Letters to the Editor

Am. J. Hum. Genet. 63:1910, 1998

Reply to Chinnery et al.

To the Editor:

We thank Chinnery et al. (1998 [in this issue]) for their appreciation of our article (Poulton et al. 1998) and for their reiteration of its main points, particularly the need to gather further data prospectively. Our article is in full agreement with all four of their reservations about direct application of current knowledge to clinical practice, and their new data on the 8344 mutation are very similar to the example we cite (Hammans et al. 1993). A recent study by White et al. (1998) that uses an empirical approach generates advice that is very similar to the predictions of our model.

We would, however, like to correct two points. First, our figure 2 (Poulton et al. 1998) refers to levels of mutant mtDNA in *ovary* and *progeny,* not in *blood* (clearly stated in the figure). To clarify the validity of our predictions, we now display the figure, along with the measured levels of mutant mtDNA (fig. 1; Marchington et al. 1998). It is clear that such accurate estimates of the level of mutant mtDNA in ovary only rarely will be available to the genetic counselor; hence, we use the 8344 mutation as an example of a mutation that "generally exhibits less variation between tissues than is seen among some of the other, more common mtDNA mutations" (Poulton et al. 1998, pp. 755–56).

Second, our discussion in the section "Models Describing the Mitochondrial Bottleneck" (Poulton et al. 1998, pp. 754–55) is far from a "recommended acceptance of a proposed simple bottleneck model" or a premature "application to prenatal mitochondrial diagnosis" (Chinnery et al. 1998, p. 1910). We did not recommend acceptance but suggested that "*once more data have been collected* [such as that described in White et al. 1998], such estimations will become usable in the medium term; reasonable fits may be more useful to patients than is the quality of information currently issued" (Poulton et al. 1998, p. 756). We also stated, *"Although most clinicians will feel that CVS* [chorionic villus sampling] *is not yet widely applicable to mtDNA disease,* there is clearly an urgent need to collect the human data needed to complete the picture" (Poulton et al. 1998, p. 756).

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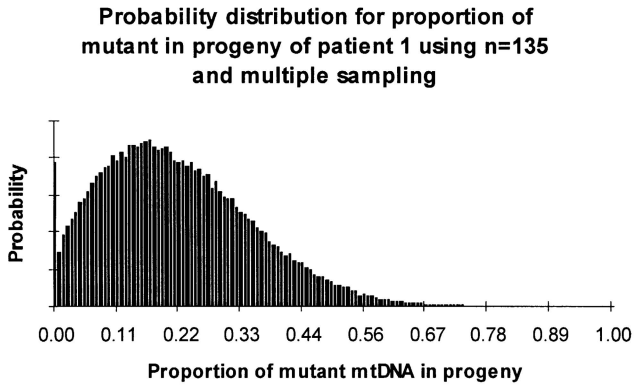

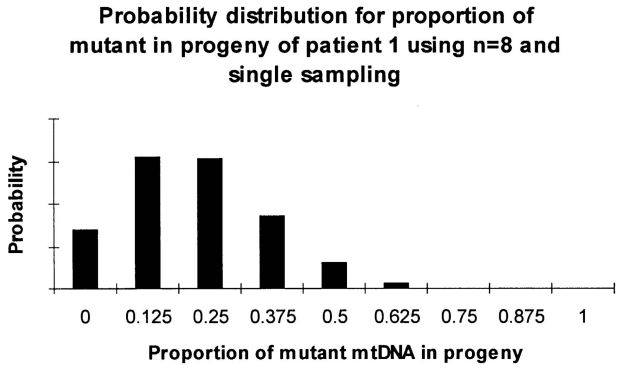

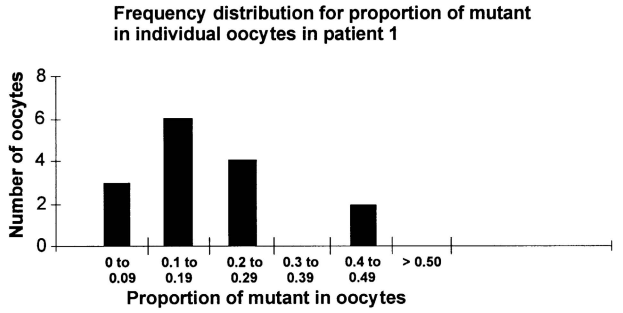

Figure 1 Fitting the repeated- and single-selection models to the data on mtDNA rearrangements: idealized plots for patient 1, for predicted percentage mutant in offspring, when 21% mutant mtDNA is in ovary, for repeated sampling ($g = 15$, $n = 135$; *top*) and for single selection ($g = 1$, $n = 8$; *middle*). Both reasonably fit the observed distribution (*bottom;* Marchington et al. 1998).