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Searching for Candidate Genes with Effects on an Agonistic Behavior, Offense, in Mice

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It is well established that the agonistic behavior of offense in mice is heritable. However, few genes have been identified or mapped for offense. For segments of chromosomes with effects on offense, a positional candidate strategy can be used to find such genes. This approach is illustrated for the effect of the male specific part (nonpseudoautosomal region; NPAR) of the mouse Y chromosome on offense. It is proposed that a positional candidate for this effect is *Sry*. The Sry protein is a transcription factor. Its mRNA is expressed in fetal and adult brain. Its protein binds to response elements in the 5' end of the aromatase and the *Fra*1 genes. Each of these genes has potential effects on several brain neurotransmitter systems involved in offense. The NPAR Y chromosomes of several pairs of inbred strains have differential effects on offense. This hypothesis would be tested by sequencing *Sry* for some of these pairs of strains.

KEY WORDS: Agonistic behavior; offense; candidate genes; Y chromosome; *Sry*; mice.

INTRODUCTION

For a long time, there have been three goals in the genetics of any behavior. These are to determine whether the behavior is heritable, to map or identify genes for the behavior, and to determine the mechanisms for the effect of genes on the behavior (Hall, 1953). For the agonistic behavior of offense in mammals [see Maxson (1992a, b) for behavioral descriptions], these issues have been studied primarily in mice. Research on the first issue began more than 50 years ago (Ginsburg and Allee, 1942; Scott, 1942), and much evidence has accumulated indicating that variation of offense behavior in mice is heritable (Maxson, 1981; Michard and Carlier, 1985). However, only a few genes with effects on offense in mice have been mapped.

These genes have been or are being identified with several approaches. First, the effects of genes involved in biological systems involved in offense have been tested with artificially induced, loss of function mutants. This includes the gene for monoamine oxidase A (MAOA) on the X chromosome (Cases *et al.*, 1995), for a serotonin receptor ($5HT_{1B}$) on chromosome 9 (Saudou *et al.*, 1994), for the estrogen receptor (Korach, 1994; Ogawa *et al.*, 1995) on chromosome 10, and for α-calcium–calmodulin kinase II on chromosome 18 (Chen *et al.*, 1994). Second, the effects of natural variants of mapped genes on offense have been determined. This includes the gene for the androgen receptor (Ohno *et al.*, 1974) on the X chromosome and a t complex gene (Lennington, 1991) on chromosome 17. Third, genes with effects on offense may be mapped to a region of a chromosome. Once such a region of a chromosome has been identified, the gene or genes with effects on offense may be identified with positional cloning (Stubbs, 1992) or positional candidates (Kuska, 1995). This approach is illustrated for the male-specific part (nonpseudoautosomal region; NPAR) of the mouse Y chromosome, which has at least one gene with effects on offense. After reviewing studies on the Y chro-

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Table I. The Mouse Y Chromosomes and the Agonistic Behavior of Offense[a]

Strain pair for Y	NPAR	PAR
DBA/1 & C57BL/10	Yes	No
DBA/1 & DBA/2	Yes	nd
CBA/Fa & C57BL6	Yes	No
NZB & CBA/H	Yes	Yes
SAL & LAL	Yes	Yes
PHH & PHL	Yes	nd

[a] NPAR, nonpseudoautosomal region of the Y; PAR, pseudoautosomal region of the Y; nd, not done.

mosome and offense in mice, possible candidate genes on the NPAR of the Y chromosome are considered.

Several groups of investigators have indicated that variants of one or more genes of the Y chromosome (NPAR) differ in effect on offense attack (Table 1). This has been proposed for the DBA/1 and C57BL/10 (Maxson *et al.*, 1979, 1989), DBA/2 and DBA/1 (Selmanoff *et al.*, 1976; Shrenker and Maxson, 1982), CBA/Fa and C57BL/6 (Stewart *et al.*, 1980), NZB and CBA/H (Carlier and Roubertoux, 1986; Guillot *et al.*, 1995), SAL and LAL (van Oortmerssen *et al.*, 1992; Sluyter *et al.*, 1994), and PHH and PHL (Weir, 1976) strains. The use in these studies of reciprocal F_1's, congenic strains, and segregating populations as evidence for effects of the Y chromosome (NPAR) on offense and other traits has been critically reviewed by Maxson (1992a).

There appear to be two limiting but interesting conditions for differential effects for most, if not all, of these pairs of NPAR Y chromosomes on offense. The first limiting condition is epistatic interactions of the NPAR Y chromosome and autosomes (Maxson *et al.*, 1979; Shrenker and Maxson, 1982; Stewart *et al.*, 1980; Sluyter *et al.*, 1994). If, as I suggest later, *Sry* is a gene for the effects of the NPAR Y chromosome on offense, this may be related to the function of Sry as a transcriptional regulator. The second limiting condition is that the differential effect of these pairs of NPAR Y chromosomes on offense depend on stimuli from the opponent male (Didier-Erickson *et al.*, 1989; Guillot *et al.*, 1995; Monahan and Maxson, 1990, 1997). Thus, one or more genes on the NPAR Y chromosome may act on brain mechanisms processing stimuli with effects on offense. Some aspects of such brain mechanisms are discussed by Guillot and Chapouthier (this issue). It is also of interest that some of these stimuli may be Y chromosomal influenced chemosignals which enable recognition of genotype (Monahan *et al.*, 1993; Schellinck *et al.*, 1993) or age and sex (Monahan and Maxson, 1990, 1997).

There is also at least one gene in the recombining (pseudoautosomal region; PAR) of the mouse Y chromosome with effects on offense (Table I). This has been reported for the NZB and CBA/H (Roubertoux *et al.*, 1994) and for the SAL and LAL (Sluyter *et al.*, 1994) strains. One of these genes may be *Sts* [see Roubertoux *et al.* (1995) for a discussion of *Sts*, steroid sulfatase]. The effect of the PAR gene(s) on offense depends on the maternal environment (Carlier *et al.*, 1991). The role of the PAR in offense is not considered further in this article.

The mouse Y has about 3×10^4 kb of DNA. About 3×10^3 kb of this is the PAR. Somewhere in the remaining kilobases of the NPAR, there may be more than 100 but fewer than 500 genes. This rough estimate of gene number on the mouse Y chromosome is based on the amount of single-copy DNA and on the range of sizes (bp) for mouse genes. Many, perhaps all, of these genes on the mouse Y chromosome have been cloned and sequenced [see Affara and Lau (1994) for a recent summary]. The single-copy genes are *Sry* (sex-determining region on the Y chromosome), *Zfy1 and 2* (zinc finger protein on the Y chromosomes 1 and 2), *Smcy* (selected mouse cDNA on the Y chromosome), and *Ube1Y1* (ubiquitin activating enzyme E1 on the Y chromosome). Multicopy genes are *Yrrm* (Y-chromosome RNA recognition motif) in about 5 copies and *Ssty* (sperm-specific transcript on the Y chromosome) in about 250 copies. There are three additional multigene families which are transcribed (Nallaseth and Dewey, 1986). These are pBC10-0.6, pBC15-1.1, and pBA33-1.8. When there is a complete physical map for NPAR of the mouse Y chromosome (Affara and Lau, 1994), it will be known whether or not there may be additional genes and therefore positional candidates for effects of it on offense behaviors.

Tissue expression of these genes is the first step in identifying positional candidates for effects of the NPAR Y chromosome on offense. It would seem unlikely that genes expressed only in sperm cells would have an effect on offense. So far mRNA expression of *Yrrm* (Ma *et al.*, 1993) and

Table II. Tissue Expression of Y^{NPAR} Genes[a]

Sry	Preimplantation embryo; gonadal ridge (somatic cells), fetal brain (diencephalon, mesencephalon); adult brain (cortex, hippocampus, hypothalamus, mesencephalon), heart, and gonad (somatic and germ cells)
Zfys	Preimplantation embryo; gonadal ridge (somatic cells), fetal meninges, choroid plexus, arteries, and kidney; adult gonad (germ cells)
Smcy	Preimplantation embryo; fetal liver and gonad; adult brain, heart, lung, liver, spleen, muscle, and gonad
Ubelyl	Adult gonad (germ cell)
pBYs	Adult brain, liver, kidney, and gonad

[a] References: *Sry* (Zwingman *et al.*, 1993; Rossi *et al.*, 1993; Lahr *et al.*, 1996); *Zfys* (Zambrowicz *et al.*, 1994); *Smcy* (Agulnik *et al.*, 1994); *Ubelyl* (Kay *et al.*, 1991); pBYs (Nallaseth and Dewey, 1986).

Ssty (Bishop and Hatat, 1987) has been detected only in germ cells. However, Northern blots were used to detect transcripts of these genes. More sensitive assays, such as RTPCR, may detect them in other tissues. Expression of mRNAs for the other genes on the NPAR Y chromosome is listed in Table II. Genes known to be transcribed in brain may be positional candidates for effects of the NPAR Y chromosome on offense. In this context, I note that low-level mRNA expression of *Ube 1yl* in adult brain was reported in one study (Kay *et al.*, 1991) but not in another (Mitchell *et al.*, 1991). This discrepancy may be due to a false positive in the RTPCR of Kay *et al.* (1991). Also, in mice transgenic for a *Zfyl* promoter and β-galactosidase reporter, fetal or adult brain expression of the *Zfy* construct is confined to arteries, meningies, and choroid plexus (Zambrowicz *et al.*, 1994). For these reasons *Sry*, *Smcy*, and the other gene families may be better positional candidates than Ube1Y1 or the Zfy's.

The following points suggest that *Sry* is a positional candidate.

(1) The *Sry* gene encodes for an HMG box transcription factor. The 3' end of the mouse *Sry* has strings of CAG repeats which code for strings of polyglutamines (Tucker and Lundrigan, 1993). Such polyglutamine repeats occur in other transcription factors. Variations in numbers of CAG repeats have been observed for such genes, and the consequent variation in number of glutamines may influence the regulation of transcription by these proteins (Willems, 1994).

(2) There are strain and natural variants for the number of CAG repeats in the 3' end of mouse *Sry* (Coward *et al.*, 1994). On some genetic backgrounds, these may affect primary sex determination.

(3) *Sry* is transcribed in the fetal diencephalon and mesencephalon of the mouse (Lahr, personal communication) and in the cortex, hippocampus, hypothalamus, and ventral tegmentum of adult males (Lahr *et al.*, 1995).

(4) Sry protein binds to response elements in the 5' end of the P450 aromatase (Haqq *et al.*, 1993) gene. P450 aromatase is an enzyme that converts testosterone to estradiol. This may be involved in the effect of the NPAR Y chromosome of the mouse on whole-brain levels of serotonin (Tordjman *et al.*, 1995). Manipulations of steroid hormones influence the whole brain levels of 5HT in rats (Biegon, 1990; Martinez-Conde *et al.*, 1985). Since the brain serotonin system is involved in offense of rodents (Miczek *et al.*, 1994), this may be a route by which the NPAR Y chromosome influences offense in mice. An Sry effect on aromatase may have other neuronal and thereby behavioral effects. SAL and LAL males differ in aromatase activity of the preoptic area of the hypothalamus (Compaan *et al.*, 1994); the NPAR Y chromosomes of these strains have differential effects on offense.

(5) Sry protein also binds to response elements in the Fos-related antigen 1 or *Fra1* (Cohen *et al.*, 1994) gene. The Fra1 protein is a component of AP1 transcription factors (Morgan and Curran, 1991). These bind to AP1 response elements in genes for neuropeptides (Goodman, 1990). This may be involved in effects of the NPAR Y chromosome on brain levels of several neuropeptides (Roubertoux *et al.*, 1992). These include met-enkephalin, B-endorphin, and ACTH, which are known to in-

fluence offense (Miczek *et al.*, 1994; Leshner, 1983).

Involvement of the number of 3' CAG repeats of *Sry* in effects of NPAR Y chromosome on offense can be tested, in part, by sequencing the 3' end of *Sry* for pairs of Y chromosomes. These include Y chromosomes of the following strain pairs: DBA/1Bg and C57BL/10Bg, CBA/Fa and C57BL/6, NZB and CBA/H, and SAL and LAL. DBA/1Bg and DBA/2Bg as well as PHH and PHL are not included here, as one or both strains may not be available. If the 3' sequence of *Sry* is the same for a pair of Y chromosomes, this part of *Sry* cannot be involved in the differential effects of this pair of Y chromosomes on offense. Whereas if for a pair of Y chromosomes the 3' sequence of *Sry* is different, *Sry* becomes a firm candidate gene for the differential effects of this pair of Y chromosomes on offense. It should be recognized that the 3' end of *Sry* may be a firm candidate for none, some, or all of the pairs of NPAR Y chromosomes with effects on offense and that this must be empirically established by DNA sequencing. Also, it should be recognized that even for pairs of NPAR Y chromosomes with differences in the 3' end of *Sry*, *Sry* may not have a role and/or other genes may have a role in differential effect of a pair of NPAR Y chromosomes on offense. This must also be empirically established.

Depending on the results of the research on *Sry* sequences for pairs of mouse chromosomes, *Sry* may also be a positional candidate for effects of the NPAR Y chromosome on hippocampal size asymmetry (van Abeelen *et al.*, 1989), hippocampal mossy fiber distribution (Hensbroek *et al.*, 1995), open-field activity (van Abeelen, 1988; Monahan and Maxson, 1991), apomorphine-induced stereotyped behaviors (Sluyter *et al.*, 1995), entrainment of circadian rhythms (Sluyter *et al.*, 1996), copulatory behaviors (Shrenker and Maxson, 1984), and discrimination learning (van Abeelen *et al.*, 1989).

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