Correspondence

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Interpretation of RFLP linkage data

SIR,

I would like to question the validity of the use of graphs of likelihood versus recombination fraction as the discriminator in the calculation of probe to gene distances, as used in recent papers in your journal[1 2] and elsewhere. I wonder whether a graph of likelihood versus map distance might not be more appropriate. Different recombination fractions are not equally likely. Whichever mapping function is used, it is more likely that the distance between a random probe and a disease locus would be, for example, between 43 and 75 centimorgans (that is, a range of 32 cM) than between 0 and 10 cM. However, according to the Kosambi function, both these ranges represent the same range of recombination fraction (0·35 to 0·45 and 0·0 to 0·10 respectively). I believe that this should be reflected by the discriminator used in range calculation.

I have computed the ranges produced by the two discriminators for some invented data. I assume the simplest case of n meiotic events (linkage phase known) with m recombinations seen. The probability at any given recombination fraction (θ) was calculated using the binomial distribution, and the 95% confidence limits for the probe-disease locus distance was calculated from this probability using the Kosambi function,[3] which has been suggested as appropriate for human female meiosis.[4] Values which approximated the data of Kingston *et al*[1] were n=25 and m=4. For these data, the most likely recombination fraction was 0·16, the lod score at this point being 2·75. Plotting this distribution against recombination fraction yielded a range in theta of 0·07 to 0·35 (7 to 43 cM), while plotting the same distribution against map distance produced a range of 7 to 58 cM. By incorporating the linear prior probability of linkage, suitable for loci known to be on the same chromosome[5] (and assuming the X chromosome to be 200 cM long), the discrepancy was reduced but not abolished, giving ranges of 6 to 41 cM and 7 to 50 cM respectively.

Interestingly, the discrepancy between the results diminished as n increased (holding the m:n ratio fixed) so that, for large values of n, either discriminator may be used. However, we suggest it would be reasonable to calculate ranges for small samples by the more conservative method, that is, the likelihood versus map distance discriminator, preferably using a number of mapping fractions.

I also noted that in the paper by O'Brien *et al*,[2] ranges of up to 50 cM were presented with no discussion of mapping functions. The lod score tables, simultaneously presented, suggest that it would not be possible to reject a θ of 0·5, which is equivalent to infinity according to any realistic mapping function.

Finally, the meaning of the term 'overall odds of linkage', as widely used, is obscure. The calculation of such odds involves division by the probability that the gene and probe are not on the same chromosome ($\theta=0{\cdot}5$). When the probe and disease locus are known to be syntenic, the odds are quoted with respect to a situation which is impossible and are, I suggest, meaningless.

I suggest that it would be more valuable to know the odds (or probability) that the probe's recombination fraction with respect to a disease locus is less than some arbitrary value indicative of significant linkage (for example, 0·3). This could be found by measuring the area under the curve of the discriminator function up to that value and comparing it to the area under the remainder of the curve. The 'odds of significant linkage, $\theta < 0{\cdot}3$' for our hypothetical case are 14:1 (if calculated on the likelihood/θ graph) or 7:1 (on the likelihood/map distance graph). The odds improve slightly to 16:1 and 9:1 after incorporation of the prior probability. These values, which I believe to have some meaning, bear no resemblance to the conventional odds of linkage at $\theta=0{\cdot}16$ (564:1) or to the overall odds of linkage (204:1).

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Haemoglobin O Arab (B121 Glu-Lys) in Turkish Cypriot population

SIR,

Hb O Arab (B121 Glu-Lys) has been reported in different ethnic groups including Sudanese, Arabs, American Negroes, Bulgarians, and recently in Turkish people.[1–7] It has not previously been reported in the Turkish Cypriot population.

We investigated blood samples of 1365 apparently healthy Turkish Cypriots by cellulose acetate electrophoresis.[8] When an abnormal haemoglobin was identified, citrate agar electrophoresis was performed.[9] Structural analysis was performed when indicated.[10]

Two haemoglobin O Arab traits and one Hb O Arab β-thalassaemia combination were detected in three different families. Further study of 24 subjects from these three families revealed 13 Hb O Arab traits and two Hb O Arab β-thalassaemia combinations. It was observed that the subjects with Hb O Arab had negroid characteristics (negroid Turkish Cypriots have the same physical characteristics as African Negroes; they represent less than 1% of all Turkish Cypriots). We investigated a further 19 subjects with negroid characteristics, two with Hb S trait, one with Hb H disease, and five with β-thalassaemia trait, but no further Hb O Arab traits were found in these subjects.

Hb O Arab was first detected in an Arab living in Israel, then in Egypt, Aden, Bulgaria, Rumania, Hungary, among American Negroes, and recently in Turkey.[1–7] It is believed to have originated in the Sudan and to have spread from there to West Africa and to many countries once occupied by or in close contact with the Ottoman Empire.[6 7]

When the history of the Ottoman Empire is considered the occurrence of Hb O Arab in Cyprus is not surprising. In 1570 the Ottomans conquered Cyprus and Anatolian Turks migrated to the island. The island was ruled by the Ottomans from the 16th to the end of the 19th century and during this period many people from Sudan and Egypt emigrated to Anatolia, Syria, Lebanon, and Cyprus.[11] Identification of Hb O Arab in Turkish Cypriots may indicate an admixture of African blood in the past. Moreover, some Turkish Cypriots show negroid physical characteristics.

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Incidence of pyloric stenosis in British Columbia over a 12 year period

SIR,

In a recent letter, Carter and co-workers[1] mentioned that the incidence of pyloric stenosis (infantile hypertrophic pyloric stenosis, IHPS) may be falling in the general population. We would like to comment on a recent study[2] done in British Columbia (BC) which investigated changes and seasonal variation in the incidence of IHPS over a 12 year period.

The BC study[2] was based on a cohort of 1234 livebirths with IHPS (988 males, 246 females) born