

in our second study (25%) was markedly lower than that sampled in our first study (75%). It is possible that this may have contributed to the reduction of effect in the second study. Nothen *et al* found that family history of schizophrenia had no effect on genotype distributions. However, the possibility remains that their patients differed from ours with respect to treatment response or to some other as yet undetermined variable.

Nothen *et al* point out correctly that the controls in the French sample were not in Hardy-Weinberg equilibrium and showed an excess of heterozygotes (though  $\chi^2$  is in fact 5.47 and not 8.7). However, the Cardiff controls did not show significant departure from Hardy-Weinberg equilibrium and nor did the further set of 98 controls typed in Cardiff. Moreover, we should remember that the significant excess of homozygotes seen in the patients as compared with Hardy-Weinberg expectations is not dependent upon the distribution of genotypes seen in the controls. Furthermore, the difference between patients and controls remains significant when the French controls are removed from the analysis ( $\chi^2=6.8$ ,  $p=0.009$ ). In view of the fact that the French controls were all members of hospital staff, whereas the controls in the first Cardiff study were married in members of families seeking DNA diagnosis for non-psychiatric diseases, we too wondered whether these differences might reflect heterozygote advantage. However, when we compared a sample of members of staff from our Institute, all of whom are graduates ( $n=37$ ), with our other controls ( $n=129$ ), no significant homozygosity effect ( $p=0.66$ ) or other differences were found and no significant departures from Hardy-Weinberg equilibrium were observed (both  $p$  values = 0.9).

Morell is correct to point out that our findings could have resulted from allelic dropout. We have also considered this possibility and have retyped our sample with a second set of primers placed internally to the first. The results we obtained were identical to those obtained from the first set of primers.

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## Severity of chest disease in CF patients in relation to their genotypes

Al-Jader *et al* (*J Med Genet* 1992;29:883-7) assessed severity of lung disease by calculating % predicted values for FEV<sub>1</sub> and FVC

and comparing single values in subjects of different ages, as did Johansen *et al*<sup>1</sup> in a similar study. Although in widespread use, this method has deficiencies, especially when analysing lung function data over time. The widely held assumption that a given % predicted value means the same for subjects of different ages is untrue; older subjects will have a lower % predicted value than younger ones with comparable lung function.<sup>2</sup>

Furthermore, older survivors with any CF genotype are likely to have milder disease and better lung function. This source of bias influences the plot of FEV<sub>1</sub> against time presented by Al-Jader *et al* and Johansen *et al*.<sup>1</sup> In each case the plot first shows a linear fall in FEV<sub>1</sub> with time followed by an upturn in the curve for older patients. On the basis of this, Johansen *et al*<sup>1</sup> claim the  $\Delta F508$  heterozygotes have less severe lung disease. However, if the three most extreme data points from the oldest patients are excluded from the graph in both studies, then the relation between FEV<sub>1</sub> and time becomes approximately linear, and the difference between heterozygotes and homozygotes is no longer apparent.

We have examined longitudinal lung function data in Grampian CF patients.<sup>3</sup> Forty-four patients were  $\Delta F508$  homozygotes, nine were G551D/ $\Delta F508$  compound heterozygotes, and 18 patients had other genotypes, including nine heterozygotes for  $\Delta F508$  and an unidentified mutation. Annual spirometric data were retrospectively collected from case notes. A regression line was constructed for each patient's lung function data over time, and a slope value calculated. A logarithmic transformation was applied to linearise the data, and mean slope values were calculated for each group. Mean slope values of the groups were not significantly different. Therefore, we too were unable to show differences in severity of lung disease in CF patients with different mutations.

Al-Jader *et al* suggest that patients with the genotype 621 + 1, G → T/ $\Delta F508$  may have more severe disease and R117H heterozygotes milder disease, but differences in lung function data were not significant. Moreover, only four patients with R117H were studied, so it is not valid to make any general inference about that mutation. There is a need for different centres to pool data before firm conclusions can be made about clinical features of CF patients with rare mutations.

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- Johansen HK, Nir M, Hoiby N, *et al*. Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet* 1991;337:631-4.
- Miller MR, Pincock AC. Predicted values: how should we use them? *Thorax* 1988;43:265-7.
- Packe GE, Miedzybrodzka ZH, Russell G, *et al*. Comparison of clinical features in cystic fibrosis patients with different genotypes. *Thorax* 1992;47:866P.

This letter was shown to Dr Al-Jader *et al* who reply as follows.

We were interested to learn that Packe *et al*<sup>1</sup> were unable to show differences in severity of lung disease with different mutations by analysis of longitudinal data; this finding is in keeping with ours<sup>2</sup> by analysis of cross sectional data.

The observation that, "older subjects have lower % predicted values for respiratory function tests than younger ones with comparable lung function"<sup>3</sup> was unknown to us. However, the paper would seem to refer to an adult population (30 to 70 years) in whom the objective was to define abnormality. We see no problem with the use of this method (FEV<sub>1</sub> and FVC, % predicted by vitalograph) versus age in our cross sectional study of patients aged 5 to 31 years. In addition to the use of respiratory function tests, we also scored chest x ray appearances (by Crispin-Norman score) in four age bands: <5.0 years, 5.0-9.9, 10.0-14.9, and >15.0 years. Patients homozygous and heterozygous for  $\Delta F508$  showed similar declines in score; from this, similar declines in lung function could be inferred.<sup>4</sup>

We question whether it is valid to remove the three most extreme data points from the oldest patients as plotted on the FEV<sub>1</sub> % predicted graphs of Johansen *et al*<sup>5</sup> and from our graphs and to consider the remaining data without these points. As we discussed in our paper,<sup>2</sup> the upturn in the curves for the heterozygous patients could relate to the death of the more severely affected patients and survival of those with a more advantageous genotype. Further work will establish whether this is so.

Regarding our patients who are heterozygous for 621 + 1G → T ( $n=7$ ) and heterozygous for R117H ( $n=4$ ), we accept that differences in lung function are not significant. We agree that there is a need for multicentre studies to examine the clinical features of CF patients with unusual mutations.

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