CJD who have the codon 102 Leu variant of PrP (ref. 2).

Our results differ from those of Palmer *et al.*[1]. This discrepancy suggests that other genetic differences between Japanese and UK populations might also be influencing CJD expression and phenotype.

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COLLINGE AND PALMER REPLY — Clearly, PrP Val 129 is rare in the normal Japanese population (15/343 chromosomes); we have found similar gene frequencies among Thais. Therefore it would be very difficult for these workers to replicate our study[1] in their population. Nevertheless, it is of interest that four of the cases described above by Tateishi's group are heterozygotes and that these are 'atypical' CJD cases of long duration (5–10% of CJD patients present like this[3]). We reported a single heterozygote in the CJD group (which turned out to be a familial case) and four heterozygotes from our suspected CJD group out of a total of 45 cases[1]. We have since screened further clinically suspected cases from the UK CJD surveillance study (kindly provided by R. G. Will) and found a further four heterozygotes. We had genotyped these cases without knowing their clinical details. Our prediction, following from our paper[1], was that these heterozygotes would turn out either to be misdiagnosed, unsuspected familial cases with pathogenic prion protein mutations, or 'atypical' CJD of long duration (phenotypically like familial CJD or GSS). This is essentially what we found (two were not CJD, one was confirmed CJD of short duration but with an atypical EEG, and the other five were clinically 'atypical' CJD). Unfortunately, Tateishi and colleagues do not mention the duration of illness in the single Val 129 homozygote, but give an overall mean with heterozygotes.

Both our data and those of Tateishi's group therefore support the idea that classical sporadic, short-duration CJD occurs in homozygotes, with the occasional heterozygotes with the sporadic illness accounting for the 5–10% of atypical cases. This is consistent with the emerging view that interaction between homologous PrP molecules may underlie the disease process and that heterozygotes are partially 'protected' from the disease.

In addition, all the autosomal dominant inherited prion disease cases are heterozygotes with respect to a pathogenic mutation (at codons 102, 117 and so on), and so also have heterologous PrP molecules. This may also interfere with the efficiency of interaction between PrP molecules and could account for the 'atypical' clinical presentation of the inherited cases (usually described as GSS, a relatively protracted illness in comparison to the dramatic sub-acute presentation of CJD). Interestingly however, codon 200 disease presents as CJD.

Perhaps Tateishi's group has heterozygotes in his CJD patients, despite the low population frequency, as a result of selection, in that such rare interesting cases are sent to centres with special expertise in these conditions. Finally, with respect to the Indiana kindred of GSS, a missense mutation (at codon 198) has now been reported in this family[4].

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Isodisomy in BWS chromosomes

SIR — Henry *et al.*[1], in demonstrating paternal disomy in cases of Beckwith–Wiedemann syndrome (BWS), have made an important advance in understanding this disease. But the authors do not discuss a surprising aspect of their data: excess homozygosity for chromosome band 11p15.5 markers is detected for the INS and IGF2 loci, but not for the flanking HRAS1 and HBB loci in BWS patients (Table 2 of ref. 1). This observation is difficult to explain if disomy for the entire paternal chromosome has occurred: as the INS/IGF2 region is also a candidate location for the BWS mutation[2], this raises the question of whether the uniparental disomy is restricted to the 11p15.5 region and has arisen by a localized mechanism.

In uniparental disomy involving an entire chromosome, the mechanism is defined by whether the two centromeres arise from the same parental chomosome (isodisomy) or different chromosomes (heterodisomy). The chance of isodisomy at any particular position along the chromosome depends both on the mechanism of the disomy (meiosis I defects cause centromeric heterodisomy, meiosis II defects centromeric isodisomy), and on the genetic distance of the locus from the centromere (a single intervening recombination tends to reverse the pattern)[3]. Although this may result in graded changes in observed homozygosity along a population of uniparentally disomic chromosomes, sharp local variations such as that observed between HRAS1 and HBB are not expected (the recombination fraction between these loci is only 0.18 in males[4]). What other mechanism(s) could account for the apparently localized homozygosity in BWS patients?

First, and perhaps most likely, it could be an artefact. Although Henry *et al.*[1] measured the frequency of homozygosity for the INS and IGF2 polymorphisms in a control group, they used published data[5] to estimate homozygosities for the flanking HRAS1 and HBB polymorphisms. These estimated homozygosities may be too high (for instance, the published data[5] suggest a figure for the HBBP/*Hin*cII system of 0.36–0.40, lower than the value of 0.51 cited in ref. 1), and it is not clear whether comparable racial groups were sampled. It is important to measure homozygosities directly in controls and to study more patients. In addition, cases with proven isodisomy for 11p15.5 should be tested with polymorphic loci on the long arm of chromosome 11: paternal disomy for such distant loci would imply that it involved the entire chromosome (Angelman syndrome provides an example of the application of this approach[6]).

Supposing that the isodisomy were indeed localized, this would imply a distinct mechanism, presumably involving the copying between chromosomes of a small portion of DNA in band 11p15.5, and occurring either during meiosis or mitosis. It is conceivable that the segment of chromosome copied could carry a pre-existing recessive mutation, explaining the requirement for iso- rather than heterodisomy. Such a mechanism would be of great biological interest and would suggest novel strategies for the localization of the BWS gene(s).

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