in 11p15.5 is more centromeric than previously thought. The first evidence for genetic heterogeneity in LQT came from Benhorin *et al.*⁴ who analysed linkage *HRAS* in a large family and found no linkage. Given our new results, such a conclusion must be confirmed with other markers^{5,6}.

Our results show that *HRAS* is excluded from the region containing the LQT gene and that LQT is more centromeric in 11p15.5 than previously thought. Until the LQT gene is found, several informative markers should be used for linkage analysis and presymptomatic diagnosis.

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Predicting the total number of human genes

Sir—We read with interest the News & Views by Fields and colleagues on human gene number in the July issue of *Nature Genetics*¹, but were somewhat concerned about the representation of our own work on this subject². In referring to our data in Table 1, Fields *et al.*¹ altered the proportion of CpG islands that are associated with genes from 56% to 66%. This has the effect of reducing our estimate for the number of genes from 80,000 to 67,000, bringing it closer to the preferred estimate derived from expressed sequence tag (EST) analysis (64,000).

The justification for changing the figure was that some of the genes included in our 'non-island' category might in fact be associated with islands that were outside the sequenced regions. We deliberately restricted our analysis to complete transcription units (including a known transcription start site and flanking sequences) in order to avoid this possibility. Even so, our result agreed closely with an independent survey of 362 human genes³ showing that 57% of genes were island-associated. If islands were being missed in these studies, they would have to be remote from their associated genes. This would be unprecedented. We therefore wonder what observation provides the basis for believing that the

percentages we determined should really be 66% rather than 56%? And why 66%, rather than 77% or 88%?

While we do not pretend that our estimate is the last word on gene number, we feel that it is unhelpful if the considered "best estimates" from different sources are altered without good reason. This is particularly so if the alteration gives the impression of a tighter consensus than is justified.

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IN REPLY—Antequera and Bird are concerned with our treating their estimate of the number of genes for observed CpG islands (about 80,000) as roughly consistent with our estimates based on other data (about 65,000). Their estimate is based on 152 complete transcription units (about 0.2% of human genes even on our estimate), and is consistent with an independent analysis³ of 362 genes (less than 0.6% of human genes). Our estimates are based on data from a variety of sources, varying from genome-wide analyses of transcription density by reassociation

kinetics to observed gene densities in sequenced regions comprising even tinier samples of the human genome. Our best estimate is based on a large sample of ESTs — representing probably half of human protein-coding genes — but even here the uncertainty in the true sampling redundancy is significant. Our explicitly hypothetical statement that "if two-thirds of human genes had associated CpG islands, the total predicted gene number would be 67,000" should be taken at face value. Very little of the human genome has been examined and the distribution of CpG islands in proximity to genes is not understood in any detail (see Fig. 2 (ref. 4)). In this context, a little over half (56%) and about two-thirds (66%) are not all that different.

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