Am. J. Hum. Genet. 62:1493–1499, 1998

Parental Origin–Dependent, Male Offspring–Specific Transmission-Ratio Distortion at Loci on the Human X Chromosome

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Summary

We have analyzed the transmission of maternal alleles at loci spanning the length of the X chromosome in 47 normal, genetic disease–free families. We found a significant deviation from the expected Mendelian 1:1 ratio of grandpaternal:grandmaternal alleles at loci in Xp11.4-p21.1. The distortion in inheritance ratio was found only among male offspring and was manifested as a strong bias in favor of the inheritance of the alleles of the maternal grandfather. We found no evidence for significant heterogeneity among the families, which implies that the major determinant involved in the generation of the non-Mendelian ratio is epigenetic. Our analysis of recombinant chromosomes inherited by male offspring indicates that an 11.6-cM interval on the short arm of the X chromosome, bounded by *DXS538* and *DXS7,* contains an imprinted gene that affects the survival of male embryos.

Introduction

Significant deviation from Mendelian inheritance has been observed in a number of instances in humans. In most cases, such transmission-ratio distortion (TRD) is associated with alleles at disease loci, but the mechanisms responsible for these observations are unknown and may be heterogeneous. A recent analysis of the transmission of alleles at the myotonic dystrophy locus revealed a preferential transmission of alleles containing larger numbers of CTG repeats (Chakraborty et al. 1996), whereas preferential transmission of alleles with smaller numbers of CAG repeats has been observed in Machado-Joseph disease patients (Rubinsztein and Leggo 1997). A seven-generation family with cone-rod retinal dystrophy has been reported that displays preferential transmission of mutant alleles (Evans et al. 1994). In retinoblastoma families, mutant *RB1* alleles are preferentially transmitted to the offspring of affected fathers but not to the offspring of affected mothers (Munier et al. 1992; Naumova and Sapienza 1994). Other cases in which TRD seems to occur in offspring of only one sex have been reported for the cystic fibrosis locus (Kitzis et al. 1988; but see also European Working Group on Cystic Fibrosis Genetics 1995), the retinoblastoma locus (Naumova and Sapienza 1994), Hirschsprung disease (McKusick 1994), and the *MEN2B* locus (Carlson et al. 1994).

We have proposed that this latter characteristic—the association of TRD with only one sex of offspring—may be a hallmark of defective imprinting (or defective imprint "erasure," similar to that proposed by Laird [1987]), at both the autosomal locus and an X-chromosome locus (Naumova and Sapienza 1994). As part of a study designed to test this hypothesis, we observed a bias against the inheritance of *AR* alleles on the preferentially active grandmaternal X chromosome among the male offspring of mothers who displayed strongly skewed patterns of X inactivation (Naumova et al. 1995). Because of the small number of families analyzed in that study, we could map the region of maximum distortion only to a broad area of the X chromosome, between Xp11 and Xq22 (only families in which mothers had skewed X-inactivation patterns were included) (Naumova et al. 1995). We have now extended our analysis to a large number of families who were not ascertained on the basis of the presence of any disease, and we have found significant overall TRD in favor of grandpaternal alleles in an 11.6-cM interval on the short arm of the X chromosome (Xp11.4-p21.1).

Subjects and Methods

Subjects

DNA from individuals from 47 three-generation families (38 CEPH families and 9 families collected by our

Received September 9, 1997; accepted for publication April 1, 1998; electronically published April 24, 1998.

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0002-9297/98/6206-0028$02.00

laboratory) were included in the analysis of transmission of alleles at loci on the human X chromosome. No genetic disorders were reported in any of these families. The offspring examined in the report by Naumova et al. (1995) are a subset of the offspring examined in the present study (a maximum of 75 offspring were examined in the previous study, whereas a total of 314 offspring have been examined in the present study).

Genotype Determination

Data were either obtained from the GenLink public database (Fain et al. 1995) or collected in our laboratories (see fig. 1). Genotypes were determined by PCR amplification of alleles at microsatellite loci. Oligonucleotide primers specific for each locus were purchased from Research Genetics. The two-dimensional map of the X chromosome (Fain et al. 1995) was used as the basis for the mapping of the distorter.

Statistical Analysis

For the test for equality of proportion of grandpaternal alleles, we used the exact binomial test of the equality of proportions of grandpaternal and grandmaternal alleles, two-sided alternative hypothesis: for the sexes combined, $P = .011$; for female offspring, $P = .628$; and, for male offspring, $P = .0032$. The confidence interval (CI) was the large-sample estimate of the CI of the estimate of the proportion of grandpaternal alleles.

Multiple Testing Considerations

Our earlier study (Naumova et al. 1995) provided suggestive evidence for a bias in the inheritance of X chromosomes by sons of mothers with strongly skewed X-inactivation patterns. This bias was ascertained for the *AR* locus but appeared at three loci: *DXS1068, AR,* and *DXS101* showed an apparent effect of maternal inactivation status (Naumova et al. 1995, table 2); *DXS1068* showed a suggestion of bias against the inheritance of grandmaternal X chromosomes ($P = .093$, exact binomial test [A. K. Naumova, L. Olien, L. M. Bird, C. Slamka, M. Fonseca, A. Verner, and M. Wang, M. Leppert, K. Morgan, and C. Sapienza, unpublished data]), and *AR* showed a possible effect of both factors (Naumova et al. 1995, table 4). From these data, it was unclear whether grandparental origin, X-inactivation status, or both factors might influence the observed bias in X-chromosome inheritance among the sons of a small number of females with skewed X inactivation.

Although we considered these data to be suggestive, we were also aware of the mouse data demonstrating a bias against the inheritance of C57BL/6 alleles (i.e., grandmaternal alleles) at X-chromosome loci among the offspring of interspecific F_1 hybrid females (that might also be expected to have some degree of X-inactivation skewing because of heterozygosity for different *Xce* alleles [Cattanach and Raspberry 1991]). Using these facts to motivate the present study, we examined the rest of our collection of families only for a bias in transmission as a function of grandparental origin, because the vast majority of the mothers of our families did not have skewed X inactivation (Naumova et al. 1996). Our hypothesis was that, if grandparental origin plays a role in the transmission of X chromosomes to sons, then this bias should be observed among a larger sample that was not selected for X-inactivation status. If the previously observed bias was based solely on X inactivation, then there should be no bias when the data were stratified according to grandparental origin of the allele (unless this character also influences X inactivation). If our original observation of bias was due to chance, then it would simply not be repeated at any of the three loci identified in the first study.

Because our first study provided suggestive evidence of TRD at three loci, it may be appropriate to correct the significance of our present result for the performance of three tests (at *DXS1068, AR,* and *DXS101* [see the Discussion section]). Such a correction will be conservative, because the three loci are not completely un-

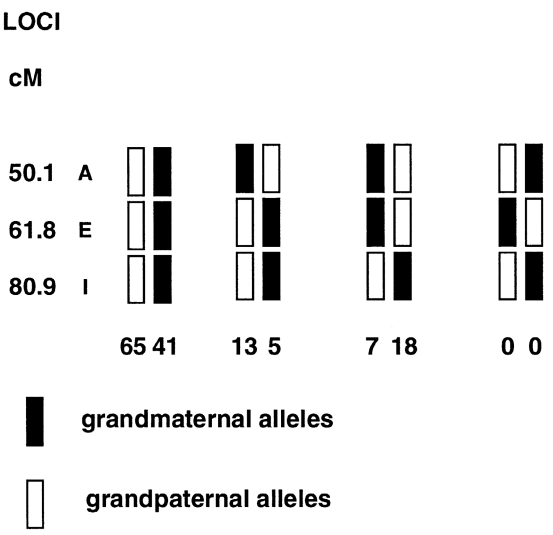

Figure 1 Mapping of *DMS1* within the p21.1-p11.2 region of the human X chromosome: haplotypes of X chromosomes of male offspring. Position 50.1 cM corresponds to the 3′ region of the *DMD* locus, 61.8 cM corresponds to *DXS1068* and/or *DXS1058,* and position 80.9 cM corresponds to the *TIMP* locus. DNA samples from 45 families (36 CEPH families and 9 families studied by our laboratory) were analyzed; 150 males were informative for all three loci, and 17 males were informative for only one or two loci (partial haplotypes of these 17 males are not shown). The chromosome representations are based on data from the GenLink database (for 21 families), supplemented by data generated in our laboratory (for 24 families) and on the two-dimensional map of the X chromosome (Fain et al. 1995).

linked. Our rationale for determining the genotype at the additional X-chromosome loci (before embarking on the mapping study around *DXS1068*) was to provide assurance that our observation was not the result of chance, or that, simply by typing a large enough number of markers, we would observe inheritance bias somewhere else on the X chromosome in our larger sample.

Familial Heterogeneity of Proportions of Grandparental Alleles

Tests of heterogeneity of the proportions of grandparental alleles at *DMS1* among families were performed for male and female siblings separately. There were a total of 45 families informative for segregation analysis: 43 families were informative for male siblings, and 40 families were informative for female siblings. Exact tests of heterogeneity were performed by means of the Markov-chain Monte Carlo method, to estimate the *P* value and standard error (SE) of the significance level for sparse contingency tables (Guo and Thompson 1989, 1992). The number of batches of generated tables was 500, the sample size of each batch was 10,000, and the "burn-in" period was 10,000 steps.

Results

Transmission of maternal alleles at 15 loci, spanning the entire length of the X chromosome (see the Subjects and Methods section), was analyzed. However, in the following statistical analyses, no corrections were made for the testing of multiple loci, because our analysis was motivated by prior expectation of TRD in favor of grandpaternal alleles over a portion of the X chromosome (i.e., at *DXS1068, AR,* and/or *DXS101* [see the Subjects and Methods section and Naumova et al. 1995]; in the Discussion section, we have used the Bonferroni correction for conducting three tests). A statistically significant deviation from the expected Mendelian ratio of 1 grandmaternal:1 grandpaternal allele was observed at only one locus, *DXS1068,* at Xp11.4. In the 45 families examined (no information for the Xp11.4 region was available in 2 families), alleles derived from the Xp11.4 region of the X chromosome of the maternal grandfather were found to be transmitted preferentially: 180 offspring inherited the grandpaternal allele, and 134 offspring inherited the grandmaternal allele ($P = .011$). Further scrutiny of the data (table 1) revealed that the observed TRD was due to preferential inheritance of grandpaternal alleles among male offspring (103 grandpaternal alleles vs. 64 grandmaternal alleles [$P = .0032$]) but not among female offspring (77 grandpaternal alleles vs. 70 grandmaternal alleles [$P = .62$]).

The region of maximum distortion (which we call "*DMS1*" [distorter male-specific 1]) was mapped, by haplotype analysis, to the interval between the 3′ end of the *DMD* locus and the *TIMP* locus (fig. 1). Of the 150 male offspring typed for at least three loci within this region, 43 had recombinant chromosomes. Further analysis of the recombinant haplotypes (fig. 2) indicated that *DMS1* maps to an 11.6-cM region between position 58 cM (*DXS538,* in the 5′ portion of the *DMD* locus) and position 69.6 cM (*MAOA* and *MAOB*).

Table 1

Inheritance of Grandpaternal Alleles at *DXS1068*

Sex of Offspring	Proportion [95% CI] of Grandpaternal Alleles
Male	.62 (103/167) [.54–.69]
Female	.52 (77/147) [.44–.69]

Because a grandparental-origin effect on TRD at X-chromosome loci is not predicted to occur in families that are not associated with any X-linked disease, we wished to determine whether the overall bias in favor of inheritance of grandpaternal alleles by male offspring was the result of the disproportionate influence of one or a few families. The structure of the families, with respect to inheritance of grandmaternal versus grandpaternal alleles at *DXS1068,* is shown in table 2. We tested for evidence of heterogeneity between families, using a Markov-chain Monte Carlo simulation method (see the Subjects and Methods section). The contingency table of (family) × (grandpaternal allele *vs.* grandmaternal allele) for male offspring has an estimated exact *P* value of .119 (SE = .0014; see the Subjects and Methods section), whereas the value for female offspring is .745 (SE = .0017). These data do not provide evidence for significant heterogeneity among the families, with respect to the inheritance of grandparental alleles at *DXS1068*.

Discussion

We have identified a region, in the human X chromosome, that exhibits sex-of-offspring–specific, non-Mendelian inheritance in "normal" families. Although most of these families (the CEPH and/or Utah pedigrees) were selected on the basis of large family size, none were ascertained through the occurrence of genetic disease. Therefore, it is unlikely that the TRD that we have observed is a result of ascertainment bias or other explanations having to do with the medical status of the families. By analogy with similar observations made in the mouse, we believe that our observations represent a phenomenon that has biological significance.

TRD at X-chromosome loci in the mouse has been reported by several investigators (Biddle 1987; Boyd 1996; Montagutelli et al. 1996; Zechner et al. 1996, 1997). Montagutelli et al. (1996) have mapped at least

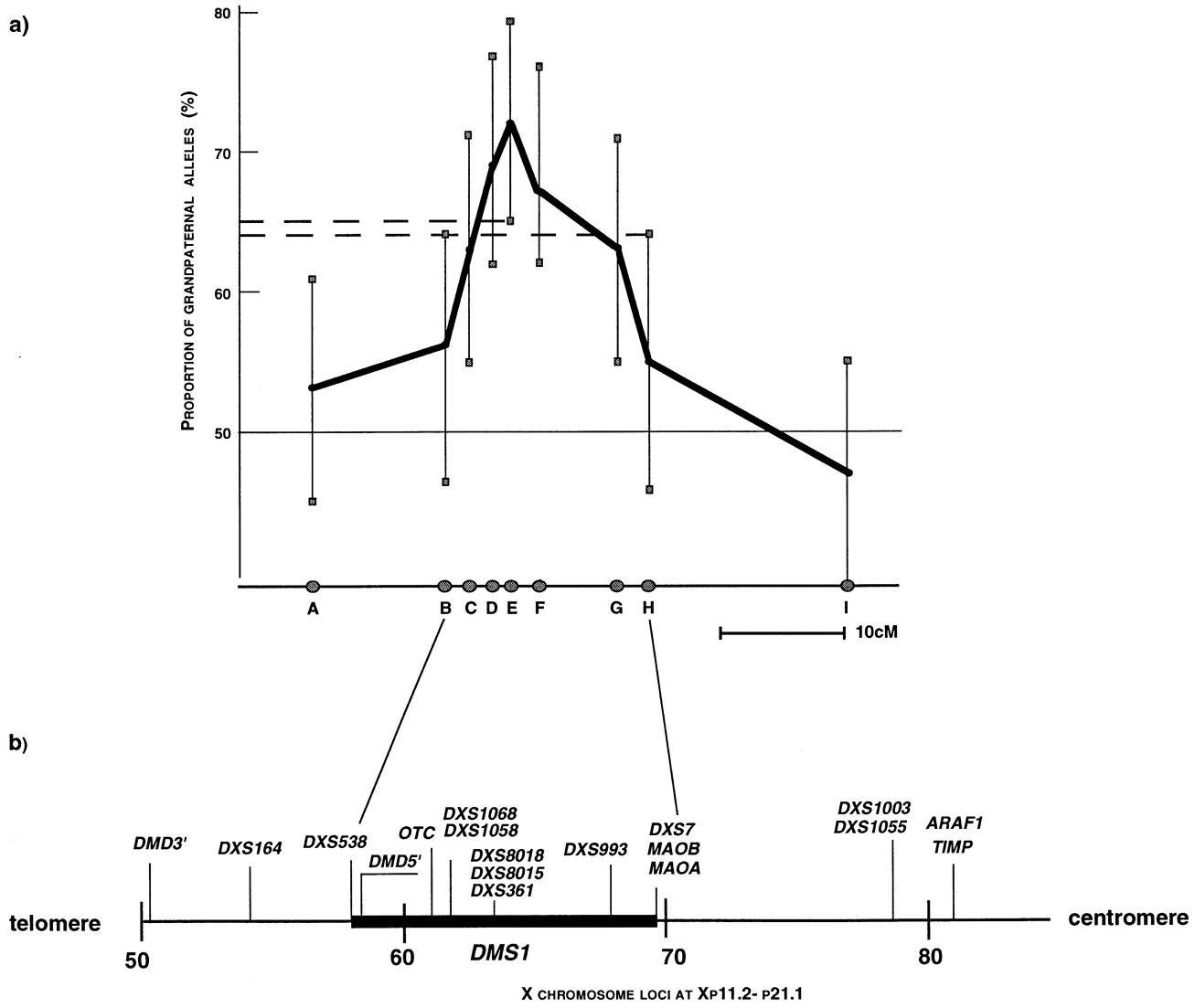

Figure 2 TRD for recombinant chromosomes. *a,* Forty-three chromosomes that are recombinant between positions 50.1 cM and 80.9 cM. These chromosomes were scored at nine loci: A, 50.1 (*DXS997, DXS1067, DXS1219, DXS1214,* and *DXS1036*); B, 58 (*DXS538*); C, 59.3 (*DXS428* and *DXS353*); D, 61 (*OTC*); E, 61.8 (*DXS1068* and *DXS1058*); F, 63.4 (*DXS361, DXS8015,* and *DXS8018*); G, 67.9 (*DXS993*); H, 69.6 (*DXS7, DXS1201, DXS228, MAOA,* and *MAOB*); and I, 80.9 (*TIMP, DXS337,* and *DXS426*). In several cases, genotypes were inferred on the basis of information from additional loci, at 55.1 (*DXS164*), 58.4 (*DMD 5′*), 65 (*DXS275*), and 78.4 (*DXS1003* and *DXS1055*). The maximum and minimum values of the CIs for each locus are represented as gray-shaded boxes. The CIs for the locus showing maximum distortion ("E" at 61.8 cM) and for loci at 58 cM and 69.6 cM are not overlapping, allowing exclusion, from the candidate region, of loci distal to 58 cM and proximal to 69.6 cM . Different numbers of individuals have been scored at each locus because not all the mothers were informative for every marker. *b,* Map of the region of the X chromosome containing the male-specific distorter *DMS1.* Distances from the telomere (in cM) are shown below the horizontal bar. Positions for the markers were adopted from the two-dimensional X-chromosome map (Fain et al. 1995). The locations for *DXS8015* and *DXS8018* were determined by sequence analysis of CA-hybridizing segments of clone RX234 from locus DXS361 (Barker et al. 1989). The candidate region for *DMS1* is represented by the thicker portion of the horizontal bar.

two "distorter" loci on the mouse X chromosome in BSS ([C57BL/6 x *Mus spretus*]F_1 × *M. spretus*) interspecific backcrosses. One distorter (*Dcsx2*) lies near *Xist,* and the other (*Dcsx1*) is linked to *DXMit87.* The mouse X-chromosome region that contains *Dcsx1* also contains the *Ihpd* (interspecific hybrid placental dysplasia) locus, which influences placental mass (Zechner et al. 1996, 1997). This locus is responsible for both placental hypotrophy in the MSS (*M. musculus* × *M. spretus*)F_1 × *M. spretus* backcross and placental hypertrophy in the MSM (*M. musculus* × *M. spretus*)F_1 × *M. musculus* backcross (Zechner et al. 1996). It is a reasonable con-

Table 2

Heterogeneity Analysis for Inheritance of Alleles at *DMS1*

No. of Offspring and Family Structure	No. of Families in Which Offspring Are	
	Male	Female
1:		
p	5	3
m	1	5
2:		
pp	3	1
pm	4	2
mm	0	3
3:		
ppp	4	0
ppm	2	3
pmm	0	3
mmm	0	0
4:		
pppp	1	0
pppm	1	1
ppmm	5	0
pmmm	2	2
mmmm	0	0
5:		
ppppp	0	0
pppmm	3	4
ppmmm	0	1
pmmmm	4	3
mmmmm	0	1
6:	0	0
pppppp	1	0
ppppmm	0	1
pppmmm	2	2
ppmmmm	0	2
pmmmmm	0	0
mmmmmm	0	0
7:	0	0
ppppppp	1	0
pppppmm	0	0
ppppmmm	0	2
pppmmmm	1	0
ppmmmmm	0	0
pmmmmmm	1	0
mmmmmmm	0	0
8:	0	0
p (3), m (5)	0	1
p (2), m (6)	1	0
p (4), m (7)	1	0
Total	43	40

Note.—"Family structure" denotes the composition of a family according to whether grandpaternal (p) or grandmaternal (m) alleles were inherited at *DMS1*. For example, for entry "pp" the number "3" in the "Male" column denotes that there were three families in which there were only two informative male offspring and that both brothers inherited the the grandpaternal allele; similarly, for entry "pm" the number "2" in the "Female" column denotes that there were two families in which there were only two informative female offspring and that one sister inherited the grandpaternal allele whereas the other sister inherited the grandmaternal allele.

jecture (Boyd 1996; Montagutelli et al. 1996) that placental hypotrophy may lead to embryonic lethality and to subsequent TRD at the *Ihpd* locus.

Ihpd is linked to *DXMit8*, which resides between *Smage1* and *Dmd*, corresponding to the Xp21.1-p21.3 region of the human X chromosome. The proximal distorter in the BSS backcrosses (*Dcsx1*) maps to *DXMit87*, ~7 cM proximal to *Dmd*. As has been pointed out by Boyd (1996) and Montagutelli et al. (1996), *Ihpd* and *Dcsx1* may be the same locus. If human *DMS1* and mouse *Dcsx1* and/or *Ihpd* are homologous loci, then they are predicted to reside within linkage groups that are conserved between the two species. Only a small part of the *Dcxs1*/*Ihpd* candidate region on the mouse X chromosome is homologous to the human *DMS1* candidate region (Herman et al. 1996), but both the human and the mouse distorter loci are linked to *DMD*/*Dmd* (see fig. 2).

A comparative overview of the observations made in both humans and mice reveals some interesting parallels: (i) TRD in the BSS backcrosses is in favor of *M. spretus* (grandpaternal) alleles (Montagutelli et al. 1996). Inheritance of *M. spretus* (grandpaternal) alleles is associated with higher placental weight, and inheritance of *M. musculus* (grandmaternal) alleles is associated with lower placental weight, in both MSS and MSM backcrosses (Zechner et al. 1996). TRD in humans is in favor of grandpaternal alleles (present study). (ii) The placental hypotrophy phenotype associated with inheritance of *M. musculus* alleles in the MSS backcross is more severe in males than in females (Zechner et al. 1996). TRD at *Dcsx1* in the EUCIB BSS backcross is stronger among male offspring than among female offspring (Montagutelli et al. 1996). TRD in humans is restricted to male offspring (Naumova et al. 1995; present study). (iii) The human and mouse distorters may lie within homologous regions of the human and mouse X chromosomes.

X-chromosome TRD in both humans and mice appears to be due to a combination of genetic and epigenetic factors (Naumova et al. 1995; Montagutelli et al. 1996). At minimum, the genetic factors operating in humans must include the sex of the offspring, and the epigenetic factors must include the parental origin of the X chromosome in the mother. Although we cannot conclude that preference for inheritance of *M. spretus* alleles among interspecific-backcross offspring represents a true preference for grandpaternal alleles, as opposed to *M. spretus* alleles, the same criticism cannot be applied to the data on humans: because the only identification assigned to the mother's X chromosomes in the families that we have examined is their parental origin, TRD that does not have a parental-origin effect would not be detected. For this reason, we assume that the major determinant of male-offspring–specific TRD in this region of the X chromosome is epigenetic, rather than genetic.

One proviso that must be attached to this explanation is that one expects X-linked recessive-lethal mutations to be transmitted from mothers to daughters but not from mothers to sons. This will be observed as a deficiency of grandmaternal alleles among sons, at any locus at which it is possible to have an X-linked recessive-lethal mutation. However, in order to obtain the proportion of grandpaternal alleles that we have observed among male offspring, a very large fraction of *DMS1* alleles would need to be recessive lethal. Recall that only 64 grandmaternal alleles were transmitted to male offspring (at *DXS1068*), whereas 103 grandpaternal alleles were transmitted (table 1). It is also a formal possibility that recessive-lethal allele mutations at multiple, linked loci in the region could account for the observed grandparental effect, but, again, this explanation requires a relatively large number of X-linked recessive-lethal mutations to be present in the population of families with no known cases of any genetic disease. We suggest that the distorter is an imprinted locus and that it may be required for viability of male embryos.

If we wish to compare the results of the present study to those of our earlier study, we may subtract the sons of skewed mothers in whom we observed TRD in our previous study. This adjustment leaves 93 sons who receive the grandpaternal allele at *AR* and leaves 71 sons who receive the grandmaternal allele ($P = .1$; exact binomial test). At *DSX1068,* 87 sons receive the grandpaternal allele, and 57 sons receive the grandmaternal allele ($P = .015$; exact binomial test); and, at *DXS101,* 62 sons inherit the grandpaternal, and 59 sons inherit the grandmaternal allele. Thus, of the three loci that showed evidence of TRD in our first study, only *DXS1068* showed significant evidence of TRD in the larger study. If the significance level for *DXS1068* is adjusted for performance of three independent tests using the Bonferroni correction, then the *P* value becomes .045.

The fact that the preference for grandpaternal alleles is incomplete (in that 38% of male offspring do inherit grandmaternal alleles in this region) could be due to a number of factors, including nongenetic factors that affect embryonic development, interfamilial genetic differences in the imprinting of the distorter locus, or a requirement for an epistatic interaction between the X-linked distorter and a specific allele at an unlinked locus, as has been observed in the mouse (Montagutelli et al. 1996). We are unable, at present, to eliminate either of the latter two possibilities, although our heterogeneity analysis did not reveal significant interfamilial differences in the inheritance of alleles at *DXS1068* (table 2). In addition, the simplest application of the epistatic-interaction hypothesis, in which a grandmaternal allele at the distorter locus is able to interact with one of the alleles at an unlinked locus but not with the other, predicts a ratio of 2 grandpaternal alleles:1 grandmaternal allele. This ratio is well within the range of our observations (table 1).

Recent reports of X-chromosome loci that are subject to parental-origin effects, from the study of patients with Turner syndrome (Skuse et al. 1997) and from the study of knockout mice that carry a mutant choroideremia gene (Van den Hurk et al. 1997), have already expanded the list of imprinted X-linked genes, from one (*Xist*) to three (although a specific locus was not identified in the study by Skuse et al., we assume that the effect observed in that study is due to the action of a locus that is distinct from the other imprinted X-chromosome loci). It is interesting to note that the distorter *DMS1* resides in an area that contains a number of genes that escape X inactivation (Disteche 1995; Miller et al. 1995; Jones et al. 1996). Further characterization of the TRD phenomenon in humans will require both the accumulation of additional genotypic data on more families and careful observation of fertility, as well as other potentially relevant phenotypes.

Acknowledgments

The authors are grateful to Drs. F. Pardo Manuel de Villena and K. Latham for discussion and to Dr. P. Fain for assistance with the GenLink database. This work was supported by National Institutes of Health grant RO1 GM52332 (to C.S.), National Institute of Diabetes and Digestive and Kidney Diseases grant DK43761 (to D.F.B.), and the Canadian Genetic Diseases Network, NCE program (support to K.M.).

Electronic-Database Information

URLs for data in this article are as follows:

GenLink, http://www.genlink.wustl.edu

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