DOI: 10.1534/genetics.104.032177

A Complex Interaction of Imprinted and Maternal-Effect Genes Modifies Sex Determination in Odd Sex (*Ods*) Mice

Christophe Poirier,* Yangjun Qin,* Carolyn P. Adams,* Yanett Anaya,* Jonathan B. Singer,[†,‡] Annie E. Hill,[§] Eric S. Lander,[†,‡,] Joseph H. Nadeau[§,††,‡‡] and Colin E. Bishop*[,§§,1]**

**Department of Obstetrics and Gynecology and [§§]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, [‡]Broad Institute, [†]Whitehead Institute for Biomedical Research and **Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142 and [§]Department of Genetics, [††]Center for Computational Genomics and Systems Biology and [‡‡]Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106*

Manuscript received June 8, 2004
Accepted for publication July 29, 2004

ABSTRACT

The transgenic insertional mouse mutation Odd Sex (*Ods*) represents a model for the long-range regulation of *Sox9*. The mutation causes complete female-to-male sex reversal by inducing a male-specific expression pattern of *Sox9* in XX *Ods*/+ embryonic gonads. We previously described an A/J strain-specific suppressor of *Ods* termed *Odsm1*^{A}. Here we show that phenotypic sex depends on a complex interaction between the suppressor and the transgene. Suppression can be achieved only if the transgene is transmitted paternally. In addition, the suppressor itself exhibits a maternal effect, suggesting that it may act on chromatin in the early embryo.

In mice and humans, *Sox9*/*SOX9* has been identified as a key regulator of the male sex determination pathway. In humans, loss of *SOX9* function has been shown to lead to XY sex reversal (Foster *et al.* 1994; Wagner *et al.* 1994), while duplication of *SOX9* leads to XX sex reversal (Huang *et al.* 1999). In mice carrying a *Wt1:Sox9* transgene, or in the Odd Sex mutant, expression of *Sox9* in the bipotential embryonic gonad leads to XX sex reversal (Bishop *et al.* 2000; Vidal *et al.* 2001).

In humans, *SOX9* regulation is complex with critical elements scattered over a distance of ~1 Mb (Pfeifer *et al.* 1999). We previously described a dominant insertional mouse mutation model for the long-range alteration of *Sox9* expression, termed Odd Sex (*Ods*). In this model, two copies of a tyrosinase transgene (Yokoyama *et al.* 1990) integrated 980 kb upstream from *Sox9* on chromosome 11 accompanied by a 134-kb deletion at the integration site (Bishop *et al.* 2000; Qin *et al.* 2004). Transgenic *Ods*/+ mice were born microphtalmic and all XX *Ods*/+ mice were sterile sex-reversed males. In wild-type embryonic genital ridges, *Sox9* has a sexually dimorphic expression pattern being restricted to the Sertoli cell lineage in the male, beginning at 11.5 days post coitum (dpc; Kent *et al.* 1996). In 11.5-dpc XX *Ods*/+ fetal gonads the transgene, through an as yet unknown mechanism, is able to upregulate *Sox9* expression, causing testes formation and sex reversal (Bishop *et al.* 2000; Qin *et al.* 2004). This mutation is dominant and fully penetrant in the original FVB/N inbred strain. In contrast, in F_1 mice, hybrids between inbred A/J females and transgenic FVB/N males, the sex reversal is suppressed, resulting in XX *Ods*/+ fertile females. In 95% of mice the suppression is complete, leading to fertile females; however, a small number of mice (2.5%) are hermaphrodites and 2.5% remained male. We have shown, using genetic mapping in an A/J × FVB/N F_2 intercross, that a single genetic locus, Odd Sex modifier 1 (*Odsm1*) on mouse chromosome 18, controlled the suppression (Qin *et al.* 2003). Here we report that the transgene is subject to imprinting and suppression can be achieved only if the transgene is transmitted paternally. In addition, the *Odsm1* suppressor itself exhibits a maternal effect, suggesting that it may functionally modify chromatin structure in the very early embryo.

MATERIALS AND METHODS

The genotype at Odd Sex was scored, *Ods*/+ or +/+, by examination of the eyes (Bishop *et al.* 2000). Mice were genotyped for the Y chromosome as described previously (Bishop *et al.* 2000). Mice were recorded as male, hermaphrodite, or female after external and internal examination of the genitalia (Qin *et al.* 2003).

RESULTS

Parental effects at *Odsm1* and *Ods*: Surprisingly, among XX *Ods*/+ *Odsm1*^{A}/*Odsm1*^{F} mice, the deficit of males seen in the F_1 generation (2.5% male) was not observed

[1]*Corresponding author:* Department of Obstetrics and Gynecology, Smith Tower, Room 880, Baylor College of Medicine, 6550 Fannin St., Houston, TX 77030. E-mail: bishop@bcm.tmc.edu

TABLE 1

Evidence for parental effects in backcross mice

Cross	Mother	Father	N2 XX *Ods*/+ progeny			Transmission	
			Males	Female + hermaphrodite	Total	*Ods*	*Odsm1*^{A}
			A. Backcrosses to FVB/N[a]				
1	FVB+/+	F_1 (AxFVB) *Ods*/+	114	0	114	Paternal	Paternal
2	F_1 (AxFVB)+/+	FVB*Ods*/+	51	12	63	Paternal	Maternal
3	F_1 (AxFVB) *Ods*/+	FVB+/+	60	0	60	Maternal	Maternal
4	F_1 (FVBxA)+/+	FVB*Ods*/+	21	2	23	Paternal	Maternal

	Females		Hermaphrodites			Males			
	B. Genotype from cross 2 progeny[b]								
D18Mit184	FF	AF	FF	FF	AF	FF	AF	FF	AF
D18Mit210	FF	AF	FF	FF	AF	FF	AF	FF	FF
D18Mit25	FF	AF	AF	FF	AF	FF	AF	AF	FF
No. of mice	2*	1	1	5*	3	24	23	3	1

[a] The numbers of males, females, and hermaphrodites, among XX *Ods*/+ progeny, are reported following paternal or maternal transmission of the transgene (*Ods*) and the suppressor (*Odsm1*^{A}). At a 5% risk, the female and hermaphrodite frequencies are <2.5% (cross 1), between 9.4 and 28.7% (cross 2), and <4.8% (cross 3).

[b] For XX *Ods*/+ mice from cross 2, the number of mice and their genotype around *Odsm1* as a function of their phenotypic sex. A, A/J-derived allele; F, FVB/N-derived allele.

in the F_2 generation, where 42% were male. One possibility was that this discrepancy between the F_1 and F_2 generations could be explained by a second locus controlling sex determination in mice heterozygous at *Odsm1*. We tested this hypothesis by reanalyzing the genome scan data for the mice heterozygous at *Odsm1* in the original F_2 intercross (Qin *et al.* 2003). We could not find any linkage disequilibrium with any marker, making the second-locus hypothesis unlikely. Unlike in the F_1 progeny, the parental origin of the suppressor, *Odsm1*^{A}, and the *Ods* transgene cannot be established in the F_2 mice. This suggested the possibility that a parent of origin effect at *Odsm1* and/or *Ods* could be responsible for the sex ratio discrepancy between the F_1 and F_2 groups.

Imprinting at *Ods*: To test this hypothesis, three backcrosses to FVB/N were set up. In the first two crosses, *Ods* was transmitted through the paternal germline while the suppressor (*Odsm1*^{A}) was transmitted through either the paternal (Table 1A, cross 1) or the maternal germline (Table 1A, cross 2). In the third cross (Table 1A, cross 3), both the suppressor and the transgene were transmitted through the maternal germline. Among the N2 XX *Ods*/+ progeny, three types of mice were recorded: males, females, and hermaphrodites. Analysis of the data showed that suppression of sex reversal (12 females out of 63 progeny—19%) occurred only when the suppressor was transmitted maternally and the transgene was transmitted paternally (Table 1A, cross 2). Sex determination in XX *Ods*/+ mice was therefore controlled by loci with a parental effect. Suppression could be achieved only through paternal transmission of the transgene, demonstrating imprinting at the *Ods* locus.

Maternal effect at *Odsm1*: To check for imprinting at *Odsm1*, all the XX *Ods*/+ backcross progeny were genotyped for markers spanning the *Odsm1* critical region: *D18Mit184*, *D18Mit210*, and *D18Mit25* (Qin *et al.* 2003). Among females and hermaphrodites, 7 out of 12 (Table 1B, asterisks) were homozygous for the FVB/N allele (FF) at each of the three microsatellites, implying they were homozygous FF at *Odsm1* (Table 1B). In these 7 mice, suppression of the sex reversal was achieved in the absence of the *Odsm1*^{A} suppressor. This indicates that the maternal *Odsm1* genotype itself, rather than the genotype of the offspring, controls the sex determination. To exclude a role for the mitochondrial genome, we set up an additional backcross to FVB (Table 1A, cross 4); the only difference between cross 2 and cross 4 is the mitochondrial genome from A/J (cross 2) and FVB/N (cross 4). In both crosses, suppression was observed, ruling out any role of mitochondrial DNA.

Thus sex reversal in Odd Sex mice can be suppressed through the action of a maternal-effect locus. Such loci are usually expressed during oogenesis, and their products play an essential role in the early stages of embryogenesis. In XX *Ods*/+ mice, male sex determination is a cell-autonomous process initiated at ~11.5 dpc by the expression of *Sox9* in the presumptive Sertoli cells. In the 2 XX *Ods*/+ females and the 5 XX *Ods*/+ hermaphrodites homozygous for *Odsm1*^{F} (Table 1B), any maternal *Odsm1*^{A} product is presumably long gone by the time sex determination is initiated. This urged us to reconfirm the association of the suppression with the A/J chromosome 18 found in the original F_2 data (Qin *et al.* 2003). To do this, we backcrossed the Odd Sex

TABLE 2

The maternal effect is linked to chromosome 18

Cross	Mother	Father	N2 XX *Ods*/+ progeny: Males	Females + hermaphrodites	Total
		A. Outcrosses to C57BL/6J[a]			
5	B6	F_1 (B6xFVB) *Ods*/+	23	3	26
6	B6-18^A	F_1 (B6-18^A × FVB) *Ods*/+	26	17	43
7	B6	F_1 (B6-18^A × FVB) *Ods*/+	26	3	29
		B. XX *Ods*/+ progenies from the consomic backcross (no. 6)[b]			
D18Mit184	AF	AA	AF	AA	AF AA
D18Mit210	AF	AA	AF	AA	AA AF
D18Mit25	AF	AA	AA	AF	AA AF
Females + hermaphrodites	7	7	1	1	1 0
Males	13	8	2	2	0 1

[a] The numbers of males, females, and hermaphrodites, among XX *Ods*/+ progeny, are reported in backrosses to C57BL/6J (cross 5), to the consomic strain (cross 6), and in an outcross (cross 7).

[b] Genotype around *Odsm1* for the females/hermaphrodites and males. At each microsatellite the genotype distribution between the two groups, females/hermaphrodites and males, was compared with a chi-square analysis. No difference between the two groups was detected. $P = 75.9\%$ at *D18Mit184*; $P = 35\%$ at *D18Mit210* and *D18Mit25*.

mutation to either C57BL/6J females (Table 2A, cross 5) or consomic females (Table 2A, cross 6) carrying chromosome 18 from the A/J strain in a C57BL/6J genetic background (B6-18^A; Nadeau *et al.* 2000; Singer *et al.* 2004). Surprisingly, complete sex reversal was observed in the F_1 progeny of FVB/N *Ods*/+ males and either C57BL/6J, 20 males out of 20 F_1 XX *Ods*/+, or consomic females, 25 males out of 25 F_1 XX *Ods*/+. In the pure C57BL/6J backcross, however, (Table 2A, cross 5) we observed 3 females/hermaphrodites out of 26 XX *Ods*/+ offspring. This could be due to the existence of additional C57BL/6J recessive suppressor loci or a penetrance reduction associated with the genetic background shift. In the consomic backcross (Table 2A, cross 6), we observed 17 females/hermaphrodites out of 43 XX *Ods*/+, representing a significant increase in the suppression ($P < 1.3\%$) and confirming linkage to chromosome 18.

We next confirmed the maternal effect by two independent methods. First, we genotyped the XX *Ods*/+ progeny from the consomic backcross (Table 2A, cross 6) around the *Odsm1* locus (Table 2B). As expected for a maternal effect, no transmission distortion was detected. Second, we crossed C57BL/6J females with F_1 (B6-18^A × FVB) *Ods*/+ males (Table 2A, cross 7). Here we ob-

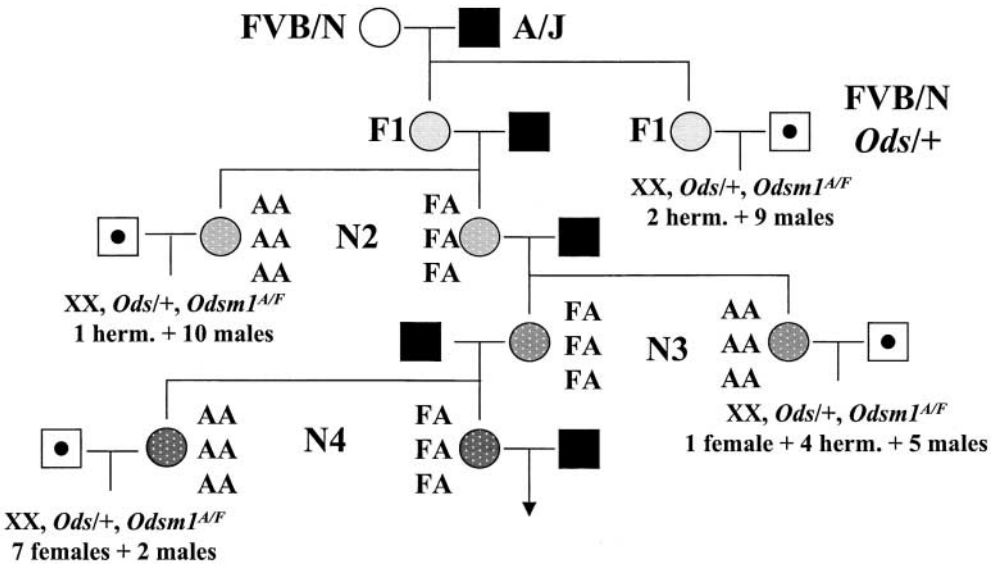

Figure 1.—Qualitative and quantitative effect of the genetic background. *Odsm1*^{F} was backcrossed from FVB/N female, open circle, to A/J males, solid square, until generation N4. Its transmission was followed by three microsatellites, *D18Mit184*, *D18Mit210*, and *D18Mit25*, from top to bottom, AA homozygous for the A/J allele, FA heterozygous. At each generation, females homozygous for *Odsm1*^{A} were mated with FVB/N *Ods*/+ males, open square with solid dot; the number of XX *Ods*/+ *Odsm1*$^{A/F}$ offspring and their sex are reported, female, hermaphrodites (herm.), and males.

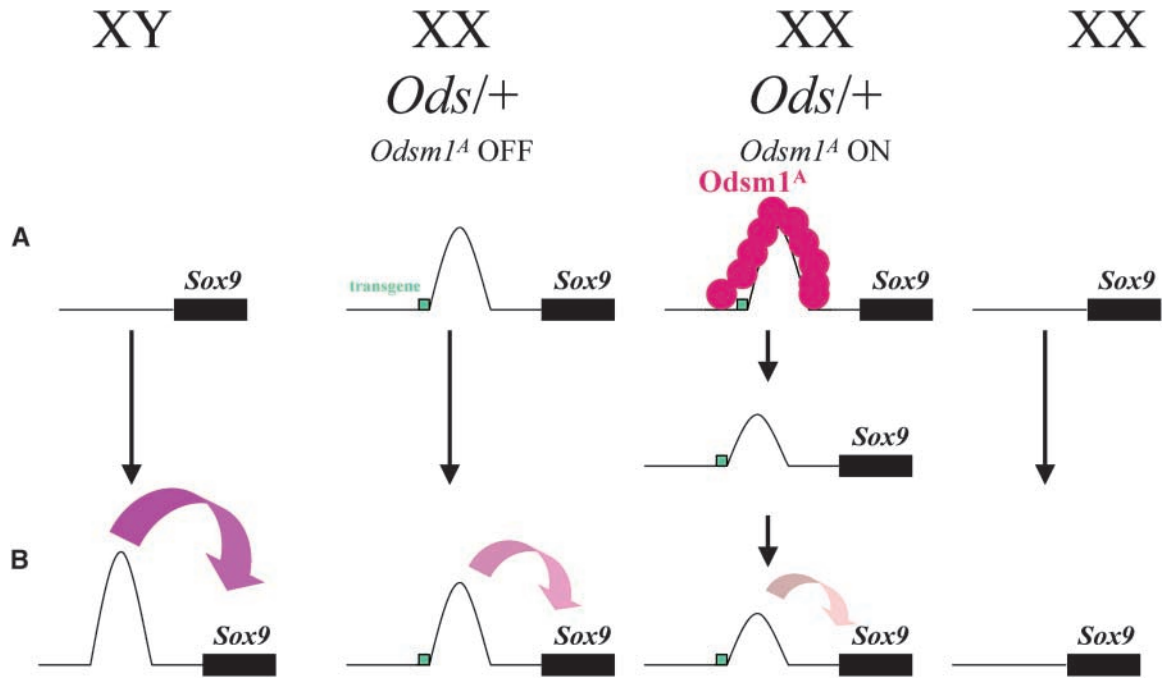

FIGURE 2.—Hypothetical model for the suppression of sex reversal. In XY and XX embryos at 0.5 dpc (A) the chromatin, around paternal *Sox9*, is in an inactive state (line). At 11.5 dpc in XY embryonic gonads, *Sry*, directly or indirectly, induces a dramatic conformation change (parabola), allowing upregulation of *Sox9* (curved arrow). In XX bipotential gonads at ~11.5 dpc in the absence of Sry, no change in chromatin conformation is detected leading to *Sox9* downregulation and female sex determination. The insertion/deletion created a change in conformation around *Sox9* in the XX *Ods*/+ fertilized egg (A); this new conformation mimicks the XY conformation at 11.5 dpc, inducing *Sox9* upregulation and consequently sex reversal. Suppressor product, Odsm1^A, is able to alter the conformation induced by the transgene in the XX *Ods*/+ fertilized egg (A); this altered conformation has a weaker effect on *Sox9* upregulation, allowing sex-reversal suppression. Green box, tyrosinase transgene; shaded circle, Odsm1^A, the suppressor product.

served only three females/hermaphrodites out of 29 XX *Ods*/+ mice. As predicted for a maternal effect, this shows a significant decrease in suppression compared to the consomic backcross, cross 6 ($P < 0.6\%$), which carries *Odsm1*^{A} maternally. Taken together the data obtained from these crosses confirmed the importance of the A/J-derived chromosome 18 in the suppression and the maternal effect itself.

Background effect: The suppression of sex reversal seen in the C57BL/6J backcross suggests the presence of other minor loci that contribute to the sex determination, with the suppressive C57BL/6J alleles recessive to the FVB/N alleles. To check this hypothesis, we started to generate a congenic line carrying the *D18Mit184-D18Mit25* genomic segment from FVB/N in the A/J strain (Figure 1). At each generation, we crossed FVB/N *Ods*/+ males with females homozygous for the A/J alleles at the three microsatellites, *D18Mit184*, *D18Mit210*, and *D18Mit25*. The external and internal genitalia of all XX *Ods*/+ offspring were observed and we scored them as male, female, or hermaphrodite. XX *Ods*/+, *Odsm1*^{A}/*Odsm1*^{F} offspring were merged in two groups; the first group consisted of mice born from F_1 and N2 females, the second group consisted of mice born from N3 and N4 females. In the first group, we observed 19 sex-reversed males and 3 hermaphrodites; in the second group, we observed only 7 sex-reversed males and 12 females/hermaphrodites. The sex distribution between these two groups, *i.e.*, the effect of suppression, was significantly different, $P = 1.7 \times 10^{-4}$ risk (from a chi-square test). From generation N2 to N4, we observed a reduction in males and concomitantly an increase in females, suggesting both a quantitative and a qualitative effect of the genetic background.

DISCUSSION

In mice, male sex determination is a cell-autonomous process initiated by the Y-located testes-determining gene, *Sry* (KOOPMAN *et al.* 1991). In XX *Ods*/+ embryos, however, *Sox9* triggers this process (BISHOP *et al.* 2000). Here, we show that the *Ods* suppressor, *Odsm1*, displays a maternal effect in addition to the zygotic effect detected in the F_2 mapping (QIN *et al.* 2003). The suppression is also dependent on the parental origin of the tyrosinase transgene, *i.e.*, imprinting, suggesting an interaction between *Odsm1* and *Ods* in the suppression.

In mice, mutations with true maternal effects are very rare and are usually associated with death of the embryos conceived by females homozygous for the mutation.

Death can occur before the morula stage (Christians *et al.* 2000; Tong *et al.* 2000; Burns *et al.* 2003; Wu *et al.* 2003), during blastocyst formation (Renard *et al.* 1994), around 9.5 dpc (Bourc'his *et al.* 2001), or even later after 14 dpc (Howell *et al.* 2001). In the cases of DNA methyltransferases, *Dnmt3L* and *Dnmt1o*, death occurred around mid-gestation and was associated with the partial loss of methylation at maternally imprinted loci, leading to an inappropriate expression of the corresponding genes (Bourc'his *et al.* 2001; Howell *et al.* 2001). Another maternal effect, without any visible consequence, was described in the transgenic mouse line TKZ751. Here, the transgene was methylated when transmitted through the paternal germline, but the methylation was controlled by a locus with maternal effect mapped to chromosome 17 (Pickard *et al.* 2001).

As for *Dnmt3L* (Bourc'his *et al.* 2001) and *Dnmt1o* (Howell *et al.* 2001), the consequence of $Odsm1^A$ maternal effect is seen relatively late in development, beginning at ~11.5 dpc. As for TKZ751 (Pickard *et al.* 2001), the maternal effect was detected only through paternal transmission of the transgene. The suppression of the sex reversal in the Odd Sex model bears striking similarities with three reported cases involving methylation: *Dnmt3L* (Bourc'his *et al.* 2001), *Dnmt1o* (Howell *et al.* 2001), and the transgenic line TKZ751 (Pickard *et al.* 2001). Methylation is known to regulate the architecture of chromatin and, once modified, the new structure can be faithfully transmitted through somatic divisions reviewed in Li (2002). Our working hypothesis is that the insertion of the transgene somehow modified the surrounding chromatin structure, thereby allowing expression of *Sox9* in XX *Ods*/+ fetal gonads through a long-distance effect (Ptashne 1986). We postulate that the product of $Odsm1^A$ modifies the chromatin structure around *Ods*/*Sox9* on the paternal chromosome in the early embryo. The new structure of the chromatin would then be transmitted through somatic divisions during embryogenesis. This new chromatin conformation would be less permissive to the expression of *Sox9* in the XX *Ods*/+ fetal gonad, reducing its level below a critical threshold leading to the suppression of the sex reversal in some cases (Figure 2).

Interestingly, two genes, *Mbd1* and *Mbd2*, encoding proteins that bind to methylated DNA, have been mapped to the *Odsm1* critical region (Hendrich *et al.* 1999). Mice homozygous for null alleles at *Mbd1* and *Mbd2* (Hendrich *et al.* 2001; Zhao *et al.* 2003) are viable and fertile but have defects in overall methylation. Moreover, cells lacking Mbd2 were unable to silence methylated transgene (Hendrich *et al.* 2001). Those genes were therefore attractive candidates for *Odsm1* but no sequence polymorphism, between A/J and FVB/N, was found in their coding sequence (data not shown).

This work was supported by grants from the National Institute of Health and the March of Dimes births defects foundation (to C.E.B.).

LITERATURE CITED

Bishop, C. E., D. J. Whitworth, Y. Qin, A. I. Agoulnik, I. U. Agoulnik *et al.*, 2000 A transgenic insertion upstream of sox9 is associated with dominant XX sex reversal in the mouse. Nat. Genet. **26:** 490–494.

Bourc'his, D., G. L. Xu, C. S. Lin, B. Bollman and T. H. Bestor, 2001 Dnmt3L and the establishment of maternal genomic imprints. Science **294:** 2536–2539.

Burns, K. H., M. M. Viveiros, Y. Ren, P. Wang, F. J. DeMayo *et al.*, 2003 Roles of NPM2 in chromatin and nucleolar organization in oocytes and embryos. Science **300:** 633–636.

Christians, E., A. A. Davis, S. D. Thomas and I. J. Benjamin, 2000 Maternal effect of Hsf1 on reproductive success. Nature **407:** 693–694.

Foster, J. W., M. A. Dominguez-Steglich, S. Guioli, G. Kowk, P. A. Weller *et al.*, 1994 Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature **372:** 525–530.

Hendrich, B., C. Abbott, H. McQueen, D. Chambers, S. Cross *et al.*, 1999 Genomic structure and chromosomal mapping of the murine and human Mbd1, Mbd2, Mbd3, and Mbd4 genes. Mamm. Genome **10:** 906–912.

Hendrich, B., J. Guy, B. Ramsahoye, V. A. Wilson and A. Bird, 2001 Closely related proteins MBD2 and MBD3 play distinctive but interacting roles in mouse development. Genes Dev. **15:** 710–723.

Howell, C. Y., T. H. Bestor, F. Ding, K. E. Latham, C. Mertineit *et al.*, 2001 Genomic imprinting disrupted by a maternal effect mutation in the Dnmt1 gene. Cell **104:** 829–838.

Huang, B., S. Wang, Y. Ning, A. N. Lamb and J. Bartley, 1999 Autosomal XX sex reversal caused by duplication of SOX9. Am. J. Med. Genet. **87:** 349–353.

Kent, J., S. C. Wheatley, J. E. Andrews, A. H. Sinclair and P. Koopman, 1996 A male-specific role for SOX9 in vertebrate sex determination. Development **122:** 2813–2822.

Koopman, P., J. Gubbay, N. Vivian, P. Goodfellow and R. Lovell-Badge, 1991 Male development of chromosomally female mice transgenic for Sry. Nature **351:** 117–121.

Li, E., 2002 Chromatin modification and epigenetic reprogramming in mammalian development. Nat. Rev. Genet. **3:** 662–673.

Nadeau, J. H., J. B. Singer, A. Matin and E. S. Lander, 2000 Analysing complex genetic traits with chromosome substitution strains. Nat. Genet. **24:** 221–225.

Pfeifer, D., R. Kist, K. Dewar, K. Devon, E. S. Lander *et al.*, 1999 Campomelic dysplasia translocation breakpoints are scattered over 1 Mb proximal to SOX9: evidence for an extended control region. Am. J. Hum. Genet. **65:** 111–124.

Pickard, B., W. Dean, S. Engemann, K. Bergmann, M. Fuermann *et al.*, 2001 Epigenetic targeting in the mouse zygote marks DNA for later methylation: a mechanism for maternal effects in development. Mech. Dev. **103:** 35–47.

Ptashne, M., 1986 Gene regulation by proteins acting nearby and at a distance. Nature **322:** 697–701.

Qin, Y., C. Poirier, C. Truong, A. Schumacher, A. I. Agoulnik *et al.*, 2003 A major locus on mouse chromosome 18 controls XX sex reversal in Odd Sex (Ods) mice. Hum. Mol. Genet. **12:** 509–515.

Qin, Y., L. K. Kong, C. Poirier, C. Truong, P. A. Overbeek *et al.*, 2004 Long-range activation of Sox9 in Odd Sex (Ods) mice. Hum. Mol. Genet. **13:** 1213–1218.

Renard, J. P., P. Baldacci, V. Richoux-Duranthon, S. Pournin and C. Babinet, 1994 A maternal factor affecting mouse blastocyst formation. Development **120:** 797–802.

Singer, J. B., A. E. Hill, L. C. Burrage, K. R. Olszens, J. Song *et al.*, 2004 Genetic dissection of complex traits with chromosome substitution strains of mice. Science **304:** 445–448.

Tong, Z. B., L. Gold, K. E. Pfeifer, H. Dorward, E. Lee *et al.*, 2000 Mater, a maternal effect gene required for early embryonic development in mice. Nat. Genet. **26:** 267–268.

Vidal, V. P., M. C. Chaboissier, D. G. de Rooij and A. Schedl, 2001 Sox9 induces testis development in XX transgenic mice. Nat. Genet. **28:** 216–217.

Wagner, T., J. Wirth, J. Meyer, B. Zabel, M. Held *et al.*, 1994 Autosomal sex reversal and campomelic dysplasia are caused by muta-

tions in and around the SRY-related gene SOX9. Cell **79:** 1111–1120.

Wu, X., M. M. Viveiros, J. J. Eppig, Y. Bai, S. L. Fitzpatrick *et al.*, 2003 Zygote arrest 1 (Zar1) is a novel maternal-effect gene critical for the oocyte-to-embryo transition. Nat. Genet. **33:** 187–191.

Yokoyama, T., D. W. Silversides, K. G. Waymire, B. S. Kwon, T. Takeuchi *et al.*, 1990 Conserved cysteine to serine mutation in tyrosinase is responsible for the classical albino mutation in laboratory mice. Nucleic Acids Res. **18:** 7293–7298.

Zhao, X., T. Ueba, B. R. Christie, B. Barkho, M. J. McConnell *et al.*, 2003 Mice lacking methyl-CpG binding protein 1 have deficits in adult neurogenesis and hippocampal function. Proc. Natl. Acad. Sci. USA **100:** 6777–6782.

Communicating editor: M. Justice