

then not have found Parchi's type 2 in sporadic CJD at all, whereas he finds this type in around 30% of cases. There are clear differences in western blotting methods between the two studies that may be important in detecting the relevant band shifts. However, our finding of four distinct patterns has been independently confirmed in a recent study of French CJD cases, which included the same new variant CJD that Parchi *et al.* studied<sup>11</sup>.

As we reported<sup>3</sup>, there seems to be further heterogeneity within the four PrP<sup>Sc</sup> types, and it seems likely that this will be only a first approximation towards a molecular classification of human prion diseases. The techniques used to date are relatively crude and relate to use of proteinase K alone. Higher resolution methods to size fragments, and the use of other proteases may detect yet further heterogeneity. In our view, both studies should be followed up with much larger-scale analyses in an attempt to relate PrP<sup>Sc</sup> types to clinicopathological phenotypes in humans and to study their transmission characteristics in susceptible animals. It will be important to standardize PrP<sup>Sc</sup> typing methods between centres with exchanges of sample sets to allow definition of an agreed classification of PrP<sup>Sc</sup> types.

For PrP conformation, or any other molecular candidate, to provide a basis for encoding prion strain specificity, it must be transmissible on passage to laboratory animals. That the PrP<sup>Sc</sup> types we have described in sporadic and iatrogenic CJD are maintained on passage of prions to transgenic mice expressing wild-type human PrP argues that the preliminary classification of PrP<sup>Sc</sup> types we have proposed has biological relevance<sup>2</sup>.

Finally, we did not claim the 'identity' of the prion strain causing BSE and vCJD. We reported that the glycoform pattern of vCJD differed significantly from other forms of CJD (as Parchi *et al.* confirm) but resembled that seen in BSE in cattle and BSE transmitted to several other species, consistent with, but not proving, the hypothesis that they are causally related<sup>3</sup>.

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## Medaka fish for mutant screens

The great success achieved by the groups led by Janni Nusslein-Volhard and Wolfgang Driever has undoubtedly established the zebrafish as a most promising model for vertebrate developmental genetics. But, we would like to champion the Japanese medaka (*Oryzias latipes*) as an equally useful experimental model.

Holder and McMahon<sup>1</sup> pointed out that the medaka was not used by the late George Streisinger, an originator of zebrafish developmental genetics, because it is difficult to score embryos for a phenotype in the clustered eggs of medaka. It is in fact quite easy to observe embryonic phenotypes in the medaka. The medaka lays a cluster of eggs every day. The entire cluster can be isolated from the mother using a net, without losing any sib embryos. Single eggs, which have hard chorions, can be isolated by rubbing the cluster between two small pieces of paper towel. The procedure is simple, and single eggs can be obtained within seconds. The embryos and chorions are transparent, and thus the phenotype can be scored in the medaka just as it is in the zebrafish.

In the medaka, more than 80 spontaneous visible mutants including about 30 morphological mutants have become available for experimental work and are currently maintained at Nagoya University<sup>2</sup>. The generation of developmental mutants of the medaka by exposure to radiation and chemicals was also reported recently<sup>3</sup>. Developmental mutants such as *Da* (double anal fin), *el* (eyeless), *fu* (fused vertebrae), *pl* (pectoral finless) and *tb* (twisted brain) are important resources for studying vertebrate development.

The medaka has been used by many investigators, including our group, in developmental and genetic studies for more than 70 years. Several inbred strains of the medaka have become available for experimental work<sup>4</sup> and a detailed genetic map is now also available<sup>5</sup>. To produce knockout fish for the analysis of gene functions, medaka embryonic stem cell lines have been established<sup>6</sup>. Thus the medaka, like the zebrafish, is a suitable species for vertebrate developmental genetics studies.

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Recent information on studies using medaka is available at the Internet 'Medakafish Homepage' (<http://biol1.bio.nagoya-u.ac.jp:8000/>).

## Natural selection bias?

Alatalo *et al.* in their Scientific Correspondence<sup>1</sup> suggest that an increase in published heritability estimates since 1988 results from a paradigm shift, increasing willingness to publish such estimates based on small sample sizes. But there have been several changes in the types of studies published since 1988 which may also contribute to this observation.

Most striking has been the increase in examination of sexual selection in birds. Before 1988, of the ten studies cited in ref. 2, nine are on insects, and one is on fish. After 1988, nine of twenty-four are studies of birds. This goes some way to explaining the decrease in sample size observed by Alatalo *et al.*, four out of seven of which are bird studies whereas only one is on insects. It tends to be easier to amass large data sets using insects, so referees may be less likely to accept low sample sizes in these cases.

A second change has been in the type of study carried out. Before 1988, seven of eleven studies were based on artificial selection. Since 1988 there has been a marked increase in studies using parent-offspring or sib-sib regression in the wild (nine of twenty-four since 1988 as opposed to one of eleven previously).

These changes suggest a more pernicious explanation for the proposed kuhnian shift. Perhaps it is not publication bias, but a bias in the design of studies carried out. Scientists cannot risk (or gain funding for) research without a high probability that a 'successful' result will be obtained. Having been convinced of the credibility of the good-genes theory, could it be possible that researchers have felt more inclined to conduct heritability studies on systems that they believe will yield orthodox results?

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