mtDNA phenotype, such as reduced levels of mtDNA or defective mtDNA in the oocyte, which would be candidate "preconceptual" factors, as suggested by Thyagarajan et al. (1991).

Is there any evidence to support this hypothesis? Neither Thyagarajan et al. (1991) nor my colleagues and I have found any evidence for major rearrangements of mtDNA in these patients, and they found no support for a single point mutation. They also use their data to show that two cases of CMD have mitochondrial morphs that are only distantly related. However, analysis of further patients would be necessary to eliminate the possibility that there are several different mtDNA mutations that are capable of producing a similar phenotype, as occurs in Leber hereditary optic neuropathy. It remains possible that the myotonic dystrophy gene results in inaccurate mtDNA replication and that there are many different mtDNA mutations, all at low levels. There are thus no hard data in support of a role for mtDNA in CMD. Wider sampling and more accurate characterization of the myotonic dystrophy gene in congenital onset cases will probably demonstrate that the reason for maternal transmission is the greater expansion of the triplet repeat during female meiosis than during male meiosis, in all cases.

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Sex-specific Recombination Frequencies: A Consequence of Imprinting?

To The Editor:

Imprinting describes a phenomenon in which there is differential gene expression dependent on the sex of the transmitting parent (Surani 1986; Monk 1987, 1988). Imprinting has been proposed as a mechanism underlying human disorders which show variation in phenotypic expression, depending on parental origin of the gene (e.g., Prader-Willi syndrome and Angelman syndrome) and/or unusual patterns of inheritance of age at onset (e.g., Alzheimer disease, myotonic dystrophy, fragile X, Huntington disease, neurofibromatosis, and others) (Hall 1990; Farrer et al. 1992).

Hall (1990), in an excellent review of imprinting and its potential role in human disease, describes specific features of pedigree patterns which may provide useful clues in identifying human traits undergoing imprinting. For example, traits subject to imprinting will show different frequencies or severity of affection among offspring, depending on the sex of the transmitting parent. At a population level, Chakraborty (1989) shows that imprinting may lead to apparent heterozygote deficiency and that it may mimic population genetic consequences of hybrid vigor.

Hall (1990) suggested two approaches for identifying possible chromosome regions which undergo imprinting among humans: (1) identification of human chromosome homology to mouse chromosome regions known to undergo imprinting and (2) identification of unusual patterns of inheritance and/or evidence of uniparental monosomy (e.g., Prader-Willi syndrome and Angelman syndrome) of specific chromosome regions.

The purpose of this letter is to propose an additional means for identifying traits and/or chromosome regions which may undergo imprinting—specifically, identifying traits showing substantial differences in recombination frequencies with linked marker loci, depending on the sex of the transmitting parent (i.e., paternal vs. maternal meioses). Sex-specific recombination rates (estimated in linkage analyses of a trait with linked marker loci) will be a consequence of imprinting; thus, utilization of this information may aid in identifying traits undergoing imprinting.

To illustrate how imprinting will lead to sex-specific recombination frequencies (and, thus, to map distances), a pedigree taken from Hall (1990) is shown in figure 1 in which maternal imprinting is occurring for an autosomal dominant trait.

In this example, there is complete expression of the trait when the gene is transmitted through the father, and there is no expression of the trait when the gene is transmitted through the mother. I have added, for illustrative purposes, genotype information at a highly informative marker (eight alleles numbered 1–8) in tight linkage with the disease gene, so that all matings

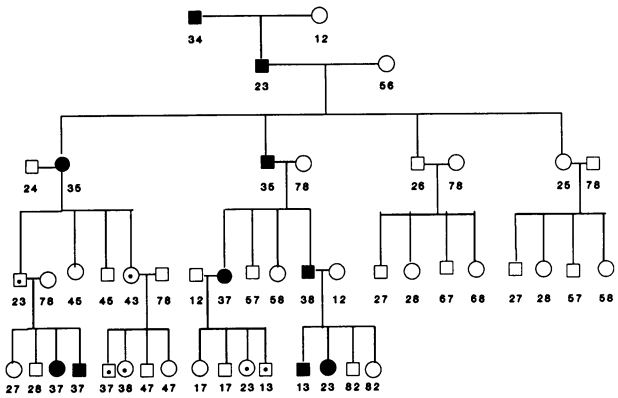

Figure 1 Pedigree in which maternal imprinting is occurring for an autosomal dominant trait. Blackened symbols represent phenotypically affected individuals. Unblackened symbols with an enclosed dot represent carriers of the gene who are phenotypically unaffected because of imprinting. Numbers (1–8) represent hypothetical alleles at a tightly linked marker locus.

are phase known and completely informative for the disease and marker locus. Estimating recombination fractions in the pedigree, we see that the unaffected carriers of the disease trait (who do not express the trait because of imprinting) appear as recombinants, thus leading to different recombination frequencies for male meioses (0/16) than for female meioses (3/8). Although, in the example, reduced penetrance must be invoked to explain individual IV-1's unaffected status, there is no way to identify the additional five members who are also carriers but who do not express the trait because of imprinting. Among these five subjects, three will appear as recombinants with a probability assigned, in part, on the basis of the estimate of penetrance in the population. The remaining two subjects (V-5 and V-6) will not contribute information, because individual IV-5 is not recognized as a carrier.

What effect will these sex-specific recombination frequencies have on lod scores calculated using classic linkage analyses? Ott (1991) shows that, when a strong difference between male and female recombination rates exists, the lod scores calculated under a model where male and female recombination rates are equated may be much lower than the overall maximum (i.e., when male and female recombination rates are not equal). One may thus miss detecting a linkage by not allowing for a difference between male and female recombination frequencies (Ott 1991).

We calculated lod scores for this hypothetical autosomal dominant disease trait and marker locus, shown in figure 1, under conditions of both equal and unequal male and female recombination frequencies. The disease-trait allele frequency was fixed at .0005, with a penetrance fixed at .9. The ILINK package of LINKAGE, version 5.10 (Lathrop and Lalouel 1984), was used to estimate recombination frequencies and to calculate lod scores. At equal recombination frequencies, the maximum lod score was 3.38, compared with 4.66 when male and female recombination frequencies were allowed to vary. The estimates for male and female recombination frequencies under the latter model were 0 and .363, respectively.

When this example is generalized, several points are evident:

1. Imprinting, when the effect is complete lack of expression of a trait, will lead to distorted estimates of recombination from meioses of the imprinting sex (i.e., female meioses under maternal imprinting and male meioses under paternal imprinting).
2. The impact of imprinting on recombination frequencies will depend on the extent of imprinting. For example, complete imprinting (defined here as complete expression or lack of expression, depending on the sex of the transmitting parent), will lead to the greatest discrepancy between male and female recombination frequencies. Thus, pooled estimates of recombination rates will vary, depending on the degree of imprinting. When equal numbers of informative male and female meioses are assumed, the observed recombination rate would be expected to be highest under complete imprinting, intermediate under partial imprinting (i.e., where some percentage of imprinted individuals are affected), and lowest under no imprinting.
3. Map distances based on pooled male and female recombination frequencies when imprinting is present will be incorrect.
4. Lod scores and estimates of recombination frequencies will depend on the proportion of male and female meioses present in any sample. It follows that there may be quite disparate results from linkage analyses across pedigrees, if the sex of the transmitting parent is not considered.
5. Imprinting, if present and unrecognized, will lead to a greater proportion of apparent recombinants among unaffected individuals than among affected individuals. This is because, as a result of imprinting, unaffected carriers will be classified as recombinants because of true recombination as well as imprinting, while affected carriers will be counted as recombinants only when they are true recombinants. A consequence of this is that linkage

findings may differ, depending on whether unaffected members are used (i.e., classic lod-score approach vs. affected-member methods).

Mechanisms other than imprinting must underlie some of the sex differences observed in map distances estimated from linkage data, since recombination frequencies estimated from male and female meioses for DNA polymorphisms also show a sex difference. Imprinting will not be a mechanism underlying these sex differences, since the effect of imprinting on recombination frequencies is due to genotypic misclassification of unaffected individuals. However, extreme differences in male and female recombination rates for a disease trait and linked markers, compared with distances estimated for marker polymorphisms in the same chromosome region, may provide a *clue* that imprinting is present. With the extensive number of DNA polymorphisms now mapped across the human genome, it may be possible to estimate an average male:female recombination frequency for markers in a particular region and to compare a specific male:female ratio for a disease trait and linked marker localized to the same region. Development of methods to differentiate male:female recombination frequency differences due to imprinting from other sources requires further research.

The magnitude of the effect of imprinting on sex-specific recombination frequencies will depend on the degree of imprinting and other parameters of the model (e.g., the degree of reduced penetrance included) in linkage analyses. Other clues (such as those discussed by Hall [1990]) may be used in combination with sex-specific recombination rates, to identify genes and/or chromosomal regions involved in imprinting.

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Calculating the Probability of Observing *b* of *a* Possible Alleles at a Marker Locus

To the Editor:

In a recent issue of the *Journal,* Ott (1992) considered the following problem: Given a marker system with the number of alleles denoted by a and a population frequency g_k for allele k ($1 \leq k \leq a$), what is the probability distribution for the number Z_n of different observed alleles in a random sample of n alleles (or $m = n/2$ individuals)?

It may be noted that an answer to this problem could be obtained numerically quite simply by applying the following recurrence relation: For $k \in \{1, \ldots, a\}$, define $U_k^n := 1$ if the sample of size n contains at least one occurrence of allele k, and $U_k^n := 0$ otherwise. Obviously, one has

$$\begin{aligned} P(U_1^n = u_1, \ldots, U_a^n = u_a) &= \left(\sum_{k:u_k=1} g_k\right) \cdot P(U_1^{n-1} = u_1, \ldots, U_a^{n-1} = u_a) \\ &+ \sum_{k:u_k=1} g_k \cdot P(U_1^{n-1} = u_1, \ldots, U_{k-1}^{n-1} = u_{k-1}, \\ &\quad U_k^{n-1} = 0, U_{k+1}^{n-1} = u_{k+1}, \ldots, U_a^{n-1} = u_a) \end{aligned}$$

and

$$P(Z_n = b) = \sum_{|\{k:u_k=1\}|=b} P(U_1^n = u_1, \ldots, U_a^n = u_a).$$