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Report

Primate *DAX1, SRY,* and *SOX9:* Evolutionary Stratification of Sex-Determination Pathway

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The molecular evolution of *DAX1, SRY,* and *SOX9,* genes involved in mammalian sex determination, was examined in six primate species. *DAX1* and *SRY* have been added to the X and Y chromosomes, respectively, during mammalian evolution, whereas *SOX9* remains autosomal. We determined the genomic sequences of *DAX1, SRY,* and *SOX9* in all six species, and calculated K_a, the number of nonsynonymous substitutions per nonsynonymous site, and compared this with the K_s, the number of synonymous substitutions per synonymous site. Phylogenetic trees were constructed by means of the *DAX1, SRY,* and *SOX9* coding sequences, and phylogenetic analysis was performed using maximum likelihood. Overall measures of gene and protein similarity were closer for *DAX1* and *SOX9,* but *DAX1* exhibited nonsynonymous amino acid substitutions at an accelerated frequency relative to synonymous changes, similar to *SRY* and significantly higher than *SOX9*. We conclude that, at the protein level, DAX1 and SRY are under less selective pressure to remain conserved than SOX9, and, therefore, diverge more across species than does SOX9. These results are consistent with evolutionary stratification of the mammalian sex determination pathway, analogous to that for sex chromosomes.

DAX1 is a member of the nuclear hormone receptor superfamily (Zanaria et al. 1994). Mutations in this transcription factor result in developmental and functional abnormalities of the steroidogenic axis, as well as the clinical phenotypes of adrenal hypoplasia congenita (MIM 300200) and hypogonadotropic hypogonadism (Muscatelli et al. 1994; Zanaria et al. 1994; Guo et al. 1995; Habiby et al. 1996; McCabe 2000). Since *DAX1* maps to the dosage-sensitive sex reversal (DSS [MIM 300018]) critical region (Bardoni et al. 1994; Zanaria et al. 1994), and transgenic overexpression of *DAX1* in mice with a Y chromosome containing a weak *SRY* allele can result in XY sex reversal (Swain et al. 1998), *DAX1* is a candidate gene for DSS. However, experimental and clinical evidence suggests that the role of *DAX1* in sex determination is more complex. Targeted deletion of *DAX1* exon 2 in mice fails to give the expected sex-reversed phenotype (Yu et al. 1998), and a female human who is genotypically homozygous for a *DAX1* mutation also does not exhibit the expected phenotype (Merke et al. 1999). It is possible, however, that *DAX1* acts as a part of a dosage-sensitive multiprotein complex, that time of expression is important, and that *DAX1* functions differently in human and mouse (Swain et al. 1998; Goodfellow and Camerino 1999). *DAX1* is a relatively recent addition to the X chromosome, since it is autosomal in marsupials (Pask et al. 1997) and maps to the stratum that was acquired by the eutherian mammal X chromosome ~80–130 million years ago (Lahn and Page 1999).

SRY encodes a protein containing a "high-mobility group" domain (HMG box), which enables it to bind DNA (Sinclair et al. 1990; Giese et al. 1994). Mutations that map to the HMG box disrupt the SRY-DNA complex and result in XY sex reversal (Pontiggia et al. 1994), and XX mice carrying the *Sry* transgene may develop as males (Koopman et al. 1991). Among eutherian mammals, the SRY sequence is rapidly evolving outside the HMG box (Tucker and Lundrigan 1993; Whitfield et al. 1993). SRY is a relatively recent addition to the sex-

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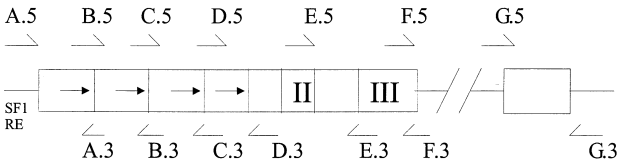

Figure 1 Genomic sequencing strategy for *DAX1*. Overlapping PCR primers (sets A–G) were used to amplify primate *DAX1; 5′* primers (A.5–G.5) are shown above the gene and 3′ primers (A.3–G.3) are shown below. The *5′* end of *DAX1* was amplified by means of the conserved SF1-response element upstream of the start codon as a primer-anchoring site.

determination pathway, appearing for the first time in mammals (Graves and Foster 1994).

SOX9, located on human chromosome 17, has also been implicated in the sex-determination pathway (Foster et al. 1994; Wagner et al. 1994). *SOX9,* like *SRY,* is an HMG family member, and mutations in a single allele of *SOX9* are responsible for XY sex reversal and campomelic dysplasia (MIM 114290) (Foster et al. 1994; Wagner et al. 1994; Morais da Silva et al. 1996). *SOX9* duplications in humans (Huang et al. 1999) can result in XX males in the absence of *SRY. SOX9* is much older evolutionarily than *DAX1* or *SRY* (Morais da Silva et al. 1996; McBride et al. 1997), may be part of an ancient "core" sex-determination mechanism that predates the mammalian radiation (Koopman 1999) and has important roles in sex determination and bone development (Bi et al. 1999). These factors may explain the highly conserved nature of *SOX9*.

The purpose of our investigations was to examine the molecular evolution of *DAX1* in relation to *SRY* and to *SOX9*. Genomic DNA was obtained from cell lines for each species ATCC numbers CRL-1857: *Pan troglodytes* (chimpanzee); CRL-1850: *Pongo pygmaeus* (orangutan); TIB-201: *Hylobates* species (gibbon); CRL-1773: *Callithrix jacchus* (marmoset); and from ClonTech Laboratories: *Homo sapiens* (human) and *Macaca mulatta* (rhesus) (fig. 1). A PCR-based approach was used to sequence the primate homologue of each gene. We used or adapted previously published primers for *SRY* (Whitfield et al. 1993) and *SOX9* (Wagner et al. 1994). PCR primers used for *DAX1* were A5 (TTGAACTACCGAGGTCATGGG) and A3 (CATGTTGTAGAGGATGCTGCC), B5 (GGGCTGCAGGAGCCGCGGGCC) and B3 (GCAGCGGTACAGGAGTGCCAC), C5 (GGGTGGGCAGAAAAGGGCTGC) and C3 (GGTGCTGCCCTGCTGCGGGTG), D5 (GGCCAGGGGGTAGAGAGGCGC) and D3 (GATCTTCTGCAGCATGCTGGG), E5 (GAGACTGTAGAAGTCTCGGAG) and E3 (GTAGGCGTACTCCTTGGTACT, F5 (AGTACCAAGGAGTACGCCTAC and F3 (CCACTGGAGTCCCTGAATGTTCTT), and G5 (ACGGGACGTGCCGGCAGTGCG) and G3 (CACTTGTGTGGCCCACATGAC). Sequences were deposited into GenBank. PCR products were sequenced using ABI 375 (PE Biosystems), and sequence data were formatted and analyzed using the GCG software package, version 10.0.

The ratios of nonsynonymous to synonymous (K_a/K_s) were estimated with the use of codeml, from the phylogenetic analysis using maximum likelihood (PAML) package (Goldman and Yang 1994). We imposed the commonly accepted primate topology (Pilbeam 1984) and estimated kappa (κ) and omega (ω, i.e., K_a/K_s), with alpha (α) and rho (ρ) fixed at zero. A single ω was used for the entire topology, since a model with separate ω for each branch did not give a significantly better fit. Codon frequencies were determined by means of the 12-parameter f3 × 4 model, but parameter estimates were largely independent of the codon-frequency model used. The tree-shape comparisons among genes were performed by likelihood-ratio tests. We compared a restricted model, having a constant ratio between respective branches of the trees for the two genes but all other evolutionary parameters unrestricted, with a more general model having separate evolutionary parameters (including the branch lengths) for the two genes. The maximum likelihood of the restricted model (18 parameters) and the maximum likelihood of the general model (26 parameters) were calculated by use of the HKY nucleotide-substitution model (Hasegawa et al. 1985), implemented in a modification of Schadt et al. (1998) (fig. 2). Our results showed that at the nucleotide level, *SRY* was highly divergent (92.5% average pairwise identity) and

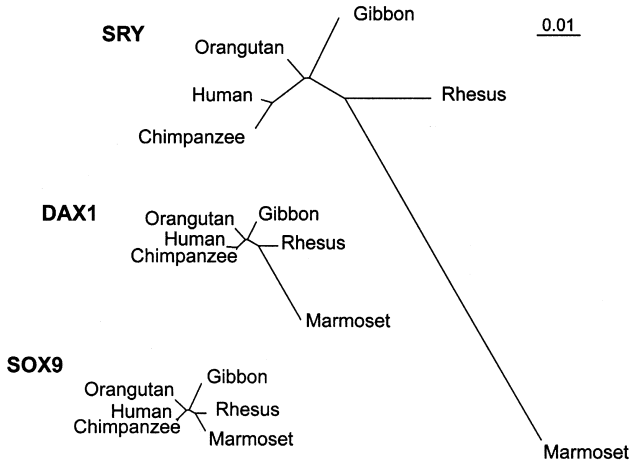

Figure 2 Phylogenetic trees for primate *SRY, DAX1,* and *SOX9,* constructed using the HKY nucleotide-substitution model (Hasegawa et al. 1985) and the commonly accepted topology. Branch lengths correlate to relative rates of evolution.

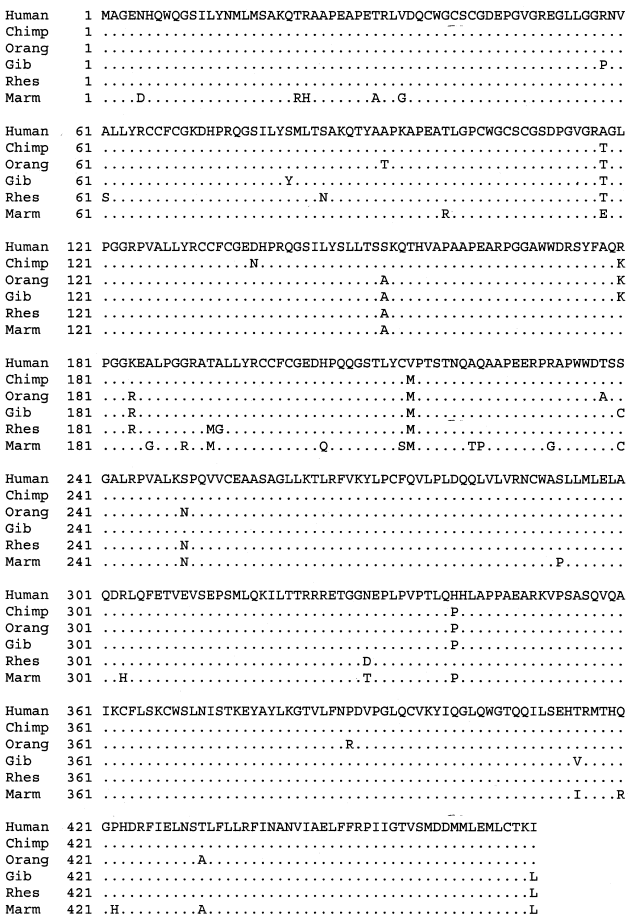

Figure 3 Amino acid alignment of primate DAX1. Amino acid identities are denoted by periods. Amino acid differences are noted.

SOX9 was very conserved (98.9% average pairwise identity) (table 1). When the overall nucleotide sequence of *DAX1* was examined, it was also conserved (98.1% average pairwise identity), falling closer to *SOX9* than to *SRY.*

We investigated the protein products of these genes at the amino acid level. We aligned the deduced DAX1 amino acid sequences for these primate species (fig. 3). The results were consistent with the nucleotide analysis. The average pairwise identities at the amino acid level were 85.8% for SRY, 96.6% for DAX1, and 99.8% for SOX9 (table 1). Inspection of the alignment suggests a clustering of amino acid changes between residues 180 and 240 of DAX1.

Proteins subjected to different functional selective pressures should accumulate amino acid differences in varying proportions relative to the silent mutations. Therefore, we calculated the frequency of nonsynonymous (K_a) and synonymous (K_s) nucleotide changes for our six primate species (Li et al. 1985) (table 2). When K_a values for *SRY, DAX1,* and *SOX9* were examined within individual species, it was clear that *SRY* had the highest values, with *DAX1* intermediate and *SOX9* lowest. K_s values were consistently lower for *DAX1* than for *SRY* or for *SOX9*. K_a values, however, were consistently higher for *DAX1* than for *SOX9*.

To examine the relative frequency of nonsynonymous nucleotide changes in comparison with the frequency of synonymous nucleotide changes, we calculated the K_a/K_s ratio for all six primate species (Goldman and Yang 1994). This ratio controls for different intrinsic rates of mutation focusing on the relative preference for amino acid changing substitutions. We found that *DAX1* ($K_a/K_s = .43 \pm .08$) was not significantly different from *SRY* ($K_a/K_s = .62 \pm .11$) and was much higher than *SOX9* ($K_a/K_s = .0061 \pm .0036$) (table 1).

Phylogenetic trees were constructed by means of the *DAX1, SRY,* and *SOX9* coding sequences. PAML was performed (Goldman and Yang 1994) (fig. 2). *Homo sapiens* (human) and *P. troglodytes* (chimpanzee) were always most closely related, and *M. mulatta* (rhesus) and *C. jacchus* (marmoset) were also sister taxa. The relationship of *Hylobates* species and *P. pygmaeus* could not definitely be resolved for the two genes *DAX1* and *SOX9*.

The shapes of the phylogenetic trees for *DAX1, SRY,* and *SOX9,* however, were distinct. We compared the tree shapes under the commonly accepted primate topology (Pilbeam 1984). Tree shape under a given topology was compared by testing whether the ratio of branch length *i,* for gene 1 (t_i), and branch length *i,* for gene 2 (s_i), is the same for all branches ($t_i/s_i = r$ for all branches i) (Goldman and Yang 1994). *DAX1* and *SRY* did not differ ($\chi^2 = 8.10$, df 8, $P = .424$), whereas *DAX1* differed from *SOX9* ($\chi^2 = 16.68$, df 8, $P = .0336$), and *SRY* differed from *SOX9* ($\chi^2 = 30.120$, df 8, $P = .0002$). Therefore, the *SOX9* tree had a distinc-

Table 1

Overall Measure of Sequence Divergence for Primate *SRY, DAX1,* and *SOX9* Nucleotide Sequences

Parameter	*SRY*	*DAX1*	*SOX9*
Nucleotide identity[a]	92.5%	98.1%	98.9%
Amino acid identity[a]	85.8%	96.6%	99.8%
K_a/K_s[b]	.62	.43	.0061
K_a/K_s SE[b]	.11	.08	.0036
Phylogenetic tree branch length[c]	.71	.18	.11

[a] Average pairwise comparisons.

[b] K_a/K_s ratios estimated by means of PAML (Goldman and Yang 1994). Imposing the topologies in figure 1 gave similar results with alternative topology for DAX1.

[c] The sum of branch lengths in the maximum-likelihood tree, as estimated by PAML, when the topology was imposed (Goldman and Yang 1994). Similar results were obtained with the use of an alternative topology.

Table 2

K_a and K_s Values for Nonhuman Primate to Human *SRY, DAX1,* and *SOX9* Nucleotide Sequences

Species and Measure	*SRY*	*DAX1*	*SOX9*
P. troglodytes:			
$K_a \times 10^2$ (95% CI)	1.44 (.35–2.53)	.47 (.05–.88)	.00 (.00–.17)[a]
$K_s \times 10^2$ (95% CI)	.82 (.00–2.46)	.30 (.00–.91)	.29 (.00–.87)
P. pygmaeus:			
$K_a \times 10^2$ (95% CI)	2.52 (1.05–3.98)	1.03 (.41–1.66)	.00 (.00–.17)[a]
$K_s \times 10^2$ (95% CI)	2.51 (.00–5.45)	1.83 (.33–3.33)	4.53 (2.15–6.91)
Hylobates:			
$K_a \times 10^2$ (95% CI)	3.56 (1.82–5.32)	1.60 (.82–2.37)	.08 (.00–.26)
$K_s \times 10^2$ (95% CI)	5.87 (1.37–10.38)	2.46 (.71–4.21)	5.98 (3.27–8.70)
M. mulatta:			
$K_a \times 10^2$ (95% CI)	4.63 (2.63–6.63)	1.12 (.47–1.77)	.00 (.00–.17)[a]
$K_s \times 10^2$ (95% CI)	13.22 (6.16–20.29)	2.78 (.91–4.65)	4.20 (1.91–6.49)
C. jacchus:			
$K_a \times 10^2$ (95% CI)	12.9 (9.44–16.43)	2.69 (1.68–3.71)	.17 (.00–.41)
$K_s \times 10^2$ (95% CI)	27.6 (16.52–38.59)	6.45 (3.53–9.34)	6.63 (3.74–9.52)

NOTE.—K_a and K_s values were estimated by means of the pairwise comparison method of Li et al. (1985).

[a] Upper bound calculated assuming a maximum of two nonsynonymous substitutions.

tive shape, differing from the tree shapes for *DAX1* and *SRY,* which were similar to each other. These results were consistent with a discontinuity in the pressures driving the evolution of *SOX9* versus *SRY* and *DAX1*.

An evaluation of rates of primate *DAX1* evolution indicates that *DAX1* may be under selective pressure for its amino acid sequence to evolve at a rate faster than *SOX9*. The K_a/K_s ratio would increase when the number of nonsynonymous changes (K_a) are well tolerated or selected, relative to the number of synonymous substitutions (K_s). Using the maximum-likelihood method for estimating K_a/K_s ratios (Goldman and Yang 1994), we found that, for the six primates that we examined, *DAX1* has a K_a/K_s ratio that was statistically indistinguishable from *SRY* and was much higher than *SOX9* (table 1). Therefore, whereas *DAX1* is more highly conserved than *SRY* at the nucleotide level, the K_a/K_s ratio distinguished *DAX1* and *SOX9* as being under different evolutionary pressures. Analysis of the phylogenetic tree shapes for these three genes confirmed this distinction. Our data suggest that, although DAX1 is a relatively conserved protein overall, it is, nevertheless, experiencing amino acid substitutions at a rate higher than is SOX9. We speculate that this selective pressure may be a consequence of the relatively recent evolutionary addition of DAX1 to the sex-determination pathway (Pask et al. 1997; Lahn and Page 1999) and/or to a role in spermatogenesis (Yu et al. 1998), since male reproductive genes evolve rapidly (Wyckoff et al. 2000). The more highly conserved nature of *DAX1,* relative to *SRY,* may reflect additional constraints on *DAX1* stemming from its role in adrenal development.

DAX1 and *SRY* may be recent additions to an evolutionary ancient "core" sex-determination program that involves *SOX9*. Our data on the molecular evolution of *SRY, DAX1,* and *SOX9* support this hypothesis for a stepwise evolution of the sex-determination pathway. Just as the human sex chromosomes may be evolving by punctuated sequential events (Lahn and Page 1997, 1999), our results are consistent with evolutionary stratification of the sex-determination pathway. We speculate that *SRY* and *DAX1* may be evolving dynamically as more recent additions to an evolutionarily stratified sex-determination pathway.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GenBank Overview, http://www.ncbi.nlm.nih.gov/Genbank/GenbankOverview.html (for *P. troglodytes SRY* [accession number X86380], *DAX1* [accession number AF322892], and *SOX9* [accession number AF322902]; *P. pygmaeus SRY* [accession number X86383], *DAX1* [accession number AF322893], and *SOX9* [accession number AF322898]; *Hylobates SRY* [accession number X86384], *DAX1* [accession number AF322894], and *SOX9* [accession number AF322897]; *M. Mulatta SRY* [accession number AF322901], *DAX1* [accession number AF322896], and *SOX9* [accession number AF322900]; and *C. jacchus SRY* [accession number X86386], *DAX1* [accession number AF322895], and *SOX9* [accession number AF322899])

Online Mendelian Inheritance in MAN (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for adrenal hypoplasia congenita [MIM 300200], DSS [MIM 300018], SRY [MIM 480000], and campomelic dysplasia [MIM 114290])

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