Bovidae family, belonging to different vertebrate classes, opens up a new understanding of SINEs distribution, previously thought to be unique to species, a few species, a genus or a family[5,6]. Its presence in a highly conserved form in two vertebrate classes raises questions as to its mode of transmission and its true phylogenetic distribution among vertebrates. SINEs appear to be inserted irreversibly and should therefore provide an ideal evolutionary and phylogenetic marker[5].

D. Kordiš
F. Gubenšek
Department of Biochemistry and Molecular Biology, J. Stefan Institute, 61111 Ljubljana, Slovenia
Email: franc.gubensek@ijs.si

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Meiotic drive and myotonic dystrophy

Sir — Myotonic dystrophy (DM) is a trinucleotide disorder and in sub-clinical individuals there is considerable variation in the length of the CTG repeat. Two groups have recently analysed the patterns of segregation of different sized alleles at this locus and both report an excess of the longer version of the allele in the progeny of sub-clinical individuals[1,2]. This excess they claim to be due to meiotic drive[1,2]. Our re-analysis of these two studies indicates that this conclusion is premature.

Meiotic drive is a form of non-mendelian transmission that is due to the differential success of the alleles at a given locus of a heterozygote individual at the gametic (that is, pre-zygotic) stage. All known examples of meiotic drive in anisogamous species have sex-specific activity, that is they act either in males or in females but not in both sexes (for example, the *t-complex* in mice is male specific)[3]. Hence, the recovery of an excess of progeny with a given allele from a heterozygous father but not a heterozygous mother (or vice versa) is, (i) evidence that the effect cannot be accounted for simply in terms of differential viability of progeny as a function of their genotype (assuming the locus is not subject to parental imprinting), and (ii) consistent with the operation of meiotic drive (or related sex-specific segregation distortion).

Both groups[1,2] examine the number of progeny with the long version of the *DM* allele from both heterozygous mothers and fathers and report an excess of the long allele only when the father is the heterozygote. This they suggest is consistent with meiotic drive acting in males. Our re-analysis of these data supports neither the finding nor the inference. We performed three tests:

(1) We re-analysed the data of Carey *et al.*[1], as per these authors, making no assumptions about the sex ratio of the source of the alleles. This test hence simply asks whether there is a difference from 1:1 in the segregation of the alleles and whether sex of parent affects this. However, Carey *et al.* (and indeed Gennarelli *et al.*[2]) fail to control for the number of statistical tests that were performed. If numerous tests are done it is to be expected that spuriously significant results will arise (Type I Errors). To allow for this, we hence follow Bonferroni's (correction) procedure in determining the significance of individual tests. Whilst Carey *et al.* correctly state that the data should be subjected to two-tailed tests, our two-tailed tests failed to replicate *P* values that they present (with one exception: the figure of $P=0.79$ in their Table 2). The *P* values given by Carey *et al.* can however be found if one employs a one-tailed test. The correct *P* values are thus two times those given by Carey *et al.* Thus, the data in Table 2 of Carey *et al.* do not support the transmission of long alleles by males in excess of 1:1, as was claimed ($P=0.08$, not 0.04 as reported).

Our reanalysis of their Table 1 is given in our Table 1. We fail to find any significant results, although there is a tendency for there to be an excess of the long allele. The re-analysis of these data also provides a *P* value less than 0.05 for the possibility that males differentially transmit the long allele ($0.05>P>0.025$, not $P=0.015$ as given). After correction for Type I Error, this effect disappears.

(2) The null hypothesis that is rejected in the above tests (the 1:1 ratio expectation for net segregation) is one of no meiotic drive and no post-zygotic selection. To provide evidence for the action of meiotic drive (and sex-specific segregation distorters in general), it is necessary to establish whether there is a significant difference between the recovery of the allele when the mother

Table 1 Re-analysis of the data given by Carey *et al.* in their Table 1 assuming a null expectation of 1:1 ratio for the segregation of the allele

Parent of origin	Large allele	Small allele	Total	d.f	χ^2	Probability	Significance after correction
Female	65	53	118	1	1.22	$0.9>P>0.1$	ns
Male	74	50	124	1	4.64	$0.05>P>0.025$	ns
Unknown	11	13	24	1	0.17	$0.9>P>0.1$	ns
Total	150	116	266	1	4.35	$0.05>P>0.025$	ns

Bonferroni's procedure yields the appropriate level for experiment-wise significance at the 5% level as being a χ^2 of ~6.6 for 1 d.f. for five independent tests (the four above plus a test of heterogeneity ($\chi^2=1.69$, $0.5>P>0.25$). If only four tests are performed there is still no significant statistic.

Table 2 Analysis using Fisher's method for partitioning Chi-squared under the null hypothesis of 1:1 sex ratio (origin), 1:1 segregation ratio (allele) and their interaction

Source	d.f	χ^2	Probability	Significance after correction
Origin	1	0.149	0.9>*P*>0.1	ns
Allele	1	5.355	0.025>*P*>0.01	ns
Origin × Allele	1	0.595	0.9>*P*>0.1	ns

Analysis of the data of Carey *et al.* Table 1. We exclude the data in which the parent of origin is unknown. The appropriate level for experiment-wise significance at the 5% level is a χ^2 of ~5.9 for 1 d.f. for three tests.

is a heterozygote and when the father is a heterozygote and not just from a 1:1 ratio. We thus treated the data as a contingency table under the assumption that no *a priori* expectations exist for either segregation ratio or the sex ratio of the parental origin of the alleles. Our analysis of both data sets finds no evidence for such a difference (χ^2=0.522, *P*>0.40 for data from Carey *et al.*; χ^2=1.551, *P*>0.20 for data from Gennarelli *et al.*: 1 d.f. in both instances).

(3) Gennarelli *et al.* have claimed that fathers occur more frequently than mothers as a source of the long allele and that sons are more likely to receive the long allele. We have hence analysed both teams' data[1,2] using Fisher's method for partitioning Chi-squared (and again applying a correction for Type I Errors). *A priori* assumptions were made about the sex ratio of the source of alleles, indeed, the null hypothesis tested here was that there was no bias of any kind (all sex ratios and segregation ratios were 1:1). Under this set of assumptions we additionally find in the data of Carey *et al.* no significant deviation of the parental sex ratio from 1:1 and, as above (but employing a slightly different analysis), no evidence that the sex of the parent affects the transmission ratio of the long and the short alleles (Table 2).

Our re-analysis of the Gennarelli *et al.* data (results not shown), reveals two significant results: (i) there is an excess of the long version of the *DM* allele (*P*<0.005) and (ii) there are more heterozygous fathers in the sample than heterozygous mothers (*P*<0.005). The latter result we do not know how to interpret. There are, however, good reasons to expect a strong ascertainment bias in favour of males when certain sampling procedures are employed[4]. There is no evidence of preferential transmission by fathers if the correction for Type I Errors is included, nor is there evidence of preferential transmission by fathers to sons as is claimed.

In sum, we find no evidence to support the conclusion that long versions of the DM allele have male-specific meiotic drive. The data are, however, consistent with selection in favour of bearers of the relatively long allele and/or segregation distortion (non-mendelian inheritance processes such as meiotic drive and biased gene conversion) acting in the same direction in both sexes. As noted above, meiotic drive operating in both sexes has not previously been reported. Any of the above forces can in principle account for the relative abundance of the long versions of DM alleles in sub-clinical individuals.

Gregory D.D. Hurst
Laurence D. Hurst
John A. Barrett
Department of Genetics, Downing Street, Cambridge, CB2 3EH, UK

IN REPLY — Whilst we accept some of the criticisms of Hurst *et al.*, we feel that their overall conclusion is unnecessarily negative and stand by our original conclusion that segregation distortion occurs for normal DM alleles. Hurst *et al.* are correct in stating that in our paper[1] the results for a one-tailed test were quoted inappropriately. However, if the total number of meioses are re-analysed using a two-tailed test without division into male and female transmissions, preferential transmission of the longer ≥19 repeat allele occurs at a statistically significant level (*P*<0.04). This represents the outcome of one test and is consistent with segregation distortion, which is the effect which we actually claimed was operating — meiotic drive was simply postulated as a possible mechanism for this effect.

Although we accept the general caveats about performing multiple analyses (and for this reason did not include in our original paper a geographical breakdown of the figures), we believe that it would be unusual to apply it in this circumstance, where the data are simply divided into the two sexes. The re-analysis by Hurst *et al.* runs the risk of artificially rendering a statistically significant result insignificant, by the application of a number of inappropriate tests followed by multiple hypotheses corrections.

Our re-analysis of the data still shows significant segregation distortion in favour of the transmission of the larger normal alleles. Larger sample numbers are required to investigate this effect more fully.

Nessa Carey
Keith Johnson
Human Molecular Genetics Unit, Department of Anatomy, Charing Cross and Westminster Medical School, London W6 8RF, UK

Pekka Nokelainen
Leena Peltonen
Department of Human Molecular Genetics, National Public Health Institute, Mannerheimintie 166, SF-00300 Helsinki, Finland

Maria-Liisa Savontaus
Vesa Juvonen
Deaprtment of Medical Genetics, University of Turku, Kiinamyllynkatu 10, SF-20520 Turku, Finland

Maria Anvret
Ulla Grandell
Department of Clinical Genetics, Karolinska Hospital, Box 60 500, S-104 01 Stockholm, Sweden

Kokila Chotai
Elaine Robertson
Kennedy-Galton Centre, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ, UK

Helen Middleton-Price
Mothercare Unit of Clinical, Genetics and Fetal Medicine and
Sue Malcolm
Molecular Genetics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

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