LETTERS TO THE EDITOR

Marfan syndrome

I read with great interest the article by Gray and Davies on Marfan syndrome[1], May's Syndrome of the month. It is a very interesting disorder for both clinicians and geneticists alike. It affects several organ systems, and its underlying biochemistry and genetics are gradually being unwound, as Gray and Davies describe. Most interesting of all, however, for this so called single gene disorder, is its vast phenotypic variability both within and between affected families, not alluded to in this article, although well described in other publications.[2]

Several mechanisms have been mooted to explain this pleitropy. The main explanations include both allelic heterogeneity, with over 30 different mutations now reported in the fibrillin gene on chromosome 15 (FBN1) in Marfan patients,[3] and locus heterogeneity, with another fibrillin gene (FBN2) found on chromosome 5 linked to the Marfan related disorder congenital contractural arachnodactyly,[4 5] and with the possibility of a second Marfan locus on chromosome 3.[6]

Recently, however, a novel third mechanism has been described that may help explain intrafamilial phenotypic variability, that of mistakenly diagnosing Marfan syndrome in unaffected relatives of Marfan patients. It stems from the Berlin Nosology for diagnosing Marfan syndrome itself,[7] which requires that in the presence of at least one unequivocally affected first degree relative there need only be involvement of two organ systems, not the usual three, and no major manifestations are mandatory. Pereira *et al*[8] using intragenic markers to FBN1 have shown in two of the 14 Marfan families they studied that some family members with only mild signs of the disease, generally affecting the skin and skeleton but not the cardiovascular system, did not carry the mutant allele found in the rest of the affected family. However, because of the strong family history and involvement of two organ systems, they had been given the incorrect diagnosis (and thus poor life expectancy) of Marfan syndrome. In fact they probably had a milder connective tissue disease and normal life expectancy.

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Selection for presymptomatic testing for Huntington's disease: who decides? A reply from the Victorian Clinical Genetics Service, Murdoch Institute, Melbourne, Australia

The letter of Binedell *et al*[1] about selection for presymptomatic testing for Huntington's disease prompts us to reply by describing our experience which has had minimal selection criteria for presymptomatic testing for Huntington's disease. Dr Binedell and colleagues comment on the fact that testing had been denied to those requesting it in several published reports. This was done on the grounds that "more caution should be exercised". We agree that the practice of withholding testing from some applicants is at odds with what occurs in genetic counselling for many other conditions. We began presymptomatic testing in Melbourne, Australia in 1989 and have now given results to 243 consultands. We have not refused to provide a result to anyone requesting such a result and we wish to summarise our experience as a confirmation of the sentiments expressed in the article by Binedell *et al.*[1]

Our protocol is based on the International Guidelines[2 3]; however, we believe that flexibility and response to individual circumstances is a key factor.

Although flexible, there are certain given criteria we adhere to, namely, we require the consultand to be aged 18 years or more and to attend the mutually agreed number of counselling sessions, including a neurological examination. We do not insist on a "supporter" being present but strongly encourage a partner to attend. Participation in the programme is wholly voluntary and withdrawal at any stage is absolutely the right of the consultand. We encourage the consultands to nominate a local medical practitioner with whom they have discussed participation in the programme, as a means of medical community support.

We have not withheld testing from a consultand, taking their self selection at face value. Where we have been concerned about a person's coping ability this situation is discussed with the consultand and in all cases they themselves have made the decision either to withdraw for the moment or to continue with the counselling until the issue is resolved. In other words, they do their own "gate keeping". We believe that this outcome is assisted through the "intimate" counselling sessions with only one professional present in the sessions. The same counsellor is present in all sessions allowing a trusting rapport to develop, this leading to the consultand being able to explain how HD has affected his/her life in a way that has often not previously been possible, either through fear or concerns of the reaction of family or friends.

There is only one "in depth" interview where an additional professional is present; that is when the neurological examination is conducted. We are fortunate in Victoria to have two highly skilled psychiatrists who are experts in the field of HD. The medical geneticist is involved in one of the counselling sessions.

There are three more points we would like to share. We have found it very useful for many in the counselling sessions to keep a "journal of feelings", one week imagining a negative result and the next week a positive result. These are the starting point of a session, with the counsellor reading them out. Partners, if present, are also encouraged to keep a similar journal. For all consultands we state that there is an "open door", either in addition to "formal" sessions or following disclosure. Consultands have expressed a feeling of security knowing they have someone who understands their circumstances. This policy has never been abused; some examples include introduction to a new partner whom the consultand wants to be fully informed, discussion on whether to consider having a child, concern regarding a sib, or even to talk about the death of an HD affected relative.

We believe the personal and flexible approach we have adopted in our programme has been appreciated by the consultands and has been a major factor in their coming to terms with their results. Often the consultands have reported that for the very first time they have been able to tell their story fully and in the telling have felt a burden lift.

We have instigated a voluntary post test programme for those who have inherited the expanded HD gene. It is here that the value of neuropsychological testing has proved itself. This testing plus a clinical examination and CT scan are offered on a one to two yearly basis and have proved to be helpful to those who have availed themselves of it.

The counselling process has been very highly rated by the consultands as determined from the preliminary results of a study that is presently being conducted looking at family wellbeing following a member undergoing predictive testing for HD. When completed, the study will provide information on the effect of the predictive testing programme on family function.

To summarise, there are five key features in the HD Predictive Testing Programme in Melbourne, a programme that has minimal selection criteria and an emphasis on mutual trust through counselling. (1) Informality with one to one counselling sessions with the same counsellor for all sessions. There is no formal psychological assessment unless this is requested by the consultand or indicated in the course of counselling. (2) Allowing single people to choose to come alone if they have no close friends, but strong encouragement for those with partners to come as a couple. (3) The encouragement to keep a two week "journal of feelings" (reviewing different results, positive and negative). These are written by the consultand (and partner) and are used as the basis of one of the counselling sessions. (4) A stated "open door" policy for all consultands, both current and past. (5) Instigation of the post test programme for gene positive consultands.

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Heterotaxia syndromes and 22q11 deletion

In a recent issue of your journal we read with interest the very accurate review by Penman Splitt *et al*[1] on defects of left-right asymmetry. The authors correctly reported that in patients with heterotaxia (asplenia and polysplenia syndromes), conotruncal defects are one of the more frequent heart malformations. It is well known that 22q11 deletion has been described in a subgroup of patients with conotruncal anomalies in the setting of DiGeorge[2–4] and velocardiofacial syndromes. In the paper of Penman Splitt *et al*[1] is was reported (personal communication to the authors) that the same microdeletion has been found in two patients, one with dextrocardia and one with left isomerism (polysplenia syndrome).

Since 1993 we have performed clinical and molecular evaluation of all patients with conotruncal anomalies observed at our hospital,[5–7] including 20 cases with heterotaxia. Fifteen had asplenia syndrome and five polysplenia. All patients underwent phenotypic and cardiac examinations. Fluorescent in situ hybridisation was used for detecting 22q11 deletion.

No patients had phenotypic features of DiGeorge or velocardiofacial syndromes, and the genetic study did not show 22q11 deletion in any case. Our experience suggests that the conotruncal anomalies in the setting of heterotaxy syndromes are not related to 22q11 deletion, and are probably secondary to distortion of cardiac looping or to the anomaly of the situs itself. Different gene(s) and different developmental mechanisms may be involved in the pathogenesis of conotruncal anomalies in patients with situs solitus and in those with laterality defects.

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

We entirely agree with Marino *et al* that the conotruncal anomalies seen in patients with heterotaxy are likely to be secondary to distortion of cardiac looping and thus the mechanism is different from that seen in cases of 22q11 deletion. Their observations confirm our impression that 22q11 deletions are rare in patients with heterotaxy. While the two cases that we referred to are exceptional, they show the extreme phenotypic diversity associated with deletions of 22q11.

First report of three cystic fibrosis patients homozygous for the 1717-1G→A mutation

We report the identification for the first time of three cystic fibrosis (CF) patients homozygous for the 1717-1G→A[1] mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The clinical presentation of CF varies widely, the most common characteristics being chronic obstructive lung disease, raised electrolyte content of sweat, and pancreatic insufficiency (PI).[2] About 15% of patients display pancreatic sufficiency (PS).[3]

The isolation of the CFTR gene[4–6] has made it possible to identify the main disease causing mutation, ΔF508, accounting for about 70% of molecular defects in the world population,[4] and over 600 rarer presumptive mutations (CF Genetic Analysis Consortium). Among these, the 1717-1G→A mutation is a splice site alteration causing a G→A base change at the 3′ end of the consensus sequence of intron 10. It was first reported in a patient of Celtic origin[1] and since then it has been detected in other populations, having an overall frequency of 1.1%.[7]

To date, a clinical correlation for this mutation has been defined only in patients who are compound heterozygotes for ΔF508, who display a similar pancreatic and pulmonary phenotype to that of homozygotes for ΔF508.[8]

In this report we describe the first three patients found to be homozygous for the 1717-1G→A mutation. They showed early pancreatic insufficiency (one meconium ileus) and two of them had early onset of respiratory symptoms, but with subsequent minimal lung involvement progression. These findings suggest that this mutation might predispose to a milder respiratory course.

Two patients (cases A and B) regularly attend the Milan CF Centre at the Department of Pediatrics, University of Milan; the third patient (case C) is followed at the Naples CF Centre, Pediatrics Department, II University of Naples.

The three 1717-1G→A homozygous patients include: case A, a female, born at term (birth weight 3550 g) to healthy, nonconsanguineous parents. At birth, she presented with meconium ileus, which was surgically treated with a 10 cm ileal resection. She had a high immune reactive trypsinogen (IRT) value at 5 days of life (173 ng/ml, normal value <40 ng/ml) and CF was confirmed by a positive pilocarpine iontophoresis sweat test (112 mmol/l chloride).[9] Global treatment for CF was started at 2 months with pancreatic enzyme supplementation (Pancrease^{R}) and chest physiotherapy (positive expiratory pressure technique). At the latest clinical visit, aged 2 years 4 months, she was normal on examination, weight was 14 kg (75th centile), height 94 cm (97th centile). Good nutritional status was obtained with a low dose of pancreatic enzyme (1785 U/kg/day of pancrelipase) associated with a high fat content diet. A chest *x* ray showed only minimal thickening of the bronchial walls in the lower lobes. *Staphylococcus aureus* was intermittently isolated from bronchial secretions. She needed only one therapeutic antibiotic course for upper respiratory tract infection, and had had no admission to hospital since the diagnosis. No alterations in hepatic or nutritional indices were ever noted. Liver ultrasound was in the normal range.

The second patient, case B, a male, was born at term (birth weight 2850 g) to healthy, non-consanguineous parents. CF presented with malabsorption and bronchiolitis, requiring four hospital admissions in the first months of life. CF was confirmed by a positive pilocarpine iontophoresis sweat test (80, 105 mmol/l chloride). Regular follow up at our specialised CF Centre and adequate treatment were started at 6 months, with pancreatic enzymes (Pancrease^{R}), mucolytic and bronchodilator aerosol, and physiotherapy. He grew impressively after the start of therapy, body weight reaching the 50th centile at 2 years, and developing along the 97th centile from 5 years. At the last clinical visit, he was asymptomatic, not clubbed, his weight was 38 kg and height 139 cm. Steatorrhoea was absent and fat absorption coefficient was 93%, with 1061 U/kg/day of pancrelipase and a high fat content diet. A chest *x* ray showed only basal bronchial wall thickening. *Staphylococcus aureus* was chronically isolated from sputum samples. He needed only one therapeutic antibiotic course per year for upper respiratory tract infection and the clinical course was mild, with no further hospital admission, after starting treatment at our Centre following diagnosis. Lung function tests were always in the normal range. As compliance with chest physiotherapy was poor, daily sporting activities were encouraged. No alterations in nutritional indices were ever noted. Liver function tests were normal until July 1995, when serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and glutamyltransferase (GT) were slightly increased (42 U/l, 47 U/l, and 53 U/l, with normal values less than 37 U/l, 41 U/l, and 49 U/l). Ultrasound liver examination showed early signs of liver disease, so ursodeoxycholic acid therapy was prescribed.

The third patient, case C, a female, was born to healthy, non-consanguineous parents. Both paternal and maternal ancestors came from the same small city near Naples. Cystic fibrosis presented early with failure to thrive, malabsorption, and bronchiolitis, and she had atelectasis in the upper left lobe, leading to hospital admissions at 1 and 3 months of age. CF was confirmed by a positive pilocarpine iontophoresis sweat test (93 mmol/l chloride). Regular follow up at the CF Center and treatment was started with pancreatic enzyme

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