LETTERS TO THE EDITOR

Marfan syndrome

I read with great interest the article by Gray and Davies on Marfan syndrome¹, 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 pleiotropy. 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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- 3 Stahl-Hallengren C, Ukkonen T, Kainulainen K, *et al*. An extra cysteine in one of the non-calcium-binding epidermal growth factor-like motifs of the FBN1 polypeptide is connected to a novel variant of Marfan syndrome. *J Clin Invest* 1994;94:709-13.
- 4 Lee B, Godfrey M, Vitale E. Linkage of Marfan syndrome and a phenotypically related disorder of two different fibrillin genes. *Nature* 1991;352:330-4.
- 5 Tsipouras P, Del Mastro R, Sarfarazi M, *et al*. Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosome 15 and 5. *N Engl J Med* 1992;326:905-9.
- 6 Colod G, Babron MC, Jondeau G, *et al*. A

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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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