Letters to the Editor

Am. J. Hum. Genet. 64:1473, 1999

Reply to Henke and Henke

To the Editor:
From published data we could not derive "common knowledge" that microsatellite mutation rates differ by orders of magnitude. The authors seem to confuse "minisatellite" and "microsatellite" mutations and seem to extrapolate from observations in minisatellites, although it is known that the predominant mutation processes are not the same (Jeffreys et al. 1994). Furthermore, although an influence of the degree of polymorphism exists, there is no "close relation." As we tried to show in our article (Brinkmann et al. 1998), the correlation is not that simple.

We also disagree with the statement that the sex ratios were to be expected from minisatellite loci. The mutation process is different, and other structures and loci are involved. In fact, the sex ratios seem to differ grossly among minisatellites—for example, 1:1 for D1S7 and 1:8 for D7S22 (Henke and Henke 1995). It is therefore unclear which of these ratios should be chosen for extrapolation to microsatellites.

We agree with the authors that application to biomedical or forensic calculations would require sex-specific mutation rates. Therefore, their data are a valuable contribution, especially if the same criteria have been met. We pooled our data for individual loci to focus on the correlation of the mutation rates with the mean length of the affected structure. The data set was too small to address the question of locus-specific ratios.

Apart from sex-specific mutation rates, further factors need to be considered when Henke and Henke's data and ours are used to determine mutation rates applicable to paternity probability calculations.

First, the mutation rates of individual alleles at a given locus vary according to size, and, as we described in our article (Brinkmann et al. 1998), longer alleles often exhibit higher mutation rates than shorter ones. Our current enlarged mutation database indicates that, at the locus FGA, the mutation ratio of short versus long alleles seems to be close to an order of magnitude (fig. 1).

Second, the complexity of the allele sequence seems to exert an influence on the mutation rate. For example, we showed that, for ACTBP2, the longer alleles exhibit a lower mutation rate because of the interruption of the AAAG repeat by an AA dinucleotide.

Third, the number of undetected mutations depends on the paternity case—that is, whether one parent or both parents are examined and whether the putative father is included or excluded. It also depends on the genotype distribution in the specific population. For example, in the trio mother 16/17; child 16/17; father 16/18, a paternal 16→17 or 18→17 mutation would be undetected.

Fourth, paternal age may affect the mutation rate. We demonstrated that the mean age of fathers in whom mutations occurred was higher than the mean age of all fathers in our database. This would mean that the mutation rate should also be classified according to age.

Finally, it needs to be stressed that ~10% of the mutation events in our study are of unknown origin. These mutations cannot be used directly for the calculation of a sex-specific mutation rate without further assumptions and elaborations.

It is clear, then, that a correct mutation rate would require knowledge of many more mutation events than we have observed in our laboratory or Henke and Henke have seen. The currently available data at least allow the definition of an overall ratio of mutations that occur in male and female gametes. We would like to have our considerations understood as an incentive to others to report their mutation events. As more data become available, more certainty will be gained for the biostatistical calculation of paternity probability in cases of single-locus exclusions due to mutations.

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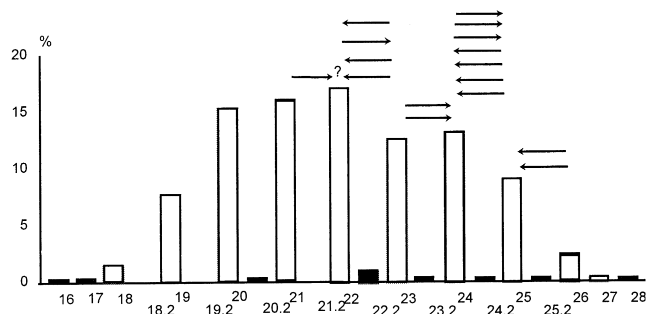

Figure 1 Allele frequencies and mutation events at the FGA locus.

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