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Cloning and developmental expression of the *soxB2* genes, *sox14* and *sox21*, during *Xenopus laevis* embryogenesis

DOREEN D. CUNNINGHAM, ZHUO MENG, BERND FRITZSCH[1] and ELENA SILVA CASEY*

Georgetown University, Department of Biology, Washington DC and
[1]Creighton University, Department of Biomedical Sciences, Omaha, NE, USA

ABSTRACT The Sox family of transcription factors is thought to regulate gene expression in a wide variety of developmental processes. Here we describe the cloning of the *X. laevis* orthologs of the SoxB2 family of transcription factors, *sox14* and *sox21*. *In situ* hybridization revealed that *sox14* expression is restricted to the hypothalamus, dorsal thalamus, the optic tectum, a region of the somatic motornucleus in the midbrain and hindbrain, the vestibular nuclei in the hindbrain and a discrete ventral domain in the developing spinal cord. In contrast to the limited expression domain of *sox14*, *sox21* is found throughout the developing central nervous system, including the olfactory placodes, with strongest expression at the boundary between the midbrain and hindbrain.

KEY WORDS: *Sox, neurogenesis, Xenopus, neural tube*

The Sox family of transcription factors belongs to the high mobility group (HMG) superfamily of proteins. Originally classified together on the basis of at least 50% identity to the HMG domain of SRY (Sox = Sry related HMG box) (Stevanovic *et al.*, 1993), subsequent phylogenetic analysis revealed this basis too stringent (Bowles *et al.*, 2000). Instead all Sox proteins share a common motif within the HMG domain, RPMNAFMVW, and cluster into 10 groups (A-J) (Bowles *et al.*, 2000). While members across groups bear little resemblance outside of the HMG domain, members within groups are similar both within and outside of the HMG domain (Bowles *et al.*, 2000). In addition to the HMG domain, the Sox group B members also share a conserved group homology domain located just C-terminal to the HMG domain (Uchikawa *et al.*, 1999, Bowles *et al.*, 2000). The Sox group B has been further divided into two subgroups, B1 and B2, based on homology in the C-terminal domains (Uchikawa *et al.*, 1999). Furthermore, SoxB1 proteins have been demonstrated to activate transcription of the δ1-crystallin enhancer whereas the SoxB2 proteins repress it (Uchikawa *et al.*, 1999).

Sox proteins act in a wide range of developmental processes with the Group B proteins acting in the development of the nervous system. Specifically, SoxB1 proteins are generally thought to be involved in maintaining a neural stem cell or progenitor population. Functional analysis of chick Sox21 suggests that it specifically counteracts SoxB1 proteins, and as a consequence, promotes the progression of neurogenesis in the developing CNS (Sandberg *et al.*, 2005). Recent analysis knocking down the translation of Sox14 revealed disruption of hypothalamic patterning in zebrafish (Kurrasch *et al.*, 2007).

Homologues of both Sox14 and Sox21 have been identified in chick (Rex *et al.*, 1997) and mouse (Hargrave *et al.*, 2000) with Sox21 also characterized in fish (De Martino *et al.*, 1999). While *Sox21* is expressed broadly throughout the CNS in chick, mouse and zebrafish, with marked expression in the midbrain-hindbrain barrier, (Rex *et al.*, 1997, De Martino *et al.*, 1999, Uchikawa *et al.*, 1999), *Sox14* expression is limited to discrete domains in the nervous system in chick and mouse. In an effort to better understand the role and regulation of SoxB2 proteins during neurogenesis and to extend the phylogenetic analysis of the SoxB2 subgroup, we have cloned the *X. laevis* orthologs of *sox14* and *sox21* and report their spatiotemporal expression patterns.

Isolation and sequence comparison of sox14 and sox21

A *X. laevis* clone containing 160 bp of sequence with homology to the amino terminus of *sox14* was obtained in a screen for HMG containing homologs using a *X. laevis* genomic library. We used inverse PCR to clone the remainder of the coding region of a gene

Abbreviations used in this paper: AM, abducens motornucleus; DT, dorsal thalamus; HMG, high mobility group; OM, oculomotor motornucleus; OT, optic tectum; TM, trochlear motornucleus; WISH, whole mount in situ hybridization.

***Address correspondence to:** Elena Silva Casey. Department of Biology, Georgetown University, 37th and O Streets NW, 705 Reiss Science Building, Washington DC, 20057, USA. Fax.: +1-202-687-4662. e-mail: emc26@georgetown.edu

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whose predicted amino acid sequence exhibits a high degree of conservation to orthologs of Sox14 (96% amino acids are conserved with those in *G. gallus,* 94% in *H. sapiens* and *M. musculus,* and 97% in *X. tropicalis*) as determined using ClustalW (Fig. 1).

Because vertebrate Sox group B genes do not contain introns (Bowles *et al.*, 2000), we isolated *X. laevis sox21* from genomic DNA using primers complementary to the 5' coding region and the 3' UTR of *X. tropicalis sox21*. We then employed inverse PCR to obtain the 5' coding region of *X. laevis sox21* sequence. The predicted ORF encodes a 262 amino acid protein which is highly conserved with Sox21 proteins found in other vertebrates (Fig. 1, 90% amino acid conservation with *G. gallus, H. sapiens* and *M. musculus,* and 96% with *X. tropicalis*). As expected, a high degree of conservation to the HMG DNA binding domain and the group B homology domain was seen for both Sox14 and Sox21 (Fig.1, blue and pink lines, respectively). In the carboxyl terminal domain of Sox21, notable features of conservation are the polyalanine stretches characteristic of these proteins (marked with * in the Figure). Interestingly, while Sox21 proteins from human, mouse, chick and *X. tropicalis* have three polyalanine stretches, *X. laevis* lacks the last stretch (Fig. 1B), and analysis of Sox21 proteins from fish reveals that zebrafish and fugu have only the first polyalanine stretch (data not shown).

We generated a phylogenetic tree using parsimony analysis (PAUP* 4.0; Swofford *et al.*, 2001). We used *X. laevis* Sox2 to root the tree, although we obtained similar results when the tree was rooted with either XlSox1 or XlSox3 (Fig. 2). Notably, the *X. laevis* SoxB2 proteins cluster with previously identified Sox14 or Sox21

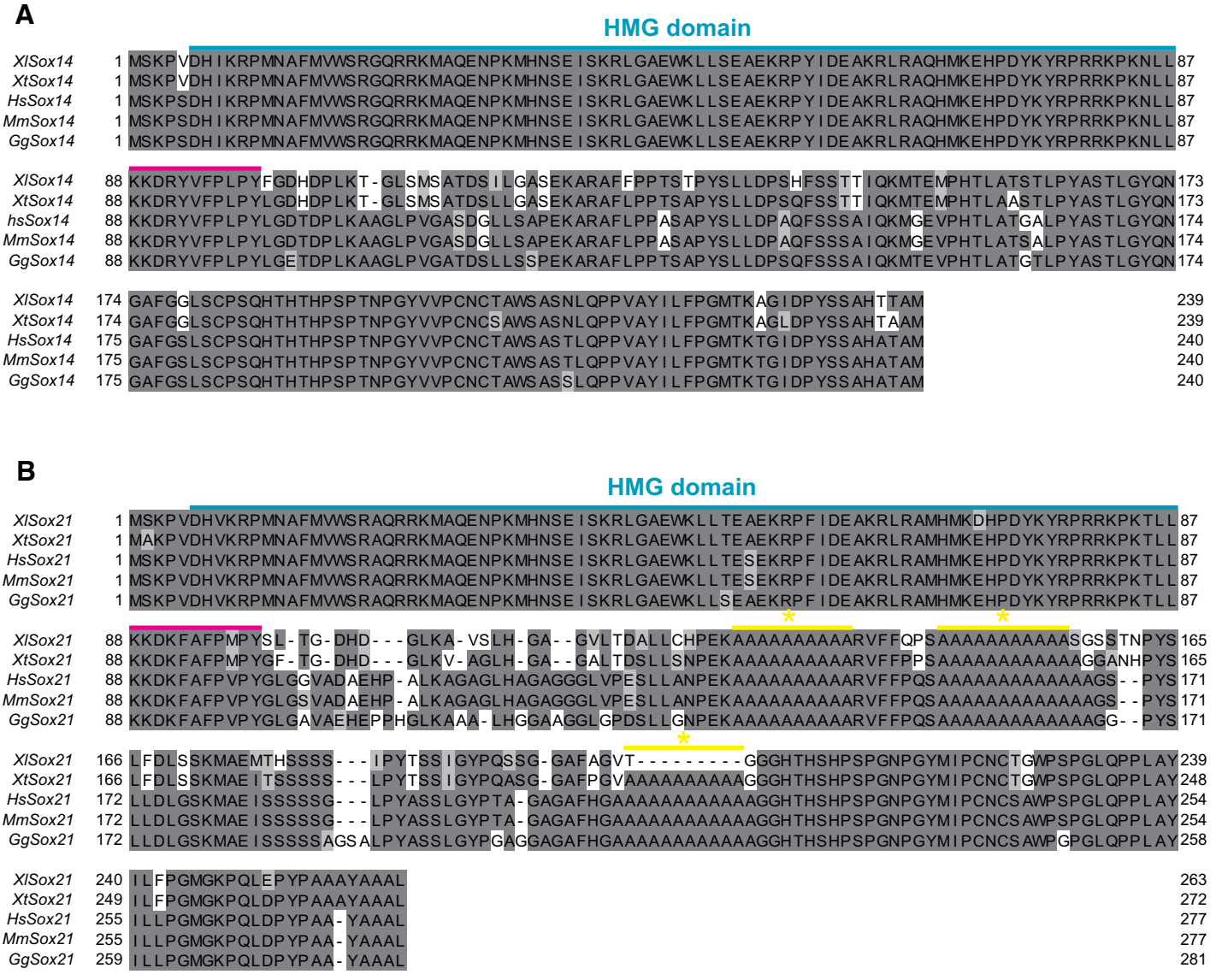
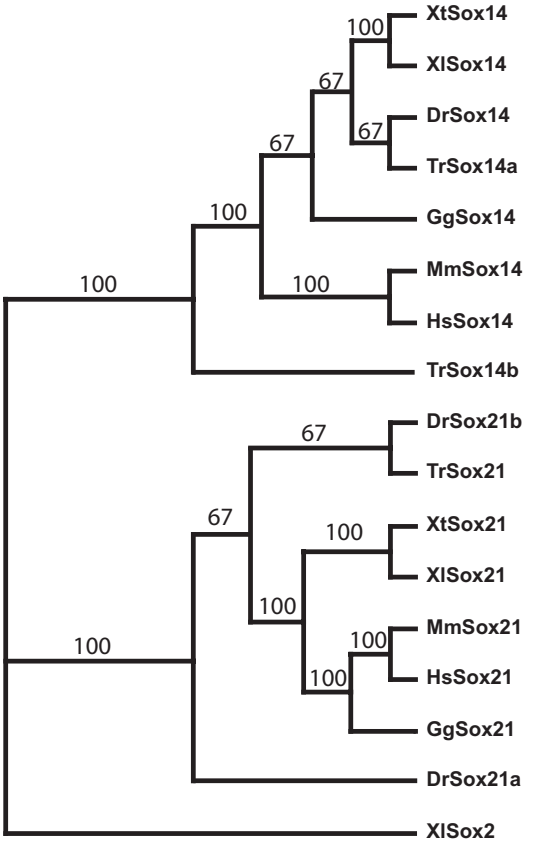


Fig. 1. Alignments of entire coding region of Sox14 and Sox21. *Sox14* **(A)** *and Sox21* **(B)** *amino acid sequences were aligned using ClustalW and shaded using JalView (Clamp* et al.*, 2004). Identical residues are shaded in dark grey and similar amino acids are shaded light grey. The high mobility group (HMG) domain is labeled and indicated with the blue bar, the group B homology domain is indicated with a pink bar and the polyalanine stretches characteristic of Sox21 are indicated by the asterisks and the yellow bar. Abbreviations used: Gg* (Gallus gallus), *Hs* (Homo sapiens), *Mm* (Mus musculus), *Xt* (Xenopus tropicalis), *and Xl* (Xenopus laevis).



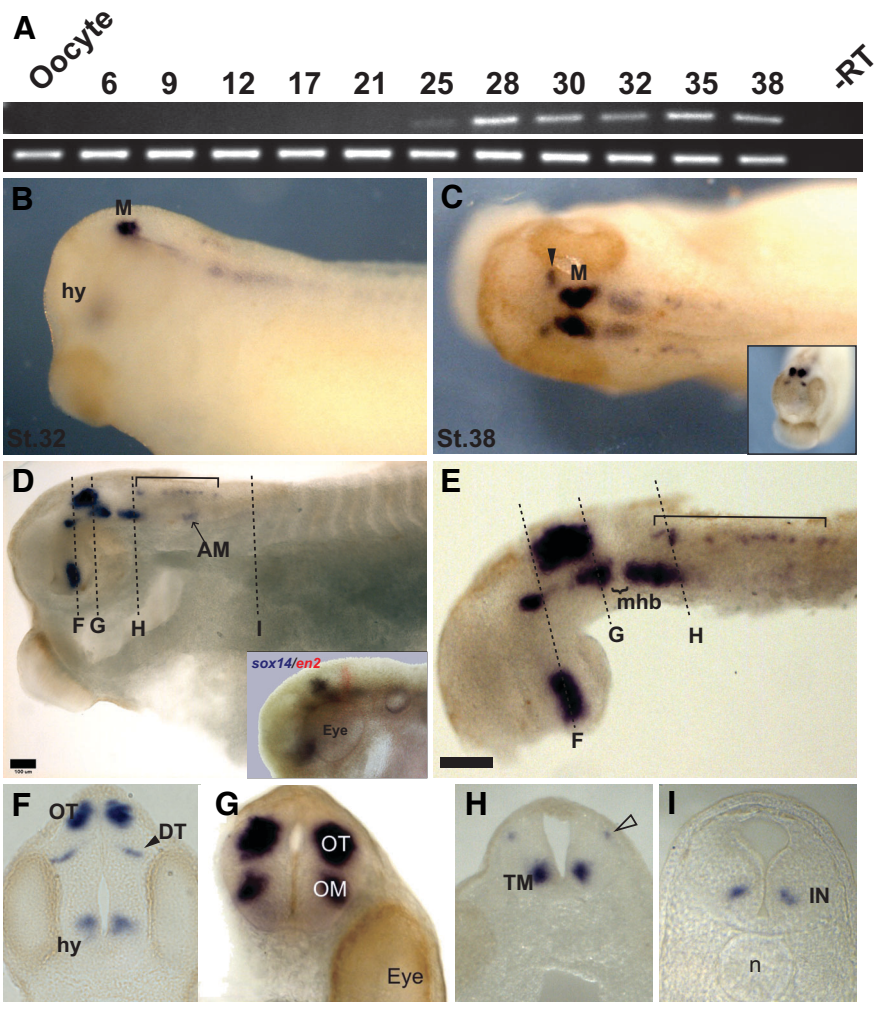


Fig. 2 (left). Phylogenetic analysis of SoxB2 protein family members. *SoxB2 sequences were obtained from Genbank or from the Joint Genome Institute (JGI). Protein identification numbers derived from previously identified genes are as follows: TrSox14a (AAQ18498.1), TrSox14b (AAQ18499.1), HsSox21 (AAC95381), GgSox21 (BAA77266.1), MmSox21 (AAN6055.1), DrSox21a (NP_571361), DrSox21B (NP_001009888.1), HsSox14 (NP_004180.1), GgSox14(NP_990092.1), MmSox14 (AAI00556), TrSox14a(AAQ18498.1), DrSox14 (AAI08034) and TrSox14b (AAQ18499.1). Sequences obtained from JGI are as follows: XtSox21 (gw1.467.21) and XtSox14 (e_gw1.344.69.1). Gg* (Gallus gallus), *Hs* (Homo sapiens), *Mm* (Mus musculus), *Dr* (Danio rerio), *Tr* (Takifugu rubripes).

Fig. 3 (right). Spatio-temporal expression pattern of *sox14*. (A) *RT-PCR analysis from oocytes and embryos to stage 38 as indicated across the top.* ODC *(lower panel) was used as the loading control.* **(B-I)** In situ *hybridization of* sox14 *at indicated stages. In all figures, anterior is to the left.* **(B)** *Lateral view;* **(C)** *dorsal view, anterior view in the inset.* **(D)** *Sagittal sections of stage 38, double* in situ *of* sox14 *and* en2 *in the inset.* **(E)** *Dissected brain from stage 38 embryo.* **(F-I)** *Transverse sections from stage 32* **(I)** *and 38* **(F-H)** *embryos. Symbols: bracket, expression in vestibular nuclei; black arrowhead, dorsal thalamus; open arrowhead, dorsal hindbrain* sox14 *positive cells; M, midbrain; hy, hypothalamus; and AM, abducens motornucleus; mhb, midbrain hindbrain barrier; OT, optic tectum; DT, dorsal thalamus; OM, oculomotor motornucleus; TM, trochlear motornucleus; IN, interneurons. Black bar equivalent to 100 μm.*

proteins, showing closest conservation with *X. tropicalis*. In addition, the indicated bootstrap values provide strong support for the clustering. We also constructed a tree using the distance neighbor-joining method (data not shown) and obtained the same results.

Sox14 *spatio-temporal expression*

To determine the temporal and spatial expression of *X. laevis sox14*, we performed RT-PCR and whole mount *in situ* hybridization (WISH) at a variety of embryonic stages. By RT-PCR analysis, *sox14* expression is first detectable at stage 25, peaks at stage 28 and this level of expression persists throughout all later stages examined (to st. 38, Fig. 3A). Using WISH we examined the spatial expression pattern of *sox14* from stages 17 through stage 48. *Sox14* is expressed by stage 28 (data not shown), with expression in the midbrain and hypothalamus clearly detectable by stage 32, as well as a faint ventral expression domain caudal to the midbrain (Fig. 3B). While expression remains strongest in the presumptive midbrain, by stage 38 additional discrete expression domains became apparent (Fig. 3C, arrowheads). In sagittal sections and dissected brains from stage 38 stage embryos, it is evident that *sox14* is expressed in the hypothalamus, the midbrain and the hindbrain (Fig. 3D and E). Within the midbrain, there are two expression domains: one dorsal domain, the optic tectum (OT), and one ventral domain, likely to be within the oculomotor

motornucleus (OM) (Fig. 3D, E and G). Caudal to the oculomotor motornucleus are *sox14* expressing-cells likely to be the trochlear motornucleus (TM) and even further caudal are the faintly labeled cells in the region of the abducens motornucleus (AM) (Fig. 3D) (Hartenstein, 1993, Guo *et al.*, 1999,Talikka *et al.*, 2004). To confirm the colocalization of the somatic motornuclei with *sox14* expression, we performed double *in situ* hybridization with *sox14* and *en2* (inset, Fig. 3D) or *pax2* (data not shown), markers of the midbrain-hindbrain boundary. The *sox14* expression overlaps with the ocular motonucleus which is directly rostral to the MHB and the trochlear motornucleus just caudal to the MHB. In the dorsal hindbrain are single *sox14* positive cells dispersed though the vestibular nuclear complex (Fig 3D and E, bracket). Anterior to the midbrain expression is a small expression domain, likely to be the dorsal thalamus (DT) (Fig. 3C-F) (Bachy *et al.*, 2001). In transverse sections of the spinal cord, *sox14* expression was also detected in a ventral domain of the spinal cord as early as stage 32 (Fig. 3I and data not shown). We presume this expression domain in the spinal cord marked by *sox14* corresponds to the subset of interneurons marked by mouse and chick *SOX14* (Uchikawa *et al.*, 1999, Hargrave *et al.*, 2000).

Sox21 *spatio-temporal expression*

We examined the temporal expression pattern of *sox21* during *Xenopus* embryo development using RT-PCR. Expression was absent from the oocyte and stages prior to the midblastula transition (st. 8), first detected at stage 10 and maintained in all subsequent stages examined (to st. 36, Fig. 4A). Using whole-mount *in situ* hybridization, *sox21* expression was first detected at stage 15 throughout the anterior neural plate (Fig. 4B). By stage 17, *sox21* expression was still throughout the presumptive CNS; however, a noticeable gap in expression was observed (Fig. 4C). The region immediately posterior to this gap had a considerably higher level of expression than neighboring regions (Fig. 4C, black asterisk). This restricted pattern of expression persisted through late tailbud with expression strongly detected in the presumptive forebrain, olfactory placode, and otic vesicle by stage 33 (Fig. 4 E,P). To identify the expression domains of *sox21*, we compared its expression to that of other well characterized brain markers, *en2*, which marks the midbrain-hindbrain boundary (Hemmati-Brivanlou *et al.*, 1991), *eomes*, which marks the telencephalon and a portion of the diencephalon (Bachy *et al.*, 2002) and *foxG1* (formerly known as *bf-1*), which also marks the telencephalon (Regad *et al.*, 2007) (Fig. 4 F-O). As labeled in Fig. 4P, we determine that *sox21* is expressed throughout the central nervous system, with strong expression in the forebrain, midbrain, and MHB and reduced expression in a region of the diencephalon.

To determine the dorsoventral expression pattern in the developing brain and spinal cord, we analyzed transverse sections of stained embryos (Fig. 4D and E). At stage 31,

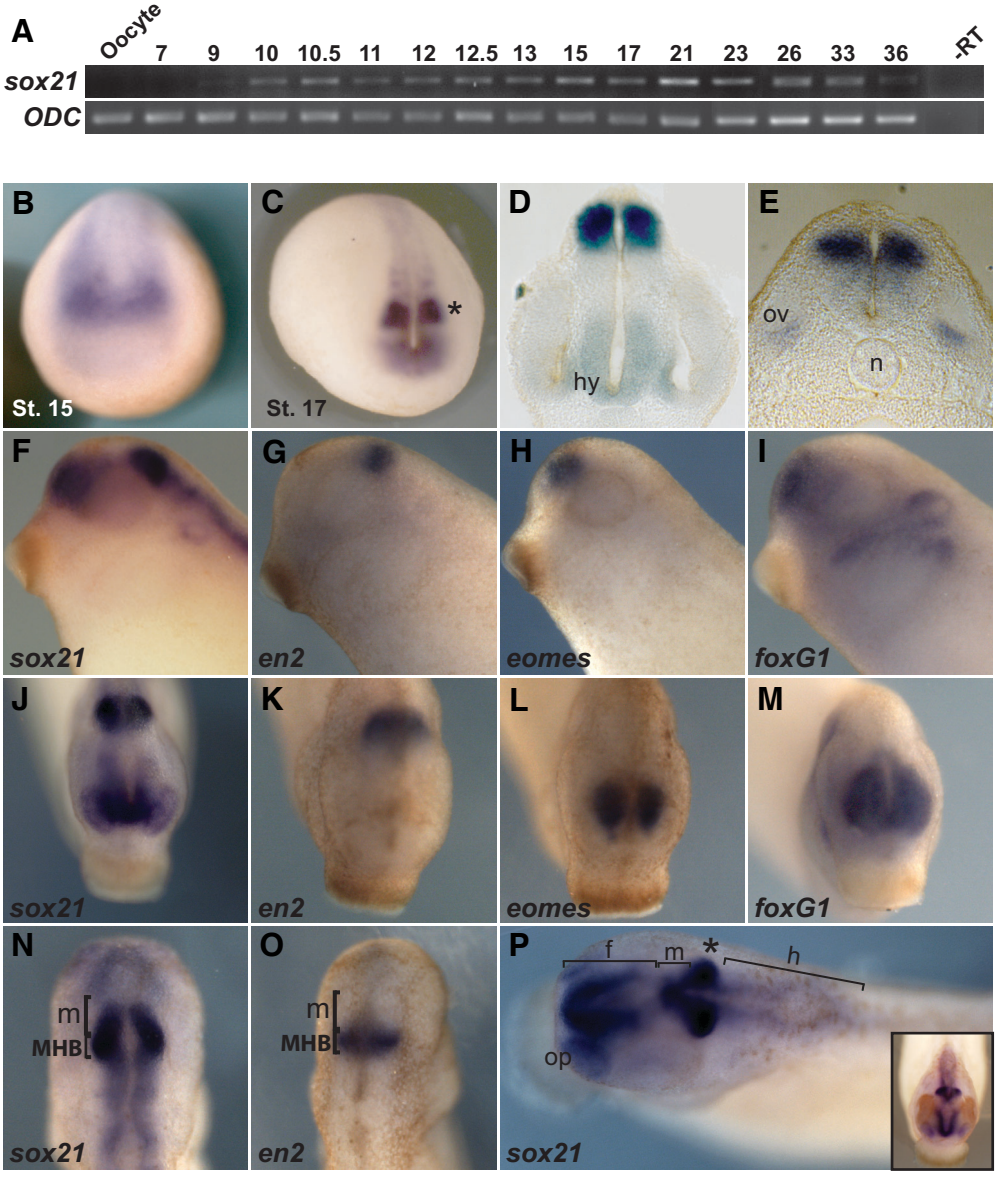


Fig. 4. Spatio-temporal expression pattern of *sox21*. (A) *RT-PCR analysis of embryos from oocyte to stage 36 as indicated across the top.* ODC *was used as the loading control.* **(B,C,F,J,N,P)** In situ *hybridization of embryos stained for* sox21 *at indicated stages and* **(F-M, O)** *for regional brain markers as indicated.* **(B,C, J-M, inset P)** *Anterior views.* **(N-P)** *Dorsal views.* **(F-I)** *Lateral views.* **(D,E)** *Transverse sections generated from a stage 31 embryo. Symbols: Black asterisks, midbrain-hindbrain boundary; f, forebrain; h, hindbrain; m, midbrain; hy, hypothalamus; n, notochord; op, olfactory placode; ov, otic vesicle.*

sox21 expression was detected in the forebrain and hypothalamus (Fig. 4D), in the dorsal region of the hindbrain and developing neural tube, and weakly in the otic vesicles (Fig. 4E and data not shown).

In summary, we have shown that *X. laevis* has at least two *soxB2* genes, *sox14* and *sox21*. They have patterns of expression distinct from each other throughout stages of early development. Here we show *sox14* marks a subset of interneurons located in the ventral portion of the spinal cord as well as in a portion of the dorsal thalamus. Except for the hypothalamus, all other *sox14* labeled cells and nuclei are directly or indirectly involved in eye movement through optokinetic and vestibular reflexes (Nieuwenhuys *et al.*, 1998). Cell cycle exit data suggest that most of the labeled cells are postmitoic neurons that have exited the cell cycle between st. 23-30 (Hartenstein, 1993). Interestingly, the onset of expression of *sox14* correlates with the onset of neuronal differentiation of the ventral midbrain and ventral interneurons of the spinal in *Xenopus laevis* (Hartenstein, 1993). Combined these data may suggest that Sox14 is a master regulator for eye movement centers as much as Atoh1 is governing development of proprioreceptive centers (Bermingham *et al.*, 2001). Indubitably, experimental evidence is needed to verify this suggestion. *X. laevis sox21* expression marks the olfactory placodes, forebrain, midbrain-hindbrain barrier, and neural tube, with a gap of expression corresponding to the dorsal thalamus. It will be interesting to investigate the roles these genes have in neurogenesis and patterning in *X. laevis*.

Experimental Procedures

Cloning and sequence analysis

Sox14: Using a probe designed to be complementary to the HMG domain of Sox genes, a *X. laevis* genomic library was screened. One clone contained 1218 bp upstream of the predicted start ATG and 160 bp downstream. We used the sequence downstream of the predicted ATG to BLAST all known EST databases and found that it that was highly homologous to *sox14* genes. Using inverse PCR we obtained a 720 bp product and corresponded with the ORF for Sox14. This product was cloned into the pGEM T-easy vector (Promega) to generate pGEM-Xlsox14.Primers used for the inverse PCR were:

F1: 5'TATGACAGTTGGAGAGGGC 3',
R1: 5' GGGAGCATGTGGGTAGTCT 3',
F2: 5' TATGACAGTTGGAGAGGGC 3',
R2: 5' CATAGACCTGGAGAGTAATTG 3'.

sox21: The following primers were designed based on the sequence of *sox21* found in the *X. tropicalis* genome v4.1 (http://genome.jgi-psf.org/Xentr4/Xentr4.home.html): F 5' ATGGCTAAACCGGTGGATC 3' R: 5' GCCAGTGCCCTTAGTCGG 3'. The amplified 789 bp product was cloned into pGEM T-easy vector (Promega) to generate pGEM-Xlsox21.

We used the sequence information from pGEM-Sox21 to generate inverse PCR primers to obtain the *XlSox21* sequence:

F1: 5' CTGGGTGACACAGCAAGGCG 3';
R1: 5' GGCAGAGATGACACATTC 3';
F2: 5' CATGTAAACTAACAGCCTTC 3';
R2: 5' CATCTATTCCTTATACCTCG 3'.

Protein alignment and tree construction

Amino acid sequences were aligned using ClustalX, available from ftp://ftp-igbmc.u-strasbg.fr/pub/ClustalX/. The alignment was color coded according to Blosum62 scores using JalView (Clamp *et al.*, 2004). The parsimony tree and neighbor-joining distance tree were constructed using PAUP4.0*.

Semi-quantitative RT-PCR analysis

RNA was extracted for RT-PCR analysis as described (Wilson and Melton, 1994). One embryo equivalent was used for each RT-PCR experiment. To assay for DNA contamination in RT-PCR experiments, an embryo was processed without reverse transcriptase and labeled as the RT minus lane in each experiment. Ornithine decarboxylase (ODC) was used as the loading control. RT-PCR primers for the ODC have been described elsewhere (Hudson *et al.*, 1997). The primers used for detection of *Xenopus soxB2* genes are:

sox21: U, 5'-TAGTTTGACAGGGGACCATGATGGG-3';
D, 5'-CCCCACCTGTAACCCCAGCAAA-3'; 64 °C, 25 cycles.
sox14: U, 5' CTTTCCACCAACATCAACAC 3';
D, 5' CCAGCTTTAGTCATACCAGG 3'; 55°C, 30 cycles.

Whole-mount in situ *hybridization*

Whole-mount *in situ* hybridizations were performed as described previously (Harland, 1991). Antisense RNA DIG labeled (Roche) probes were synthesized using either pGEM-XLsox14 or pGEM-XLsox21 and detected using BM purple (Roche). Double *in situ* hybridization were performed as described previously (Hollemann *et al.*, 1998), DIG labeled *sox14* and fluorescein labeled (Roche) *en2* and *pax2* probes were employed.

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