Correspondence

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.

RAOUL C M HENNEKAM AND ED J P LOMMEN
Clinical Genetics Center Utrecht,
PO Box 18009, 3501 CA Utrecht;
and Sint Josephziekenhuis,

References

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.

N Fitch
Lady Davis Institute for Medical Research,
The Sir Mortimer B Davis–Jewish General Hospital,
3755 Chemin Côte Ste Catherine,
Montreal, Quebec, Canada H3T 1E2.

Alpha, 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 2×2 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 χ² with or without continuity correction, a Fisher exact test, or a Mantel-Haenszel χ². 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
and a proper segregation analysis are essential to answer the original question. A model involving more than one locus might also be necessary.

**David J Harris**

*Division of Genetics, The Children’s Mercy Hospital, 24th at Gillham Road, Kansas City, Missouri 64108, USA.*

This letter was shown to Dr Cox, who replies as follows.

**SIR,**

As discussed in our paper *(J Med Genet 1987;24:52–9)* and in the comments by Dr Harris, the number of cases available for obtaining risk figures is very small and inadequate. Furthermore, there is considerable variability between the results of various studies. Statistical tests may not be appropriate until a larger sample size is available.

Although the statistical analysis does not show a clear difference in risk for families with and without a severely affected child, we feel it could be misleading to give all parents a risk of 29%. Because of the recurrence of severe liver disease in certain families, some other genetic or environmental predisposing factor may be present in these families and should not be ignored. In addition to the series we have included, there are a number of single families reported with multiple sibs affected with severe liver disease. The less favourable prognosis in Great Britain *(Arch Dis Child 1983;58:882)* may be due to differences in the referral pattern, in which children with transient or mild symptoms may never be referred to major centres. There would therefore be a selection for those families with a severely affected child, particularly when there is more than one. For parents who have had a child with severe liver disease, a risk of 29% or 40% would probably lead to consideration of prenatal diagnosis. However, a 29% risk for parents who have not had such a child is probably unduly pessimistic.

We have made approximate estimates given the data available. Careful follow up studies of patients in many centres is mandatory to obtain improved risk figures and we hope other investigators will initiate such studies.

**Diane Wilson Cox**

*The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.*

**Possible evidence for genetic predisposition to nondisjunction in man**

**SIR,**

Preliminary data from a community genetic survey at two district hospitals showed a high prevalence of chromosomal aneuploidy, particularly Down’s syndrome, with marked temporal variation between the two districts.

In Jahra hospital serving an Arab population of 300 000, mostly (80%) Bedouins, 31 babies with autosomal trisomies were ascertained among 6874 consecutive live births (4-5/1000). Twenty-nine cases (93-5%) were Bedouins or Kuwaitis with Bedouin ancestors and two were other Arabs. The mean maternal age was 31-1 years. Parental consanguinity was observed in 29 cases with an average coefficient of inbreeding (ZE) of 0·044, which is similar to that of parents with the traditional ‘Bedouin’ practice of consanguineous marriages. Among this group, two sibs, one with trisomy 21 and the other trisomy 18, had young first cousin parents. Another family had two sibs with trisomy 21.

In Farwania hospital serving a mixed Arab and non-Arab population of 400 000 with only 15% Bedouin, 14 babies with autosomal trisomies were ascertained among 8045 consecutive births (1·7/1000). Of these, six cases (42-9%) were Bedouins or Kuwaiti-Bedouins, six cases were other Arabs, and two cases were Asian. The mean maternal age was 32·7 years. Parental consanguinity was observed in eight cases with an average coefficient of inbreeding (ZE) of 0·0225.

The overall prevalence of Down’s syndrome in the two districts was 2·5/1000 which was more than double that of 1·1/1000 reported from Kuwait maternity hospital1 (table). The usual prevalence of Down’s syndrome is 1 to 2/1000 live births but higher prevalence rates have been reported from West Jerusalem2 and among Negev Bedouins3 (2·4

**TABLE** Autosomal aneuploidies in Jahra and Farwania hospitals in 1986.

<table>
<thead>
<tr>
<th></th>
<th>Jahra</th>
<th>Farwania</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of live births</td>
<td>6874</td>
<td>8045</td>
<td>14919</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>25(21)*</td>
<td>12(101)</td>
<td>37(31)</td>
</tr>
<tr>
<td>Prevalence rate</td>
<td>3.6</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Edwards’ syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>4(4)</td>
<td>1(0)</td>
<td>5(4)</td>
</tr>
<tr>
<td>Prevalence rate</td>
<td>0.6</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Patau’s syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>2(1)</td>
<td>1(1)</td>
<td>3(2)</td>
</tr>
<tr>
<td>Prevalence rate</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Prevalence rate per 1000 live births; figures in brackets are the number of cases examined cytogenetically.

*One case a de novo 14.21 translocation.
†Two cases de novo translocations (14.21, 21.21).
Alpha 1 antitrypsin deficiency.

D J Harris

doi: 10.1136/jmg.25.2.135-a

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