth fingers, a normal left leg, and a hypoplastic femur, aplasia of the tibia, and a small foot with a hypoplastic hallux on the right side (fig 2). Their fathers are brothers. They were investigated physically and radiologically, but showed no anomaly. However, one of the sisters of the second case had mildly hypoplastic big toes on both sides which might be the mildest recognisable symptom of this disorder (fig 3).¹

We have tried to see whether a metacarpophalangeal profile analysis was useful in distinguishing relatives with clinical non-penetrance from unaffected relatives. In the above mentioned family, as well as in family 4 reported by Majewski *et al.*,¹ this analysis proved not to be useful.

In 1986, Lurie and Ilyina² published a comparable case, who had in addition distally 'bifurcated' femora. They thought this to be a separate entity and proposed the name Gollop-Wolfgang complex. A distally bifurcated femur may also be a component of the aplasia of tibia-ectrodactyly syndrome as was shown by Majewski *et al.*¹ However, as the distal femur, tibia, and foot ectrodactyly and the (developmentally homologous) distal humerus, radius, and hand ectrodactyly are probably on different developmental fields,³ and so are aetiologically non-specific and possibly heterogeneous, it remains

FIG 1 Radiological appearance of left hand of case 1.

FIG 2 Radiological appearance of both hands of case 2.

FIG 3 Hypoplastic right hallux of sister of case 2.

possible that separate entities, caused by single gene disturbances, exist.

We thank Dr B Hamel (Nijmegen, The Netherlands) for making the x rays of family 4 of Majewski *et al* available for us.

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- ¹ Majewski F, Kuster W, ter Haar B, Goecke T. Aplasia of tibia with split-hand/split-foot deformity. Report of six families with 35 cases and considerations about variability and penetrance. *Hum Genet* 1985;70:136-47.
- ² Lurie IW, Ilyina HG. Gollop-Wolfgang complex in a 3-month-old girl. *Am J Med Genet* 1986;suppl 2:191-4.
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Fryns syndrome

SIR,

The review of Fryns syndrome (*J Med Genet* 1987;24:271-4) prompts me to point out that this

review omitted the first case of this syndrome which was described by Fitch *et al* (*J Med Genet* 1978;15:399-401), one year before Fryns' original report was published. Our infant had the coarse face with the broad, flat nasal bridge, large nasal tip with anteverted nostrils, thin upper lip, macrostomia, missing nails on the fifth fingers and hypoplastic nails on all other digits, hypoplasia of the terminal phalanges, absent left hemidiaphragm, and cerebral malformations. The parents were second cousins.

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Alpha₁ antitrypsin deficiency

SIR,

In their paper in *Journal of Medical Genetics* (1987;24:52-9), Cox and Mansfield attempt to estimate the risk of severe liver disease in a fetus of genotype PI ZZ given the severity of liver disease in the proband. The estimates are derived from pooling data from several studies in the United States, Canada, Norway, and Great Britain. The authors give point estimates of the risk, which appear to be different in the two groups, with the suggestion that this information will be useful for families seeking counselling.

The difficulty with the presentation is that the conclusion is based upon a very small sample, with 15 sibs of probands having resolved or no liver disease and 20 with severely affected probands, as shown in tables 4 and 5. Although the estimates are 13% and 40% respectively, it is doubtful that these represent different rates. I constructed a 2x2 table and used the SAS procedure FREQ which produces a number of statistics to accommodate different analytical viewpoints. None of the hypothesis testing probabilities suggests rejecting the null hypothesis of equal rates in the two groups, whether one considers χ^2 with or without continuity correction, a Fisher exact test, or a Mantel-Haenszel χ^2 . If one prefers to use an epidemiological approach, the odds ratio is 4.33 for a severe proband to have a severely affected sib; however, the 95% confidence interval runs from 0.80 to 23.4. This interval clearly includes 1, so that the conclusion of a difference in risk cannot be supported. For the time being, the mean risk of severe liver disease appears to be 29%, with a 95% confidence interval between 14.6 and 46.3. This appears to be different from the 7% risk estimate of the Swedish study. Clearly, more data