LETTERS TO THE EDITOR

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.

Twin 1 has a daughter with mild learning difficulties and similar appearance with a normal heart (on clinical and ECG examination) but twin 2 had an affected daughter who died following surgery for Fallot's tetralogy with absent pulmonary valve and hemitruncus. In addition, this child's heart showed severe pulmonary regurgitation and peripheral pulmonary artery stenosis and the left pulmonary artery took its origin from a branch of the aorta. Twin 2 has subsequently had another child with a 22q11 deletion but a normal heart on echocardiography.

DNA studies using six microsatellite polymorphisms on six different chromosomes gives a probability of greater than 99% that the twins are monozygous.

Thus this family supports the observation of Goodship *et al* that cardiac defects can be discordant in MZ twins with 22q11 deletions

and indicates that the intrauterine environment or the twinning process itself may have played a role in the development of a cardiac defect.

This family is also of interest in that both twins have triphalangeal thumbs and twin 1 was also born with 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.

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

We read with interest the publication of Martorell *et al*¹ "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 the authors 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 publications^{2,3} 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.⁴ 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 ($r^2 = 0.64$, $p < 0.05$) 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 observe 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 exercised².

The practice of withholding testing from applicants is clearly at odds with the psychotherapeutic model of genetic counselling, as discussed by Sharpe²: "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 perceive their rationality or competence". It also contradicts the notion of providing information in response to the counsellee'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 people.

as being in conflict with upholding the principle of individual autonomy³ 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.⁴ 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 apportioning of blame ("Which of us was unable to cope with the test result?") 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 service and clients. Our major concern is that 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 judge 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 a result on their lives. We feel that it 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 predictive 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.³ Less concern, however, has been voiced with 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 applicants (and their partners) cope with 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. 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 possibly 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".² In having to learn to tolerate our own uncertainties, we are learning how to sit with clients while they live with theirs.

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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 β -amyloid precursor protein (APP) gene on chromosome 21,¹ the genes coding for the putative integral membrane proteins, presenilin 1 and 2, located respectively on chromosomes 14 and 1,^{2,3} and an as yet unmapped fourth locus. The chromosome 14 gene accounts for the majority of early onset cases with autosomal dominant inheritance.² Besides these dominantly inherited genes, the $\epsilon 4$ allele of apolipoprotein E (ApoE) is associated with late as well as with early onset AD.⁴⁻⁷ The ApoE $\epsilon 4$ allele is, therefore, thought to constitute a major risk factor for this disorder, raising the question of a possible interaction between ApoE and the genes responsible for autosomal dominant AD. The ApoE genotype can influence the age at onset in AD patients with APP mutations,^{8,9} but no such effect was observed in a series of families with chromosome 14 encoded AD.¹⁰ 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 large pedigrees 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.¹¹ Linkage to the AD3 locus has already been reported for two pedigrees (FAD-RO1 and FAD-ROU-011)¹² (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 $\theta = 0.00$ for marker D14S268 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-511.¹³ Means were compared using the Mann-Whitney U test.

Age at onset and ApoE genotypes are shown in the table. Mean age at onset was not significantly affected by family membership or genotype. The $\epsilon 3\epsilon 4$ genotype was associated with the earliest onset in family FAD-RO1, but also with the latest in the same family, and in kindred FAD-SAL-005. These results clearly confirm that the ApoE genotype does not modulate age at onset in patients with AD3 gene mutations. This might reflect the absence of an interaction between presenilin 1 and ApoE. However, the mechanism by which heterozygous mutations in the presenilin 1 gene causes AD is still unknown. The effect of ApoE genotype on the age at onset in patients with the APP717 Val→Ile mutation might, on the contrary, reflect the high affinity binding of ApoE allele $\epsilon 4$ to the β -A4 peptide which results from APP cleavage.⁵

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Age at onset of AD according to families and ApoE genotypes

Family	ApoE genotype			Age at onset Mean (SD) (years)
	$\epsilon 2\epsilon 3$ age at onset (years)	$\epsilon 3\epsilon 3$ age at onset (years)	$\epsilon 3\epsilon 4$ age at onset (years)	
FAD-RO1		41, 44, 45, 46, 48, 49	40, 49, 51	45.9 (3.8)
FAD-SAL-511		45, 54, 55	51	51.3 (4.5)
FAD-ROU-011	40		60	50 (14.1)
Age at onset	40	47.4 (4.6)	50.2 (7.1)	47.9 (5.8)
Mean (SD) (years)				