LETTERS TO THE EDITOR

Molecular diagnosis of myotonic dystrophy

The data summarised in the editorial by Suthers *et al*¹ on the molecular diagnosis of myotonic dystrophy are very useful, but I fear that the example of Bayesian calculation used to estimate the risk of congenital myotonic dystrophy (CMD) to a fetus may be incorrect. In table 2 the authors use the conditional probability of the size of fetal (CTG)_n amplification and the conditional probability of fetal (CTG)_n amplification being the same or greater than the mother's as independent probabilities (that is, they multiply them). This is only valid if the two observations are independent in the statistical sense, in other words if information about the value of one of them gives you no information about the other. This is manifestly not the case, as to know that (to take an extreme example) the fetal (CTG)_n amplification is > 4.5 kb also tells you that it is very likely to be greater than the mother's. In order to use both sets of data the authors would need to set up two joint conditional probability tables (one for children with CMD and one without). The data are not available in the editorial for this to be derived.

On a further point the authors use a probability of 0.01 as a conservative estimate of the true proportion of infants with CMD who have band sizes the same as their mother's. This was based on the observation that no instances were seen out of 22 cases. Assuming a binomial distribution the 95% confidence limits of the estimate of the true proportion of infants with CMD who have band sizes the same as their mother's from this sample size are 0.0 to 0.13, so that the estimate of 0.01 would not appear to be conservative enough.

Taking these two points together, readers should be cautioned against using the model calculations in table 2 to estimate risks in real clinical situations.

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- 1 Suthers GK, Huson SM, Davies KE. Editorial. Instability versus predictability: the molecular diagnosis of myotonic dystrophy. *J. Med Genet* 1992;29:761-5.

This letter was shown to Dr Suthers *et al* who reply as follows.

Dr Winter's comments on our suggested approach to risk calculation in the differential prediction of congenital and non-congenital myotonic dystrophy (DM) are very reasonable. We are grateful for the opportunity to discuss the matter further.

It is not yet clear whether fetal (CTG)_n copy number and fetal (CTG)_n amplification being the same or greater than the mother's are truly independent events. Among congenitally affected children, copy number is independent of the probability of an increase in copy number as all congenitally affected

children reported to date show an increase. It is not known whether these probabilities are independent among children who have the non-congenital form of DM. The experience with the (CGG)_n triple repeat at the fragile X locus would suggest that these probabilities are not independent.^{1,2} In the short term the concerns raised by Dr Winter can be addressed by incorporating only the fetal (CTG)_n copy number as a conditional probability in a Bayesian risk calculation; the probability of the fetal copy number being larger than the maternal copy number contributes less to the posterior probability.

We acknowledge that our estimate (0.01) of the proportion of congenitally affected fetuses who do not show an increase in copy number may be too low. The number of congenitally affected children who have been examined is small, and we cautioned that the conditional probabilities were based on few observations. Using the data of Tsilfidis *et al*³ the best estimate of the proportion of congenitally affected children who fail to show an increase in (CTG)_n copy number is 0.0; however, as only 22 children were studied, the 95% confidence interval for this proportion is indeed 0.0-0.13. It could be argued that one should calculate a risk interval (rather than a point estimate) for the fetus being affected with congenital DM, thereby making allowance for the small number of children studied. On the other hand, in view of the limited data, it may be more appropriate to use the best estimate of this proportion.

This discussion touches on the general difficulty of taking raw biological data and applying it in a clinical setting. The dynamics of the DM mutation are complex and not well documented. Until more data are available to address the issues raised by Dr Winter, we would urge careful clinical consideration in the application of mutation analysis to the differential prediction of congenital and non-congenital DM.

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- 1 Fu YH, Kuhl DPA, Pizzuti A, *et al*. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell* 1991;67:1047-58.
- 2 Yu S, Mulley J, Loesch D, *et al*. Fragile-X syndrome: unique genetics of the heritable unstable element. *Am J Hum Genet* 1992;50:968-80.
- 3 Tsilfidis C, MacKenzie AE, Mettler G, Barcelo J, Korneluk RG. Correlation between CTG trinucleotide repeat length and frequency of severe congenital myotonic dystrophy. *Nature Genet* 1992;1:192-5.

Weyers' ulnar ray/oligodactyly syndrome

We read with interest the paper by Turnpenny *et al* on 'Weyers' ulnar ray/oligodactyly syndrome and the association of midline malformations with ulnar ray defects'.¹ In 1985 we published a case of craniosynostosis and unilateral ulnar aplasia associated with pulmonary stenosis.²

The child was a 5 month old male who showed synostosis of the coronal and metopic sutures, supraorbital flattening, downward

slanting palpebral fissures, low set and posteriorly rotated ears with poorly developed helices, severe microretrognathia, a high arched palate, and a short neck with redundant retronuchal skin. He also had a heart murmur, markedly hypoplastic right forearm with radial deviation, and oligodactyly (only the thumb and the second finger were present). On x ray examination, besides the aplasia of the ulna there was aplasia of the third, fourth, and fifth metacarpals and corresponding fingers and a short, proximally dislocated radius. He shows no anomaly of the left arm and the lower extremities. At the time of publication the following syndromes were considered for the differential diagnosis: Baller-Gerold syndrome which includes craniosynostosis but in which only the radius is involved; Lowry syndrome which shows craniosynostosis but involvement of the fibula only; Herrmann-Pallister-Opitz syndrome which shows craniosynostosis and severe, symmetrically malformed limbs; and Sakati syndrome which shows craniosynostosis and polysyndactyly with shortening of the limbs.

The case was considered to be sporadic, since the parents were normal and non-consanguineous and the family history was negative for craniofacial anomalies or limb defects. We think that our patient, who shows craniosynostosis, high arched palate, microretrognathia, and ulnar defect could add further evidence of a possible defect of the same developmental field involving the limb buds and midline.

Nevertheless, the hypothesis of the presence of a single gene which could cause dysmorphogenesis of midline body structures and loss of specificity in radioulnar differentiation is limiting and seems not to fit with the unilaterality of the limb anomaly present in our patient.

This observation suggests that the developmental timing of these two areas of the body, even though correlated in some way, are also influenced by more complex and independent mechanisms.

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- 1 Turnpenny PD, Dean JCS, Duffy P, Reid JA, Carter P. Weyers' ulnar ray/oligodactyly syndrome and the association of midline malformations with ulnar ray defects. *J Med Genet* 1992;29:659-62.
- 2 Calabro A, Lungarotti MS, Latini S, Molinari D. Craniosynostosis and unilateral ulnar aplasia. *Am J Med Genet* 1985;20:203-4.

The contribution of genetic factors to the pathogenesis of type I (insulin dependent) diabetes mellitus

In a recent review article on the genetics of type I (insulin dependent) diabetes mellitus, Cavan *et al*¹ correctly state that diabetes is probably "influenced by several genes as well as by environmental factors". To support this view they mention the low concordance rate in identical twins and the average disease risk of about 6% in sibs of a diabetic proband. The discussion then emphasises the importance of the HLA antigens, particularly DR and DQ, by applying such terms as