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Expression of *Sox genes* in tooth development

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ABSTRACT Members of the *Sox* gene family play roles in many biological processes including organogenesis. We carried out comparative *in situ* hybridization analysis of seventeen *sox* genes (Sox*1-14, 17, 18, 21*) during murine odontogenesis from the epithelial thickening to the cytodifferentiation stages. Localized expression of five *Sox* genes (*Sox6, 9, 13, 14* and *21*) was observed in tooth bud epithelium. *Sox13* showed restricted expression in the primary enamel knots. At the early bell stage, three *Sox* genes (*Sox8, 11, 17* and *21*) were expressed in pre-ameloblasts, whereas two others (*Sox5* and *18*) showed expression in odontoblasts. *Sox* genes thus showed a dynamic spatio-temporal expression during tooth development.

KEY WORDS: *Sox, tooth development, in situ hybridization*

Teeth develop from sequential and reciprocal interactions between epithelium and neural crest-derived mesenchyme. The first morphological sign of tooth development is an epithelial thickening on the first branchial arch. The thickened epithelium then progressively takes the form of the bud, cap and bell configurations. Primary enamel knots appear as thickened inner enamel epithelium at the early cap stage, but disappear by the late cap stage. Subsequently, epithelial cells differentiate into enamel-producing ameloblasts and dentin-producing odontoblasts differentiate from mesenchymal cells (dental papilla). It is known that many signaling pathways such as Bmp, Fgf, Wnt, and Shh play critical roles in regulating tooth development (Tucker and Sharpe, 2004).

Sox proteins are characterized by a highly conserved DNA binding motif, HMG (high mobility group) domain, and twenty *Sox* genes have been identified in mice. Members of the *Sox* gene family show dynamic and diverse expression patterns during development and mutation analyses in humans and mice provide evidence that they play multiple roles during development (Pevny and Lovell-Badge 1997, Hosking and Koopman 2008, Wegner 1999, Oommen *et al.*, 2012). *Sox2* has been shown to be expressed in rodent tooth germs including the incisor cervical loops (Ohazama *et al.*, 2010; Juuri *et al.*, 2012, 2013; Zhang *et al.*, 2012). The expression of other members of *Sox* family in tooth development however remains unstudied.

We carried out comparative *in situ* hybridization analysis of sixteen *Sox* genes (*Sox1-14*, *17*, *18*, *21*) during murine odontogenesis, and reveal dynamic spatio-temporal expression of *Sox 2, 4, 5, 6, 8, 9, 11, 12, 13, 14, 17, 18 and 21* in molar tooth development.

Results

Sox genes are classified into nine subgroups according to homology within the HMG domain and other structural motifs, as well as functional assays (Pevny and Lovell-Badge 1997, Wegner 1999).

Group B

Sox1, *Sox2* and *Sox3* belong to the B1 group of Sox family. *Sox2* expression has been shown in tooth development (Ohazama *et al.*, 2010; Juuri *et al.*, 2012, 2013; Zhang *et al.*, 2012). *Sox2* is expressed in tooth epithelium at the initiation stage (E10.5 and E11.5; Fig. 1 F,G). At the bud stage (E13.5) and the cap stage

Abbreviations used in this paper: E, embryonic day.

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(E14.5), *Sox2* showed restricted expression in lingual bud epithelium (Fig. 1 H,I). Significant expression of *Sox2* is not found in tooth germs at E18.5 (Fig.1J). Although *Sox1* and *Sox3* belong to same group (B1) as *Sox2*, neither *Sox1* nor *Sox3* expression could be detected in tooth germs from E10.5 to E18.5 (Fig. 1 A-E, 1 K-O). *Sox14* and *Sox21* belong to the B2 group of Sox family. At the initiation stage, weak expression of *Sox14* was observed in presumptive tooth epithelium, whereas *Sox21* showed no expression (Fig. 1 P,Q,U,V). At the bud stage (E13.5), *Sox21* was weakly expressed in the collar of tooth bud epithelium, although no expression of *Sox14* was observed in tooth germs (Fig. 1R,W). At the cap stage (E14.5), neither *Sox14* nor *Sox21* expression could be detected in tooth germs (Fig. 1S,X). At the cytodifferentiation stages (E18.5), weak *Sox21* expression was observed in pre-ameloblasts localized at the presumptive cusp region, and *Sox14* showed no expression in tooth germs (Fig. 1T,Y).

Group C

Sox4, *Sox11* and *Sox12* belong to the C group of Sox family. *Sox4* and *Sox11* were expressed in presumptive tooth epithelium and mesenchyme at both E10.5 and E11.5, whereas *Sox12* showed no expression (Fig. 2 A,B,F,G,K,L). At E13.5, *Sox4* was strongly expressed in tooth mesenchyme and the centre of bud epithelium, and *Sox11* expression was observed in basal epithelium of tooth bud epithelium (Fig. 2C,H). Punctate expression of *Sox12* was observed in both tooth epithelium and mesenchyme (Fig. 2M). At the cap stage, *Sox4* was expressed in inner enamel epithelium, stellate reticulum, dental papillae and mesenchyme facing buccal outer enamel epithelium, whereas outer tooth enamel epithelium showed weak expression (Fig. 2D). *Sox11* was expressed in the cervical loop of molar tooth epithelium and outer enamel epithelium, whereas *Sox12* expression could not be detected in tooth germs at this stage (Fig. 2I,N). At cytodifferentiation stages, *Sox11*

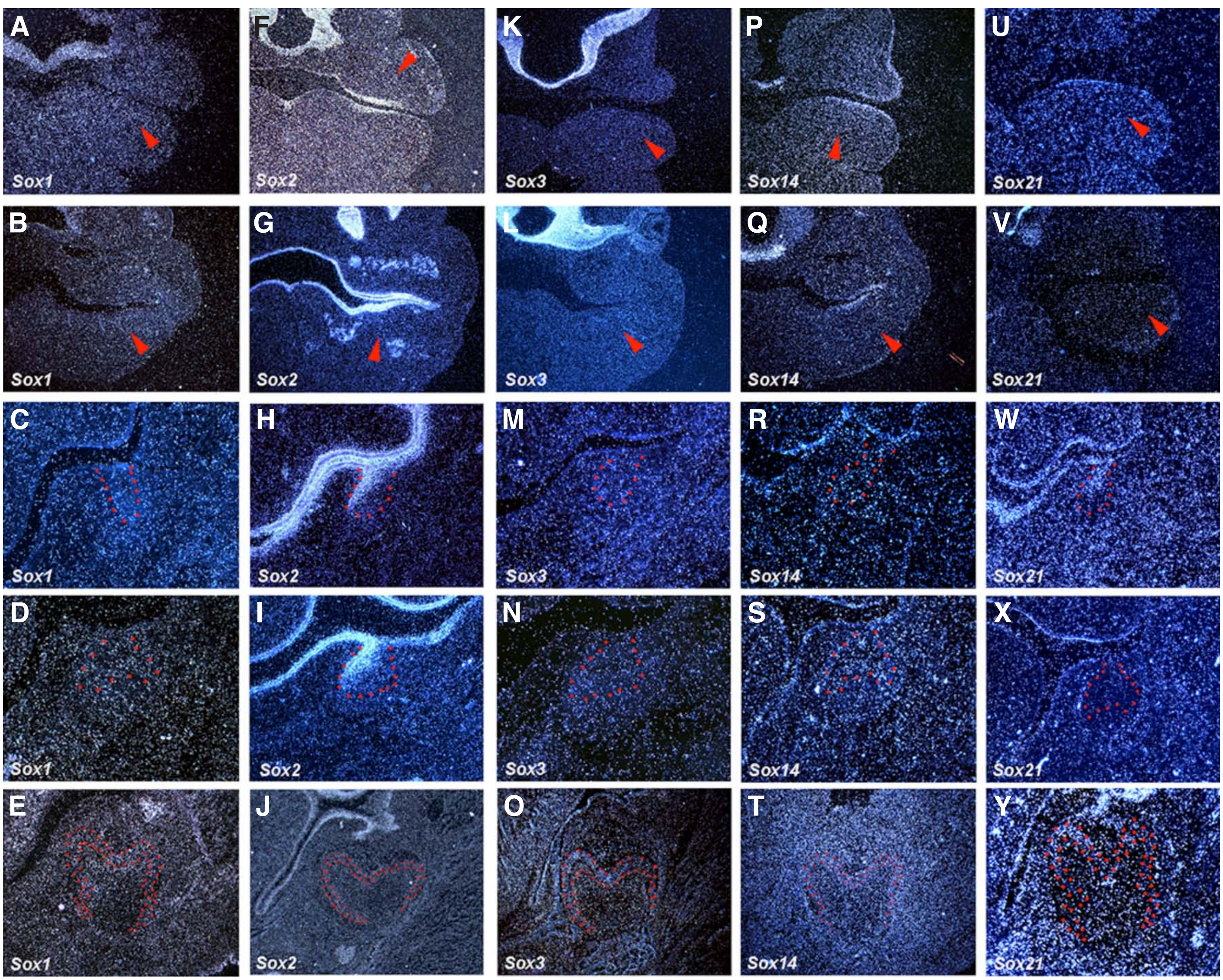

Fig. 1. The expression of *Sox* genes (Group B) in rodent tooth development. In situ *hybridisation of* Sox1, Sox2, Sox3, Sox14 *and* Sox21 *on frontal head sections at E10.5, E11.5, E13.5, E14.5 and E18.5. Tooth epithelium is outlined in red. Arrowheads indicate the presumptive tooth region.*

expression was observed in pre-ameloblasts, whereas neither *Sox4* nor *Sox12* show expression in tooth germs (Fig. 2 E,J,O).

Group D

Sox5, *Sox6* and *Sox13* belong to the group D Sox genes. At E10.5, *Sox5* showed restricted expression in tooth mesenchyme, whereas *Sox6* and *Sox13* expression were observed in both presumptive tooth epithelium and mesenchyme (Fig. 3 A,F,K). At E11.5, expression of *Sox6* was observed in tooth epithelium, whereas *Sox5* showed weak expression in mesenchyme (Fig. 3 B,G). Faint expression of *Sox13* was observed in both tooth epithelium and mesenchyme at this stage (Fig. 3L). At the bud stage, *Sox6* and *Sox13* showed restricted expression in lingual bud epithelium and at the tip of bud epithelium, respectively (Fig. 3 H,M). No expression of *Sox5* could be detected in tooth germs (Fig. 3C). At the cap stage, *Sox5* was weakly expressed in dental papillae, whereas *Sox13* expression was observed in the primary enamel knot (Fig. 3 D,N). *Sox6* showed restricted expression in lingual outer enamel epithelium (Fig. 3I). At cytodifferentiaton stages, *Sox5* showed weak expression in dental papillae and odontoblasts, whereas neither *Sox6* nor *Sox13* were expressed in tooth germs (Fig. 3 E,J,O).

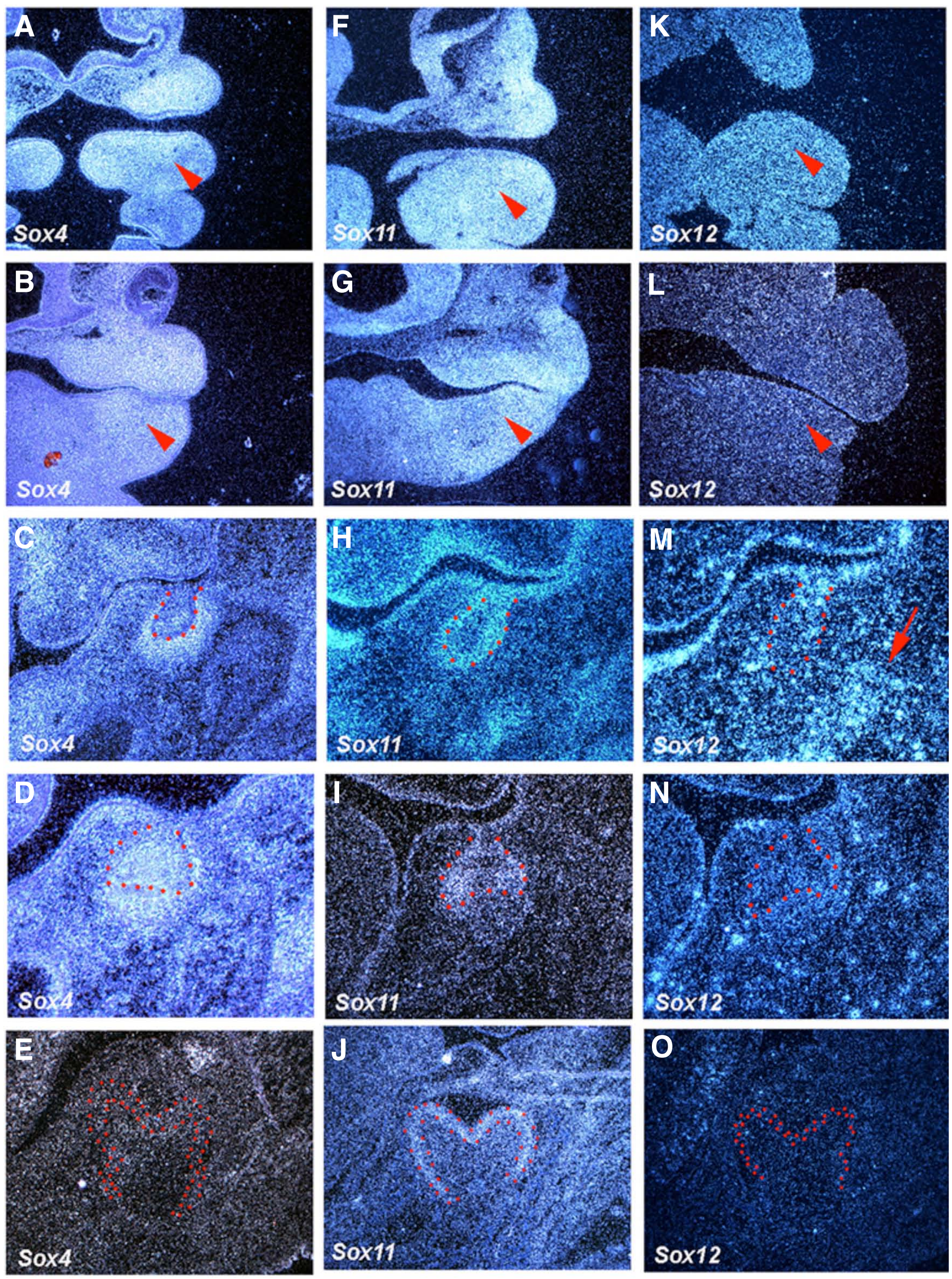

Fig. 2. The expression of *Sox* genes (Group C) in rodent tooth development. In situ *hybridisation of* Sox4, Sox11 *and* Sox12 *on frontal head sections at E10.5, E11.5, E13.5, E14.5 and E18.5. Tooth epithelium is outlined in red. Arrowheads indicate the presumptive tooth region. Arrow indicates the presumptive alveolar bone region.*

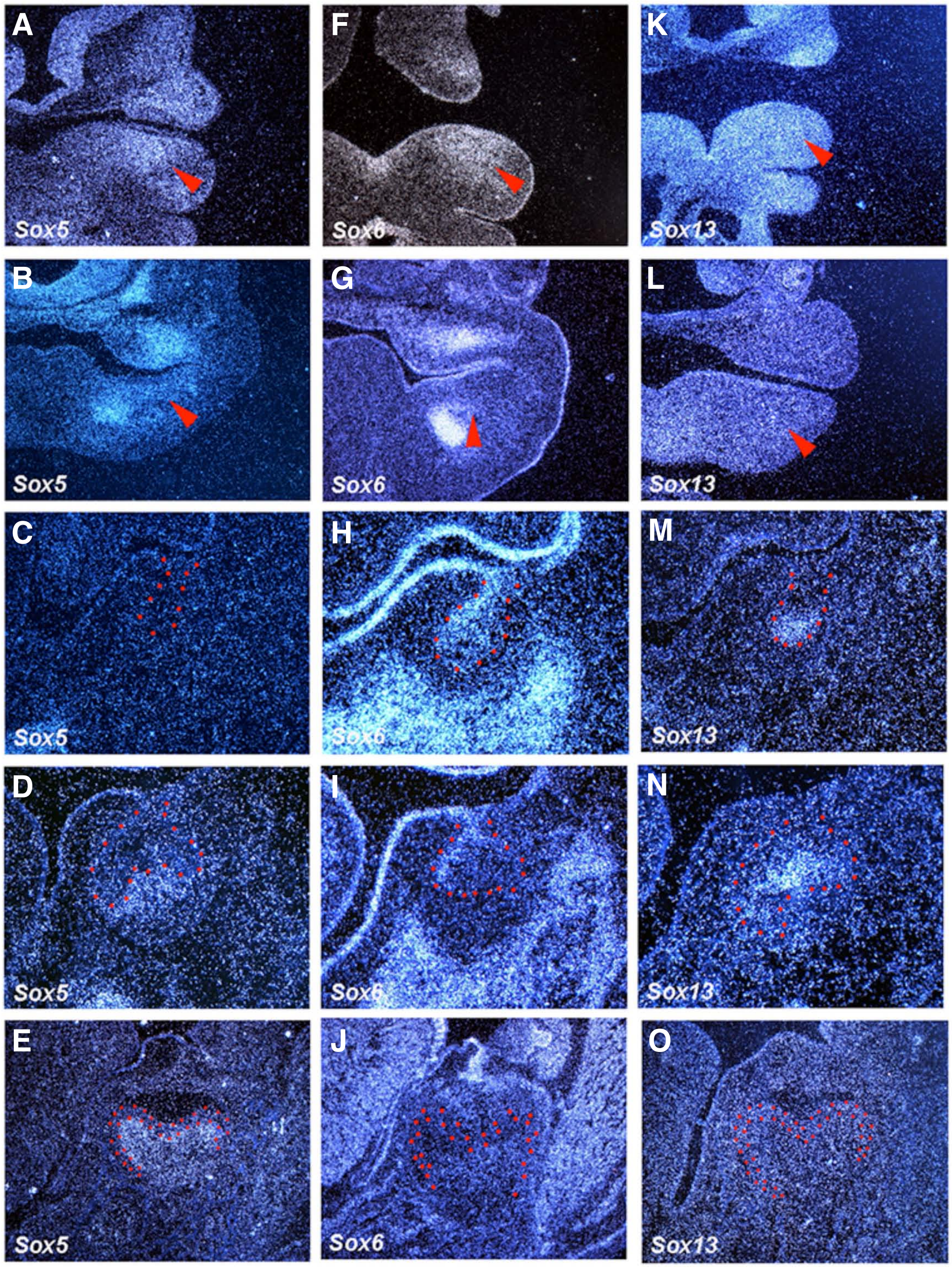

Fig. 3. The expression of *Sox* genes (Group D) in rodent tooth development. *In situ hybridisation of* Sox5, Sox6 *and* Sox13 *on frontal head sections at E10.5, E11.5, E13.5, E14.5 and E18.5. Tooth epithelium is outlined in red. Arrowheads indicate the presumptive tooth region.*

Group E

Sox8, *Sox9* and *Sox10* belong to the group E Sox genes. *Sox10* showed no expression in tooth germs from E10.5 to E18.5 (Fig. 4 K-O). *Sox9* showed expression in both tooth epithelium and mesenchyme at E10.5, which became weak at E11.5 (Fig. 4 F,G, Mitsiadis *et al.*, 1998). No expression of *Sox8* could be detected in tooth germs at E10.5 or E11.5 (Fig. 4 A,B). At bud stage, *Sox9* was weakly expressed in tooth epithelium, whereas no *Sox8* expression was observed in tooth germs (Fig. 4 C,H). At the cap stage, weak expression of *Sox8* was observed in inner enamel epithelium and dental papilllae, whereas *Sox9* showed expression in outer enamel epithelium and collar of tooth epithelium (Fig. 4 D,I). At E18.5, weak expression of *Sox8* was observed in pre-ameloblasts, whereas *Sox9* was expressed in rostral developing pulp and caudal stellate reticulum (Fig. 4 E,J).

Group F

Sox7, *Sox17* and *Sox18* belong to the group F Sox genes. A punctate expression pattern of *Sox7* and *Sox18* were seen throughout the mesenchyme at E10.5-E14.5 (Fig. 5 A-D, 5 K-N).

Sox17 showed similar expression, but weaker than those of *Sox7* and *Sox18* at these stages (Fig. 5 F-I). At E18.5, *Sox17* was expressed in pre-ameloblasts, whereas *Sox18* showed restricted expression in mesenchyme underneath presumptive cusp and facing cervical loops (Fig. 5 J,O). *Sox7* showed no expression in tooth germs at E18.5 (Fig. 5E).

Transgenic mice

It has been shown that epithelial conditional *Sox2* mutation using *ShhCre* led to no significant changes of molars (Juuri *et al.*, 2013). In common with previous reports, significant anomalies could not be detected in molars in *Sox2* mutants using *K14Cre* mice (Fig. 6B). To further analyze the role of *Sox2* in tooth development, we examine mice overexpressing under the *keratin 5* promoter (*Krt5-Cre;Rosa26Sox2/+*). However, no obvious differences could be detected in molar tooth germs in *Krt5-Cre;Rosa26Sox2/+* mice (Fig. 6C). Our data from *in situ* hybridization analysis shows *Sox6* showed similar a expression pattern to *Sox2* in tooth development (Fig. 1 F-J, 3 F-J). In order to investigate the role of *Sox6* in tooth development, we examined *Sox6* mutant mice (*p100H*

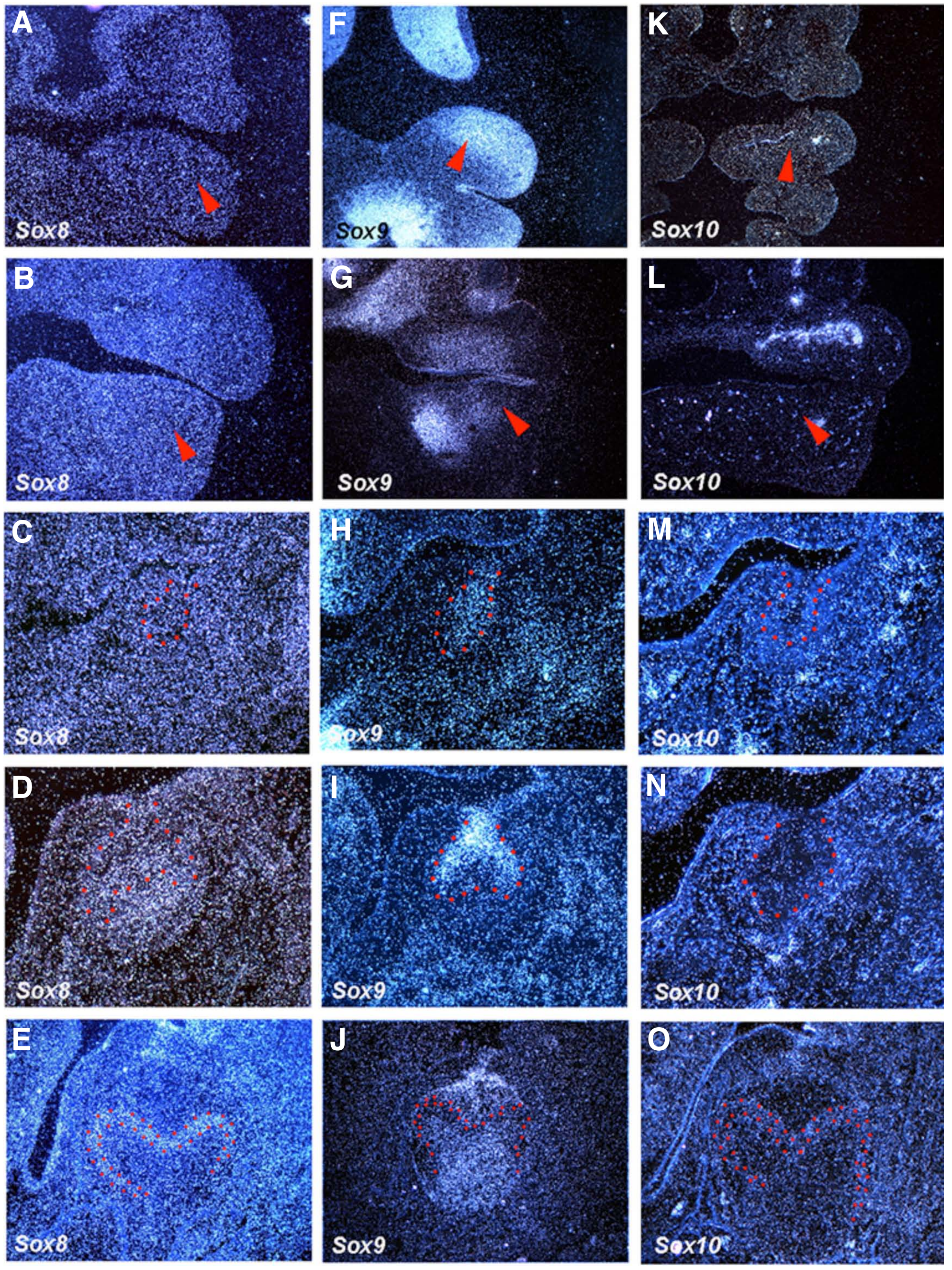

Fig. 4. The expression of *Sox* genes (Group E) in rodent tooth development. In situ *hybridisation of* Sox8, Sox9 *and* Sox10 *on frontal head sections at E10.5, E11.5, E13.5, E14.5 and E18.5. Tooth epithelium is outlined in red. Arrowheads indicate the presumptive tooth region.*

homozygotes). Significant differences however could not be detected in mutant molars (Fig. 6D).

Discussion

Members of the *Sox* gene family show dynamic and diverse expression patterns during development of many organs, and analysis of mutations in mice suggest that member of Sox gene family play multiple roles during development (Pevny and Lovell-Badge 1997). Our results also show dynamic spatio-temporal expression of *Sox genes* in developing tooth germs.

It has been shown that *Sox2* plays a critical role in regulating molar dental lamina growth (Juuri *et al.*, 2013). *Sox2* is also expressed in the lingual bud and cap epithelium, although *Sox2* mutant molars show no significant morphological changes (Juuri *et al.*, 2013). We found that *Sox6* have a similar expression pattern to *Sox2* in tooth development. No siginificant anomalies however could be detected in *Sox6* mutant molars. It has been shown that there is the redundancy between different Sox group members, and it is possible that *Sox2* function is compensated by *Sox6* in

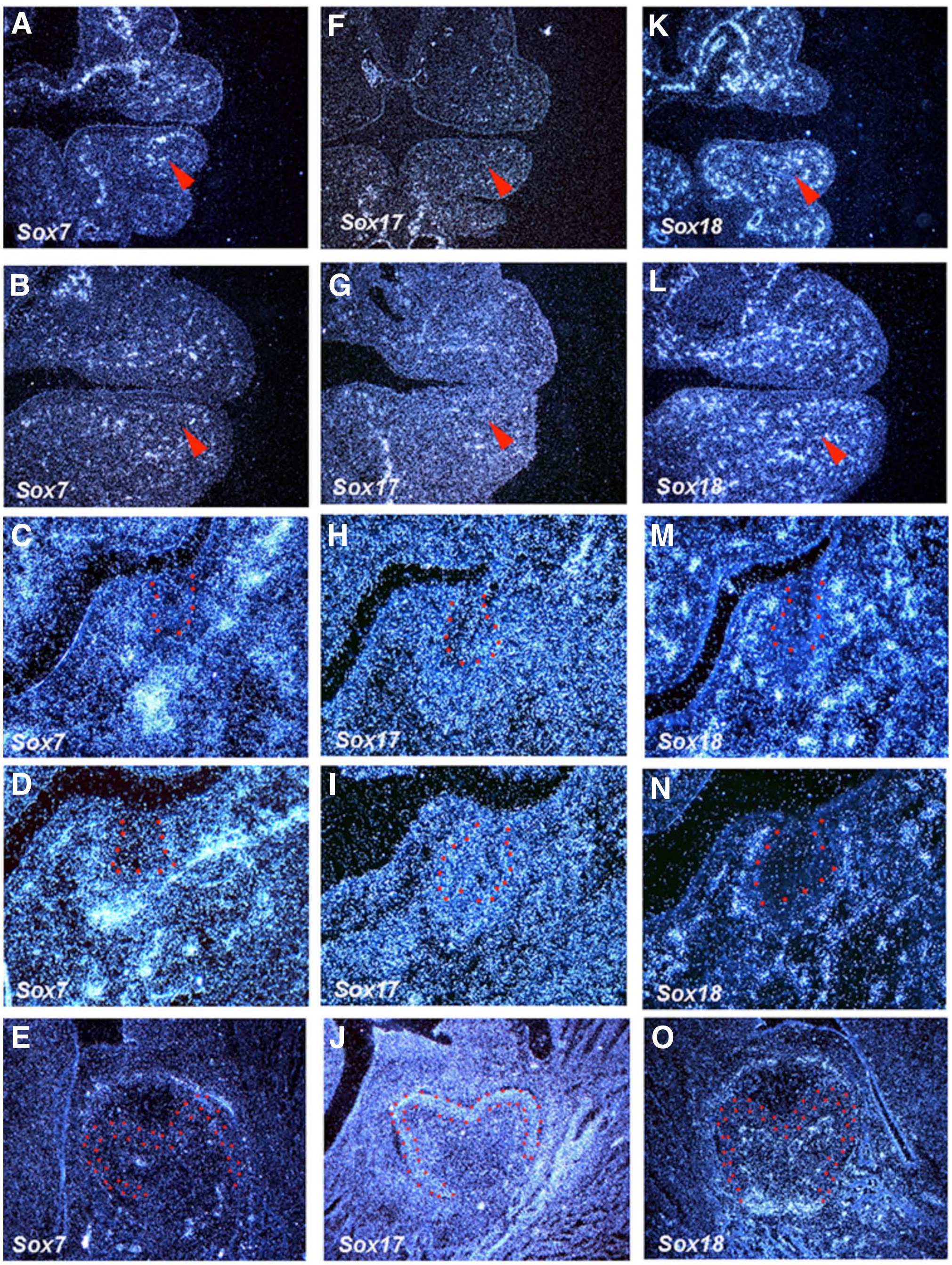

Fig. 5. The expression of *Sox* genes (Group F) in rodent tooth development. *In situ hybridisation of* Sox7, Sox17 *and* Sox18 *on frontal head sections at E10.5, E11.5, E13.5, E14.5 and E18.5. Tooth epithelium is outlined in red. Arrowheads indicate the presumptive tooth region.*

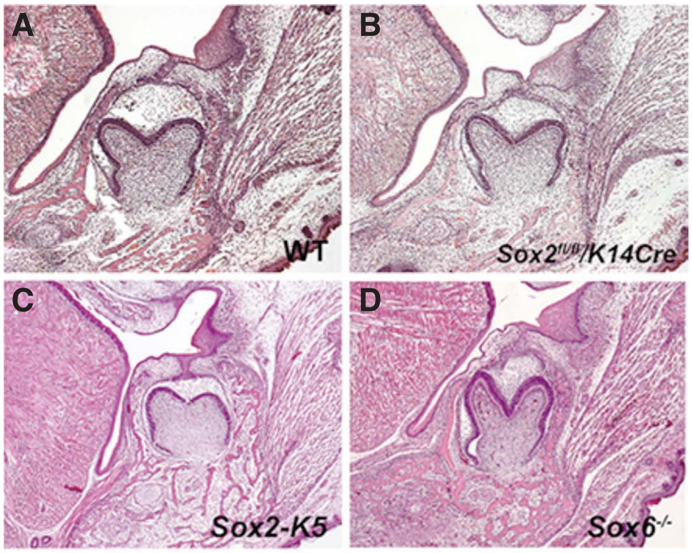

Fig. 6. Molar tooth phenotypes in *Sox2fl/fl;K14Cre, Krt5-Cre;Rosa26Sox2/+* and *Sox6* mutant mice. *Frontal sections showing the first lower molars of WT* **(A)**, Sox2fl/fl;K14Cre **(B)**, Krt5Cre;Rosa26Sox2/+ **(C)** *and* Sox6 **(D)** *mice at E18.5.*

molar tooth development (Ito 2010).

Oligodontia have been shown in patients with *Sox5* haploinsufficiency (Lamb *et al*., 2012). We found that the expression of *Sox5* was observed in tooth mesenchyme at early stages of tooth development. Although the first tooth inductive signals are known to be derived from tooth epithelium at E9.5 and E10.5, mesenchymal cells provide signals back to the tooth epithelium at E11.5 (Ferguson et. al., 2000). *Sox5* has been shown to be associated with Bmp and Shh signaling (Chimal-Monroy *et al*., 2003, Hojo *et al*., 2013). Both signaling pathways are known to be activated in tooth mesenchyme at early stages, and are essential for tooth development (Yang *et al*., 2014, Hardcastle *et al*., 1998, Li *et al*., 2011, Jeong *et al*., 2004). *Sox5* might play a critical role in initiation of tooth development by regulating these signaling pathways.

The primary enamel knot is known to play a role in regulating tooth shape. Expression of many molecules including Shh have been identified in the primary enamel knots (Tucker and Sharpe, 2004). Our results showed the expression of *Sox13* in the primary enamel knots, and *Sox13* has been shown to be involved in Shh signaling (Katoh and Katoh 2008). It is possible that *Sox13* regulate tooth shape through involving Shh.

Sox18 mutations has been shown to result in the extensive detachment of developing oral epithelium from the underlying mesenchymal tissue due to abnormal hemidesmosome formation (Oommen *et al*., 2012). Abnormal teeth including enamel hypoplasia and extensive dental caries have been described in blistering diseases such as epidermolysis bullosa that is caused by disorder of hemidesmosomes (Kirkham *et al*., 2000, Wright *et al*., 1993). It is known that the interaction between odontoblasts, ameloblasts, and basement membrane play a critical role in enamel/dentin formation (Tucker and Sharpe 2004, Fukumoto *et al*., 2005). We found *Sox18* expression in odontoblasts. It is possible that *Sox18* is involved in enamel/dentin formation.

Materials and Methods

Production and analysis of transgenic mice

The production of mice with mutation of *Sox6* (*p100H*) have previously been described (Hagiwara *et al*., 2000). *Krt5-Cre;Rosa26loxp-STOP-loxp-Sox2-IRES-eGFP* (*Krt5Cre;Rosa26Sox2/+*), *Keratin(K)14Cre* and *Sox2fl/fl* mice were bred as described by Liu *et al.,*2013), Andl *et al.,* (2004) and Teranova *et al.,*2006), respectively. CD1 mice were used for radioactive *in situ* hybridization. The day on which vaginal plugs were found was considered as embryonic day (E) 0.5. To accurately assess the age of embryos, somite pairs were counted and the stage confirmed using morphological criteria such as relative size of maxillary and mandibular primordia, extent of nasal placode invagination, and the size of limb buds. Mouse heads were fixed in 4% paraformaldehyde, embedded and serially sectioned at 8 μm. Sections were split over 4-10 slides and prepared for histology and radioactive *in situ* hybridisation. Decalcification using 0.5M EDTA was performed after fixation of E18.5 mice.

In situ hybridization

Radioactive *in situ* hybridization with ^{35}S-UTP-radiolabelled riboprobes was performed as described previously by Ohazama *et al*., 2008.

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Yan Zhang, Seong-Oh Kim, Sibylle Opsahl-Vital, Sunita P. Ho, Jean-Baptiste Souron, Charles Kim, Kurt Giles and Pamela K. Den Besten
Int. J. Dev. Biol. (2011) 55: 953-960
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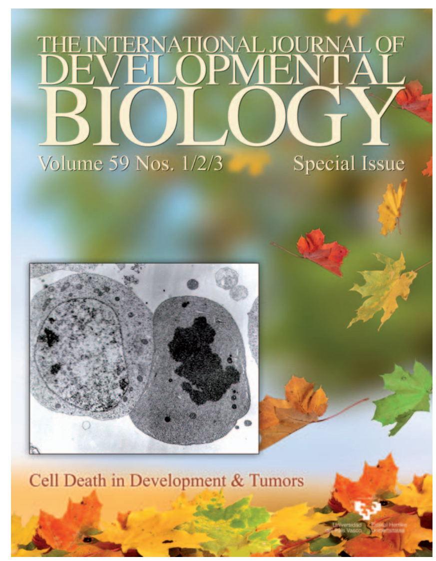

5 yr ISI Impact Factor (2013) = 2.879