Explaining the X-linkage bias of placentally expressed genes

To the editor:

A recent study elucidates the interplay of selective forces that result in increased X-chromosome linkage of genes expressed predominantly in sex-limited tissues such as the testis and ovary[1]. The study also reports increased X linkage of genes that are highly expressed in the placenta. In the report and accompanying commentary, the bias of placentally expressed genes is ascribed to the placenta being a 'female' tissue[1,2]. Although the placenta develops jointly from maternal and fetal tissues, however, anatomical and molecular genetic studies indicate that an explanted placenta is composed predominantly of fetal trophoblast. Therefore, most DNA sequences in placental cDNA collections are likely to be fetal, rather than maternal, in origin[3,4]. This is evident from scrutiny of the placental cDNA collections used by Khil *et al.*[1], which shows that known trophoblast-specific genes are well represented.

Although the explanation for the placental bias proposed by Khil *et al.*[1] therefore requires clarification, we suggest that their finding is nevertheless consistent with Rice's proposal that increased X linkage is a feature of sexually antagonistic genes[5]. The fetal component of the placenta is a key site of imprinted-gene expression[6]. It has been proposed that imprinting evolved as a form of sexual antagonism acting on the parental alleles at loci expressed in offspring that influence the level of maternal investment[7]. Paternal alleles are predicted to favor increased maternal investment in offspring, and maternal alleles to favor reduced investment. Consistent with this theory, experimental overexpression of maternally inherited alleles or underexpression of paternally inherited alleles causes reduced growth of fetal and placental tissues[6]. In mammals, the paternally inherited X chromosome is epigenetically inactivated in most of the fetal extraembryonic tissues that contribute to the placenta of female embryos. Therefore, placentally expressed genes that undergo X inactivation are effectively imprinted, with maternal expression, and, under the parental conflict theory, are predicted to favor reduced maternal investment. Consistent with this theory, mouse embryos carrying supernumerary X chromosomes of maternal origin have reduced placental growth[8,9].

In spite of the expectation that imprinting should evolve at any locus mediating maternal investment in offspring, imprinted genes are scarce; this fact may be explained by the existence of mechanistic barriers to the evolution of parental allele–specific expression[10]. But the presence, in placental tissues of fetal origin, of the paternally silenced X chromosome provides a preadapted mechanism for the evolution of maternal-specific gene expression which, from a joint consideration of Rice[5] and the parental conflict theory[7], predicts increased X linkage of placentally expressed genes that reduce placental growth and maternal investment. It is, therefore, unnecessary to ascribe 'femaleness' to the placenta in order to explain the findings of Khil *et al.*[1], because sexual antagonism is played out, at one remove, in the fetal trophoblast between maternally and paternally inherited alleles.

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In reply:

In our earlier work[1], we found that genes with sex-biased expression profiles are enriched on the X chromosome in mouse. Moore *et al.* suggest an alternative interpretation for a part of our data. In their correspondence, Moore *et al.* note correctly that, in essence, the genetic composition of placenta is not maternal but fetal. The main constituent of a mature placenta is extraembryonic trophoblasts of fetal origin[2]. Based on this genetic inhomogeneity of the placenta, Moore and coauthors claim that the placentally expressed genes cannot be considered 'female' and suggest an alternative explanation for the overrepresentation of these genes on the X chromosome based on the conflict theory of imprinting[3].

Although the combination of the parental conflict model and Rice's model[4] suggested by Moore and coauthors is applicable, their proposal is incomplete. First, Moore *et al.* state that the placenta is not a female tissue. But the expression of the genes in placenta is influenced by their environment, which is largely female, and it is the expression of these genes that in turn influences their chromosomal locations. Second, although Rice's model, also used by us, deals with sexually antagonistic genes, it does not set limits on their origin or the specificity of their expression. Rice's model concludes that female-advantageous genes should be enriched on the X chromosome[4]. Therefore, the goal is to identify these female-beneficial genes. We used preferential expression of a given gene in a female-limited tissue, placenta, as an indication that its effect is beneficial to females. Whereas it is not impossible for a gene that is expressed mainly in a sexually nondimorphic tissue to have a female-