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.

CTG repeat length in muscle from patients affected with myotonic dystrophy (DM)

We read with interest the publication of Martorell et al.4 “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 muscle 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., 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.5 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 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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as being in conflict with upholding the principle of individual autonomy and self-selected applicants are denied testing. We suggest that this has a number of important repercussions. It may be that a testing protocol which incorporates a selection ethos encourages people to "fake good", evidence of this being suggested by scores on the validity scales of psychometric tests administered as part of the pretest protocol. We suggest that placing at risk subjects in what they may perceive to be a highly evaluative situation lays considerable burden on them. Indeed, one couple that we have seen recently reported experiencing conflict and accounting of blame "...which over time was unmanageable with the test..."(2) after perceiving themselves as having been denied a test result.

We have felt it important to consider the implications of this selection role for our sero-criteria for presymptomatic testing. The concept of selection will militate against the open relationship necessary to carry out the client focused aim of pretest counselling, which is facilitating insight and understanding that will help people in their decision making process concerning predictive testing and subsequent adjustment to the result. We cannot expect people to be open and reflective with counsellors whom they see as having the power to control whether they should be given a result that they are highly motivated to receive. Those considering predictive testing are bound to experience ambivalent feelings as regards their motives for testing and the impact of the result on their lives. We feel that is important that test applicants be given an opportunity to explore their vulnerabilities and prepare for potential difficulties in dealing with an adverse result and that introducing selection to the pretest counselling agenda will undermine this process.

The ethical principle of "do no harm" is the one frequently quoted in this debate and guidelines for presymptomatic testing protocols have drawn attention to the potentially harmful effects of testing under certain circumstances, notably where the person is seriously depressed or psychologically ill. Likewise, there has been voiced concern over regard to the potential harm in refusing or delaying testing, or attempting to carry out the aims of pretest counselling with the agenda of selection ever present. The question of how such autonomy in testing (a patient's right to consent) is being told that they are not ready to receive a test result has not been given any attention.

In consideration of this dilemma in our own centre, we have not abandoned exclusion criteria completely but have tried to separate the gatekeeping/selection role from the continuing counselling. We attempt to make this distinction explicit to those going through testing, subsequent to the preliminary clinic appointment, and the gatekeeping role is restricted to the preliminary consultation and thereafter the decision about receiving a test result is exclusively the client's. While this seems to work in promoting exploration and reflection of difficult thoughts and feelings by the person, it does not always sit comfortably with ourselves. Observers of our team meetings frequently witness our struggling with uncertainty, risk, and the fear of possible adverse outcomes of predictive testing. We are often tempted to return to the security of rigid criteria by enforcing guidelines. On reflection, this experience may provide insight into and empathy with the people that we see in our clinic. We have to remind ourselves that the "special agony of this situation is that 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 theirs.


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): the 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 17, and the chromosome 14 gene accounts for the majority of early onset cases with autosomal dominant inheritance.1 Besides these dominantly inherited genes, the e4 allele of apolipoprotein E (ApoE) is associated with late as well as with early onset AD.4,6 The ApoE e4 allele is, therefore, thought to constitute a major risk factor for this disorder, raising the question of a possible interaction between ApoE and the other genes responsible for autosomal dominant AD. The ApoE genotype can influence the age at onset in AD patients with APP mutations,4,5 but no such effect was observed in a series of families with chromosome 14 encoded AD.6 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.

Fifteen consenting patients from three families with early onset AD were evaluated 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.4,11 Linkage to the AD3 locus has already been suggested in two presymptomatic (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 q = 0.05 for markers D14S17 and D14S1698, 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, respectively, in patients from families FAD-RO1, FAD-ROU-011, and FAD-SAL-51112. Means were compared using the Mann-Whitney U test.

Age at onset of AD among families and ApoE genotypes

<table>
<thead>
<tr>
<th>ApoE genotype</th>
<th>e2/e2 age at onset (years)</th>
<th>e3/e3 age at onset (years)</th>
<th>e4/e4 age at onset (years)</th>
<th>Age at onset Mean (SD) (years)</th>
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</thead>
<tbody>
<tr>
<td>FAD-RO1</td>
<td>44, 44, 45, 46, 48, 49</td>
<td>40, 49, 51</td>
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<tr>
<td>FAD-SAL-511</td>
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<td>51</td>
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<tr>
<td>FAD-ROU-011</td>
<td>40</td>
<td>60</td>
<td>50</td>
<td>50 (14.1)</td>
</tr>
</tbody>
</table>

Age at onset Mean (SD) (years)