Monozygotic twins with 22q11 deletion and discordant phenotypes

I was interested to read the report of Goodship et al (J Med Genet 1995;32:746–8) of monozygotic (MZ) twins with a 22q11 deletion who were discordant for cardiac defects. I have recently met a similar family where all the affected members have had a 22q11 deletion detected by FISH.

Twin 1 has a typical facial appearance of the velocardiofacial syndrome (figure) with nasal speech but no cardiac defect detectable clinically or on ECG. Twin 2 required a pharyngoplasty for nasopharyngeal insufficiency and had surgery for an ASD during childhood. She has a very similar facies and both had mild learning difficulties during childhood.

Facial appearance of twin 1.

This family is also of interest in that both twins have triphalangeal thumbs and twin 1 was also born with a postaxial polydactyly. These digital defects also appear to have arisen as a new dominant mutation. Twin 1’s child with the 22q11 deletion also has abnormal thumbs which have accessory ossicles visible radiologically. However twin 2’s living child has clinically normal thumbs but a 22q11 deletion so the digital anomaly does not appear to be segregating with the deletion.

We read with interest the publication of Martorell et al1 “Comparison of CTG repeat length expansion and clinical progression of myotonic dystrophy over a five year period”, which appeared in the August issue of this journal. These authors found that the CTG expansion length in peripheral blood cells of DM patients (with varying clinical severity of symptoms and various sizes of repeat amplification) increased over a time span of five years.

They compare their data with a similar follow up study comparing CTG expansion sizes in muscle2 in which they observed no progression in the size of the CTG length in repeated muscle biopsies from three adult DM patients. According to Martorell et al,1 one possible explanation for this finding would be a negative selection in muscle above a maximum size limit. In this case continued CTG expansions would be seen only in relatively young DM patients.

We have compared the size of the CTG expansion in muscle and lymphocytes in 19 DM patients of different ages (including three children) and varying clinical severity and our data support such a hypothesis.

In accordance with previous publications3 we have found that the size of the expansion was always greater in muscle than in blood, with no correlation in adults with age at onset or severity of the phenotype.1 However, surprisingly, the smallest difference between the size of the expansion in muscle and the size of the expansion in lymphocytes was observed in the affected children (two with congenital DM and in one 11 year old patient with onset in early childhood). In these three young patients, this difference ranged from 2.1 kb to 4.2 kb while in adult patients it ranged from 5.3 kb to 9.0 kb. A significant correlation (r² = 0.64, p < 0.05) was found between patients’ age and the difference in the expansion between muscle and lymphocytes. In summary, although we have not analysed repeated biopsies from the same person (owing to the difficulty of obtaining such samples), we would like to point out that our data suggest that the size of the CTG repeat in muscle increases with age in young DM affected patients, apparently reaching a plateau in adulthood. Moreover, in young DM cases, it seems that the progression in the size of the CTG expansion in muscle may be greater than that observed in peripheral blood. It would be interesting to see if this finding is confirmed in other studies.

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Selection for presymptomatic testing for Huntington’s disease: who decides?

With the transfer of presymptomatic testing for Huntington’s disease from research to clinical service, the conflict between making judgements about the candidate’s eligibility to receive a test result and the non-directive ethos of clinical genetics has been felt by many of us. Evidence for adherence to eligibility criteria, rather than reliance on self-selection among at risk subjects, is apparent in published reports. In a survey of all centres offering presymptomatic testing in the United States,1 the majority of the centres (18 out of 26) had postponed or denied testing at least once. Reasons for this included “inappropriate requests* for testing (eg, to confirm a diagnosis of possible HD), as well as decisions based on personal or situational factors affecting the individual that indicate that more caution should be exercised*”.

The practice of withholding testing from applicants is clearly at odds with the psychotherapeutic model of genetic counselling, as discussed by Sharpe; “the geneticist must explicitly acknowledge that at all times decision making remains under the control of the patient; that the geneticist must act in accordance with a patient’s decisions irrespective of how the geneticist ‘may observe their rationality or competence’”. It also contradicts the notion of providing information in response to the counsellor’s specific questions: an applicant for predictive testing who is suspected to be symptomatic may want to know whether (s)he carries the gene for HD, rather than whether (s)he is currently affected.

There are clearly occasions when the clinician’s concern to “do no harm” is perceived

* It is unclear whether these requests came from clinicians or individual patients.
none of the possibilities are harmless". In having to learn to tolerate our own uncertainties, we are learning how to sit with clients while they live with their.

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2 Shaper NF. Presymptomatic testing for Huntington disease: is there duty to test those under the age of eighteen years? Am J Med Genet 1994;46:250-3.

Apolipoprotein E genotype does not affect age at onset in patients with chromosome 14 encoded Alzheimer's disease

At least four genes are responsible for autosomal dominant early onset Alzheimer's disease (AD): APP, a 5-amyloid precursor protein (APP) gene on chromosome 21, the genes coding for the putative integral membrane proteins, presenilin 1 and 2, located respectively on chromosomes 14 and 1,3 and the chromosome 14 gene accounts for the majority of early onset cases with autosomal dominant inheritance.5 Besides these dominantly inherited genes, the ε4 allele of the apolipoprotein E (ApOE) is associated with late as well as with early onset AD.6,7 The ApOE ε4 allele is, therefore, thought to constitute a major risk factor for this disorder, raising the question of a possible interaction between ApOE and the autosomal genes responsible for autosomal dominant AD. The ApOE genotype can influence the age at onset in AD patients with APP mutations,8 but no such effect was observed in a series of families with chromosome 14 encoded AD.9 In order to confirm the latter result in an independent series, we evaluated the effect of ApOE genotype on the age at onset in three families with early onset AD in which linkage to the AD3 locus on chromosome 14 was established.

Analysis of these cases was performed using a standardised procedure in order accurately to determine their age at onset and their clinical profile. ApOE genotypes were identified from blood DNA, as previously described.10 Linkage to the AD3 locus has already been documented in (FAD-RO1 and FAD-ROU-011)11 (Bellis et al, submitted). Linkage analysis in family FAD-SAL-511, which included six affected members, generated a peak lod score of 1.81 at D14S77 to D14S213 for marker D14S213, located 1 cM centromeric to D14S77, suggestive of linkage to the AD3 locus. Furthermore, three heterozygous missense mutations in the presenilin 1 gene, Leu392Val, Pro264Leu, and Cys410Tyr, were found. Interestingly, in patients from families FAD-RO1, FAD-ROU-011, and FAD-SAL-511,12 Means were compared using the Mann-Whitney U test.

Age at onset and ApOE genotypes

Age at onset of AD according to families and ApOE genotypes

<table>
<thead>
<tr>
<th>ApOE genotype</th>
<th>ε2/3</th>
<th>ε3/3</th>
<th>ε4/4</th>
<th>Mean (SD) (years)</th>
<th>Age at onset Mean (SD) (years)</th>
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<tbody>
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<td>age at onset (years)</td>
<td>age at onset (years)</td>
<td>age at onset (years)</td>
<td>age at onset</td>
<td>age at onset</td>
</tr>
<tr>
<td>FAD-RO1</td>
<td>41, 44, 45, 46, 48, 49</td>
<td>40, 49, 51</td>
<td>40, 49, 51</td>
<td>45 (3.8)</td>
<td>39 (3.8)</td>
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<tr>
<td>FAD-SAL-511</td>
<td>45, 54, 55</td>
<td>51</td>
<td>51</td>
<td>51.3 (4.1)</td>
<td>49 (3.5)</td>
</tr>
<tr>
<td>FAD-ROU-011</td>
<td>40</td>
<td>60</td>
<td>50 (2.7)</td>
<td>47.9 (5.8)</td>
<td>47.9 (5.8)</td>
</tr>
</tbody>
</table>

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