**Name of journal: *World Journal of Medical Genetics***

**ESPS Manuscript NO: 11618**

**Columns: REVIEW**

**Role of SOX2 in foregut development in relation to congenital abnormalities**

Schilder K *et al.* SOX2 and congenital foregut abnormalities

Kim Schilder, Joshua K Ochieng, Cornelis P van de Ven, Cristina Gontan, Dick Tibboel, Robbert J Rottier

**Kim Schilder, Joshua K Ochieng, Cornelis P van de Ven, Cristina Gontan, Dick Tibboel, Robbert J Rottier,** Departments of Pediatric Surgery of The Erasmus MC-Sophia Children’s Hospital, 3000 CA, Rotterdam, The Netherlands

**Cristina Gontan,** The Department of Reproduction and Development of the Erasmus MC, 3015 CN, Rotterdam, The Netherlands

**Robbert J Rottier,** Cell Biology of the Erasmus MC, 3000 CA, Rotterdam, The Netherlands

**Author contributions:** Schilders K, Ochieng JK, Gontan C and Rottier RJ wrote the first draft of the manuscript; van de Ven CP and Tibboel D added all patient information; Schilders K, Tibboel D andRottier RJ provided critical input and comments; all authors edited the manuscript.

**Correspondence to: Robbert J Rottier, PhD,** Departments of Pediatric Surgery of The Erasmus MC-Sophia Children’s Hospital, PO Box 2040, 3000 CA, Rotterdam, The Netherlands. r.rottier@erasmusmc.nl

**Telephone:** +31-10-7044140 **Fax:** +31-10-7044468

**Received:** May 28, 2014 **Revised:** July 14, 2014

**Accepted:** September 04, 2014

**Published online:**

**Abstract**

The uptake of the two essential ingredients for life, oxygen and nutrients, occurs primarily through the oral cavity, but these two lifelines need to be separated with high accuracy once inside the body. The two systems, the gas exchange pulmonary system and the gastro-intestinal feeding system, are derived from the same primitive embryonic structure during development, the foregut, which need to be separated before birth. In certain newborns, this separation occurs not or insufficiently, leading to life threatening conditions, sometimes incompatible with life. The development of the foregut, trachea and lungs is influenced and coordinated by a multitude of signaling cascades and transcription factors. In this review, we will highlight the development of the foregut and pulmonary system and focus on associated congenital abnormalities in light of known genetic alterations with specific attention to the transcription factor Sox2.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** SOX2; Congenital foregut abnormalities; Lung development

**Core tip:** Foregut abnormalities are complicated congenital diseases which still lack knowledge of the origin. This review highlights foregut development and associated abnormalities, specifically focussing on the transcription factor SOX2.

Schilder K, Ochieng JK, van de Ven CP, Gontan C, Tibboel D, Rottier RJ. Role of SOX2 in foregut development in relation to congenital abnormalities. *World J Med Genet* 2014; In press

**FOREGUT DEVELOPMENT**

Gastrulation is the process that adds complexity to the developing organism and results in a triploblastic animal by formation of the three germ layers, ectoderm, mesoderm and endoderm. At embryonic day 8 (E8.0) in mice (comparative to 3 wk in human), the sheet of endodermal cells starts to invaginates ventrally at the anterior and posterior intestinal portals, which subsequently migrate towards each other to form the primitive gut from the future mouth to anus[[1](#_ENREF_1)]. At E9.0, the notochord delaminates from the dorsal endoderm and will eventually be situated between the primitive gut and the neural tube. The notochord serves in this phase of development as a strong signaling center, secreting morphogens like Sonic hedgehog (Shh) to pattern the endoderm as well as the neural tube[[2](#_ENREF_2)]. Another signaling center associated with the early patterning and morphogenesis of the foregut is the heart mesoderm, which secretes Fibroblast growth factors (Fgf). High levels of Fgf signals activate lung specific genes while lower levels of Fgf activate liver specific genes[[3](#_ENREF_3)]. The prospective lung field, the area which will eventually lead to the emergence of the primitive lung bud, is subsequently patterned by retinoic acid (RA) signaling. The RA receptor RARα is required to maintain RA signaling and to assist the effects of RARβ, which induces the expression of Fgf10. RA signaling integrates the Wnt and Tgfβ pathways by inhibiting the expression of the Wnt antagonist Dickkopf-1 (Dkk1) and by preventing the expression of Transforming growth factor beta (Tgfβ)[[4](#_ENREF_4),[5](#_ENREF_5)]. Overall, the foregut is regionalized as shown by the various dorsal-ventral gradients of morphogens and subsequent transcription factors. This pattern of expression is essential for proper development of the trachea, esophagus and lungs, and disturbances in these patterns result in various trachea-lung defects (see below).

***Lung development***

The lung primordium arises from the ventral foregut as a primary bud, just anterior to the developing stomach around embryonic day 9.5 in mice or week 4 in humans[[6](#_ENREF_6),[7](#_ENREF_7)]. The lung bud splits in two buds, the future left and right bronchus, elongates and the proximal part separates into oesophagus and trachea, while distally the bronchial tree is formed through a process called branching morphogenesis[[6](#_ENREF_6)].

Development of the lung can be divided into five distinct, but overlapping phases based on morphology (Table 1)[[8](#_ENREF_8)]. During the earliest phase, the embryonic phase, the lung buds are formed from the primitive foregut, the mayor bronchi are formed and the tracheal-esophageal tube is dividing. Several signaling cascades direct the early embryonic morphogenetic events and cell fate decisions including Tgf-β, Bone Morphogenetic Proteins (BMPs), Shh, Wnt, and Fgf families, which will be discussed in more detail[[9](#_ENREF_9),[10](#_ENREF_10)]. As development of the lung advances, the embryonic endoderm undergoes progressive fate decisions that generate epithelial progenitor cells with increasingly restricted developmental potential over time. The next phase, the pseudoglandular phase is characterized by the commencement of differentiation of epithelial cells. Also, the bronchial tree and all terminal bronchioles are formed. The pseudoglandular phase is followed by the canalicular phase and the saccular stage[[6](#_ENREF_6)]. During the canalicular phase, the conducting airways are completed and the respiratory portions of the lung as well as the capillary bed are formed, while during the saccular phase the terminal tubes narrow, giving rise to small saccules and the endoderm begins to differentiate into specialized alveolar type I and type II cells[[6](#_ENREF_6)]. The last phase, the alveolar phase, is characterized by the establishment of secondary septa resulting into alveolar formation, which mainly takes places after birth[[8](#_ENREF_8),[11](#_ENREF_11)].

***Regulation of foregut and lung development***

The morphogenesis of the foregut and lung is subsequently regulated by a myriad of transcription factors and signaling cascades. The molecular and cellular events contributing to lung development and the separation of the trachea and esophagus have been extensively described in recent reviews[[6](#_ENREF_6),[10](#_ENREF_10),[12](#_ENREF_12)]. Regionalization of the different parts of the gut is controlled by the localized expression of *Homeobox* (Hox) genes[[13](#_ENREF_13)]. Hoxa3 and Hoxb4 are expressed in the foregut endoderm, whereas Hoxc5 and Hoxa13 are expressed in the midgut and hindgut endoderm, respectively[[13](#_ENREF_13),[14](#_ENREF_14)]. During tracheal-eosophageal development, Shh is specifically and dynamically expressed during the patterning of the ventral foregut whereas its expression is transiently expressed in the tracheal endoderm[[15](#_ENREF_15)]. During the early stages of branching morphogenesis, Shh is expressed in the epithelium, with the highest levels of expression in the tips. Later, there is downregulation of Shh in the proximal parts of the airways while distally the expression sustains[[16](#_ENREF_16)].

**SOX GENES AND FOREGUT DEVELOPMENT**

Transcription factors that show specific expression profiles in the endoderm, include members of the SRY-related High-Mobility Group (HMG) transcription factors[[17](#_ENREF_17),[18](#_ENREF_18)]. The Sry gene (Sex-determining region on the Y chromosome), was the first identified member of the Sox family of transcription factors[[19](#_ENREF_19),[20](#_ENREF_20)]. Sox family members are highly conserved across species and they were originally identified by homology, as they contain an HMG box closely related to that of the Sry gene[[21](#_ENREF_21)]. Therefore, Sry gave the Sox gene family its name; Sry-related HMG box, hence “Sox”, followed by a number corresponding to the order of discovery[[19](#_ENREF_19)]. Sox proteins have properties of both classical transcription factors and architectural proteins[[22](#_ENREF_22)]. They function as classical transcription factors, either activating or repressing specific target genes through interaction with different partner proteins.

All Sox factors bind DNA via their HMG domain and recognize the same consensus motif 5’-(A/T)(A/T)CAA(A/T)G-3’[[23](#_ENREF_23)]. The transcriptional function of Sox proteins dependent on the cell type and the promoter context, and they often have functional redundancy among each other[[22](#_ENREF_22)]. In contrast to other transcription factors which mainly target the major groove, Sox proteins interact with the minor groove of the DNA helix and, as a consequence, induce a sharp bend in the DNA[[22](#_ENREF_22)]. The DNA bending capacity of Sox proteins can be functionally important for several reasons. It may bring different regulatory regions of the target gene into close proximity. Thereby, it facilitates the formation of enhanceosomes, *i.e.,* functionally active complexes of transcription factors on different gene enhancer sequences[[24](#_ENREF_24)]. It also allows the interaction of distant enhancer nucleoprotein complexes with the basal transcription machinery[[25](#_ENREF_25),[26](#_ENREF_26)]. The local changes in chromatin structure induced by Sox proteins may facilitate the recruitment of higher-order architectural factors (like polycomb or trithorax protein groups)[[27](#_ENREF_27)]. Bending of DNA by Sox proteins could also act in a negative way by preventing the binding of other factors to adjacent sites in the major groove[[27](#_ENREF_27)].

Sox proteins have been identified in all animal species (birds, reptiles, amphibians, fish, insects, and nematodes)[[28](#_ENREF_28)] and mutations in several of the *SOX* genes have been implicated in the pathogenesis of human congenital anomalies and syndromes (Table 2).

*Sox* genes are expressed in diverse and dynamic patterns during embryogenesis. During development members of the Sox family are expressed in almost every tissue of the embryo, and also in a number of adult tissues[[29](#_ENREF_29),[30](#_ENREF_30)].The expression of a specific Sox transcription factor is not necessarily restricted to a particular cell type or lineage. Their expression pattern during development appears to correlate with early cell fate decisions. For example, Sry is expressed in the undifferentiated male gonad and is quickly down regulated once the decision is made to initiate male development[[31-33](#_ENREF_31)].

To date, four members from the Soxgene family are known to be involved in lung organogenesis, Sox2, Sox9, Sox11 and Sox17[[8](#_ENREF_8),[34-39](#_ENREF_34)]. *Sox9* was found throughout lung morphogenesis as a downstream gene of Shh and modulated by Bmp4 and Noggin. Using epithelial specific gain and loss function mouse models, Sox9 has been shown to play a crucial role in branching morphogenesis through controlling a balance between proliferation and differentiation[[40](#_ENREF_40)]. In another study, knock out of Sox9 in the mesenchyme demonstrated that it plays a crucial role in differentiation of the lung tracheal epithelium[[41](#_ENREF_41)]. Sox9 is required for formation and patterning of tracheal cartilage by a mechanism mediated by Fgf18[[42](#_ENREF_42),[43](#_ENREF_43)]. Sox9 promotes proper branching morphogenesis by controlling the balance between proliferation and differentiation and regulating the extracellular matrix and can be used as a marker for the distal epithelium[[40](#_ENREF_40)]. *Sox11* has been suggested to be involved in development and plays a key function in tissue remodeling, including the lung[[35](#_ENREF_35)]. Sox11 deficient mice die immediately after birth because of significant lung hypoplasia and other tissue defects[[35](#_ENREF_35)]. *Sox17* was shown to be crucial early after gastrulation for the formation of definitive endoderm, which gives rise to the lung, liver, pancreas, stomach, and gastrointestinal tract[[44](#_ENREF_44)]. In the lung, Sox17 is expressed in the respiratory epithelial cells at embryonic day 18 in mice and becomes primarily restricted to ciliated cell in the postnatal and adult lung[[36](#_ENREF_36)]. Ectopic expression of Sox17 in lung epithelial cells inhibits peripheral epithelial cell differentiation and results in the activation of the cell cycle and the initiation of progenitor-like cell behavior in mature lung cells[[36](#_ENREF_36)]. Sox17 has been shown to impair the expression of Tgfβ1 responsive inhibitors, p15, p21 and p57, while inhibiting TGF-beta1 and Smad3 transcriptional activity[[36](#_ENREF_36)].

***Sox2***

The mouse *Sox2* gene has been mapped to chromosome 3[[45](#_ENREF_45)]. Sox2 plays crucial roles during different stages of vertebrate embryonic development and its expression is temporally and spatially regulated[[46](#_ENREF_46)]. Sox2 expression starts at the morula-stage of embryo development. In blastocysts it is specifically detected within the cells of the inner cell mass (ICM). Expression continues in the epiblast, the tissue that will give rise to the embryo and germ cells[[47](#_ENREF_47)]. Sox2 is also expressed in embryonic stem cells (ES cells), which are derived from the ICM. During early gastrulation, Sox2 expression in the embryo is restricted to the anterior ectoderm, which gives rise to neuroectoderm and anterior surface ectoderm, while the extraembryonic expression becomes confined to the chorion[[48](#_ENREF_48),[49](#_ENREF_49)]. At later stages of embryonic development, Sox2 is expressed in the brain, neural tube, eyes, sensory placodes, branchial arches, gut endoderm, and the germ cells[[47](#_ENREF_47),[50-55](#_ENREF_50)]. When the arches develop, Sox2 continues to be expressed in the primitive foregut endoderm. Later, Sox2 is present in the epithelium of foregut-derived organs, includingthe tongue, esophagus, trachea, proximal lung and stomach[[39](#_ENREF_39),[47](#_ENREF_47),[50](#_ENREF_50),[56](#_ENREF_56),[57](#_ENREF_57)].

The lack of *Sox2* expression in mice results in early embryonic lethality[[47](#_ENREF_47)]. *Sox2* null mutant mouse embryos implant but fail to develop an egg cylinder or epiblast, and they die before gastrulation becauseSox2 is required in the ICM of the blastocyst[[47](#_ENREF_47)]. Other mutations that only affect *Sox2* regulatory elements can cause deafness, defects in the inner ear, circling behavior, and a yellow coat color[[45](#_ENREF_45)]. The use of two *Sox2* hypomorphic mutants showed a dose-dependent roleof Sox2 in the development of the retina and the differentiation of the foregut endoderm[[54](#_ENREF_54),[58](#_ENREF_58)]. Heterozygous mutations in *SOX2* have been associated in human with severe structural malformations of the eye, bilateral anophthalmia (absent eye) and microphthalmia (small eye), and anophthalmia-esophageal-genital (AEG) syndrome[[57](#_ENREF_57)]. In AEG infants the esophagus and trachea fail to separatenormally and the trachea is connected to the stomach by an abnormaldistal esophagus[[57](#_ENREF_57),[59](#_ENREF_59),[60](#_ENREF_60)]. These symptoms underwrite the developmental functions for Sox2, as found in Sox2 hypomorphic mice described above.

**Sox2 in foregut and lung development:** Sox2 is expressed throughout the early foregut epithelium, but becomes restricted to the dorsal epithelial cells at embryonic day 9.5, whereas Nkx2.1 is reciprocally expressed in the ventral epithelium[[58](#_ENREF_58),[61](#_ENREF_61)]. Sox2 is expressed in the epithelial cells of the foregut at E9.5. From E11.5 until E14.5, Sox2 is exclusively expressed in the epithelial cells of the non-branching developing airways and it remains expressed in the epithelial cells of the conducting airways after birth. So Sox2 is exclusively expressed at the non-branching airways[[39](#_ENREF_39)].

Previously, it was shown that ectopic expression of Sox2 in epithelial cells of the lung result in abnormal alveolar formation, enlarged airspaces and a decrease in the number of airways, indicating that Sox2 modulates branching morphogenesis. Also, an increased number of neuroepithelial cells and (pre-) basal cells was observed. This indicates that Sox2 is important in cell fate choice and epithelial differentiation[[39](#_ENREF_39)]. More recently it was shown that Sox2 regulates the emergence of lung basal cells by directly activating the transcription of the basal cell master gene Trp63, and the emergence of bronchioalveolar stem cells[[62](#_ENREF_62)].

The proper dorsal-ventral patterning of Sox2 and Nkx2.1 is critical for foregut morphogenesis. Down-regulation of Sox2 leads to the formation of esophageal atresia/tracheoesophageal fistula (EA/TEF) in Sox2 hypomorphic mutants[[58](#_ENREF_58)], whereas deletion of Nkx2.1 leads to defects in foregut separation and the formation of EA/TEF associated with high Sox2 expression in the epithelium[[58](#_ENREF_58),[63](#_ENREF_63)]. Similarly, the epithelial cells in the fistula of Sox2 hypomorphic mutants express high levels of Nkx2.1 suggesting that low level of Sox2 is required for Nkx2.1 expression to expand dorsally and reprogram the dorsal epithelium to a respiratory fate[[58](#_ENREF_58)]. These findings suggested that the dorsal-ventral arrangement of Sox2 and Nkx2.1 is essential for foregut separation and the subsequent differentiation of epithelial progenitor cells into oesophageal and tracheal epithelium and lung buds[[12](#_ENREF_12)].

Using Chromatin Immuno Precipitation (ChIP) it was shown that SOX2 directly binds to the promoter region of the *NKX2.1* gene in human embryonic stem cells and this binding resulted in the inhibiton of NKX2.1 transcription[[64](#_ENREF_64)]. Other interesting SOX2 target genes that are involved in early lung morphogenesis are members of the Notch (JAG1) pathway and Shh pathway (GLI2, GLI3)[[65](#_ENREF_65)]. Since the activity of Sox2 depends on its interaction with other proteins it is of high importance to reveal its interacting partners. Recently some of these partners were identified in embryonic and neural stem cells[[65](#_ENREF_65),[66](#_ENREF_66)]. One of the partners identified is Chromodomain-Helicase-DNA-Binding Protein7 (CHD7), which plays a major role in CHARGE syndrome. As mentioned before, SOX2 plays a role in AEG syndrome which shows many similarities with CHARGE syndrome. SOX2 and CHD7 also regulate common target genes, like *MYCN*, *JAG1* and *GLI2/3*. These genes are involved in syndromes that are characterized by the same malformations as AEG and CHARGE syndromes. Gene networks like this *SOX2-CHD7*-regulated network can be used to better understand the molecular basis of various human diseases and therefore associating partners in the lung epithelium could help us to reveal the mechanisms underlying lung-related abnormalities[[65](#_ENREF_65)].

**FGF SIGNALING**

Another study using *in vitro* organ cultures demonstrated that Fgf10 signaling inhibits Sox2 expression in the mouse foregut[[58](#_ENREF_58)]. Mesenchymal expression of Fgf10 around the distal ends of the lung epithelium functions as a chemoattractant by binding to the epithelial expressed Fgf receptor 2b (Fgfr2b) leading to branching and outgrowth of the epithelium[[67](#_ENREF_67),[68](#_ENREF_68)]. The functional interaction between Fgf10 and Fgfr2b was shown by the high similarity between the Fgf10-null and Fgfr2b-null mouse mutants[[3](#_ENREF_3),[69](#_ENREF_69)]. Fgf10 knockout mice developed normal trachea, but completely lacked lung structures[[69](#_ENREF_69),[70](#_ENREF_70)], whereas targeted deletion of Fgfr2b prevented branching, causing the trachea to terminate as a blind-ended sac[[71](#_ENREF_71)]. Conditional gene inactivation studies further demonstrate that both Fgf10and Fgfr2b are required for a normal branching program and proper proximal–distal patterning of the lung[[72](#_ENREF_72)]. Recently, it was shown that ubiquitous overexpression of Fgf10 throughout the lung could rescue lung agenesis in Fgf10 knockout mice, suggesting that precise localization of Fgf10 expression is not required for lung branching morphogenesis. Rather, Fgf10 signaling prevents cells from expressing Sox2 by the activation of β-catenin. As the lung bud grows, the cells become more distant from the Fgf10 source and start to adopt a more proximal cell fate expressing Sox2. When Sox2 is ectopically expressed in the distal epithelial cells of the developing airways, these cells are no longer responsive to Fgf10 and differentiate into proximal cells, which results in reduced branching and formation of cyst-like structures[[39](#_ENREF_39),[62](#_ENREF_62)].

**WNT SIGNALLING**

Receptor tyrosine kinases (RTKs), like the Fgfr, are able to activate Wnt/β-catenin through the Erk/MAPK mediated phosphorylation of the Wnt co-receptor Lrp6 on Ser1490 and Thr1572, leading to an increased cellular response to Wnt. Moreover, RTKs directly phosphorylate β-catenin on the Tyr142 residue, which causes its release from membrane bound cadherin complexes[[73](#_ENREF_73)]. In turn, Fgfr2b expression is induced by activation of epithelial β-catenin activation, which results in an increase of Fgf10 signaling[[74](#_ENREF_74)]. This regulation of distal epithelial progenitors by β-catenin suggests the progressive signaling cascade where Fgf10 regulates branching morphogenesis via Wnt signaling. Epithelial specific expression of Wntless (Wls), a cargo receptor protein important for directing Wnt ligands, has recently been shown to be important for lung differentiation and vasculature development probably by modulating the secretion of Wnt ligands[[75](#_ENREF_75)].

At embryonic day 9.5, Wnt signaling is active in the ventral side of the unseparated foregut tube, where the Wnt ligands Wnt2 and Wnt2b are highly expressed[[61](#_ENREF_61),[76](#_ENREF_76)]. Wnt2 and Wnt2b are secreted by mesenchymal cells of the ventral foregut and signal through the canonical β-catenin pathway to specify lung progenitors in the foregut endoderm[[61](#_ENREF_61),[76](#_ENREF_76)]. Conditional inactivation of β-catenin in the foregut endoderm results in the absence of both trachea and lung, whereas expression of a constitutively active β-catenin mutant results in the expansion of the earliest respiratory marker, Nkx2.1, and a loss of the Sox2 positive domain[[61](#_ENREF_61)]. Later in development, Wnt/β-catenin signaling is required for proper proximal-distal patterning of the lung[[74](#_ENREF_74)]. Wnt7b is expressed in the endoderm of the early foregut and its deletion does not disrupt foregut separation, but results in irregular lung branching morphogenesis and vasculature development[[77](#_ENREF_77)]. Mesenchymal Wnt2 and epithelial Wnt7b cooperate with Pdgf signaling to promote mesenchymal differentiation[[78](#_ENREF_78)].

Respiratory endodermal specific expression of a constitutive active β-catenin isoform showed that canonical Wnt signaling is not required for the development of alveolar epithelium[[79](#_ENREF_79),[80](#_ENREF_80)]. However, the formation of proximal epithelium was impaired, because ectopic Wnt signaling induced the expression of Tcf1 and Lef1 at the expense of Sox2 and Trp63[[79](#_ENREF_79)]. On the other hand, conditional deletion of β-catenin in respiratory epithelium resulted in the loss of alveolar structures. Selective loss of bronchiolar lineages with continued proliferation may result in cystic lesions of the lung resembling an anomaly known in humans as CPAM[[80](#_ENREF_80)].

Ectopic expression of Wnt5a in the respiratory epithelium resulted in increased Fgf10 expresison and a reduction in epithelial Shh expression[[81](#_ENREF_81)]. The precise dose and timing of Fgf and Wnt signaling lead to the induction of Shh expression in the respiratory epithelium[[3](#_ENREF_3),[76](#_ENREF_76)]. The paracrine effect of Shh on the surrounding mesenchyme results in the Foxf1 and Gli1/Gli3 mediated expression of Bmp4.

**BMP SIGNALING**

Bmp signaling plays prominent roles in foregut separation and lung development, however the molecular mechanisms controlling temporal-spatial Bmp signaling dynamics in foregut organogenesis are poorly understood[[82](#_ENREF_82)]. In the unseparated foregut tube, Bmp4 is expressed in the ventral mesenchyme, while Bmp7 and the Bmp antagonist Noggin are enriched in the dorsal endoderm[[83](#_ENREF_83)]. Ablation of Noggin resulted in increased Bmp signaling in the foregut and the formation of EA/TEF[[84](#_ENREF_84)]. These embryos showed abnormal delamination of the notochord from the early definite endoderm epithelial sheet, resulting in epithelial cells of endodermal origin being present in the notochord[[84](#_ENREF_84)]. Subsequent deletion of either Bmp4 or Bmp7 in these Noggin null mice rescued the separation defects[[83](#_ENREF_83),[84](#_ENREF_84)]. Recently, it was shown that Noggin is required to attenuate Bmp signaling in order to allow the notochord to delaminate form the dorsal foregut endoderm[[85](#_ENREF_85)]. Tissue specific ablation of Bmp4 in the early foregut endoderm resulted in tracheal agenesis accompanied by reduced cellular proliferation in the epithelial and mesenchymal compartments. However, the trachea does not separate from the foregut and Nkx2.1 expression is conserved in the ventral endodermal epithelium, suggesting that Bmp4-mediated signaling is essential for separation but not for the initial specification of the tracheal epithelium[[86](#_ENREF_86)]. Similarly, conditional inactivation of Bmpr1a and Bmpr1b in the foregut leads to tracheal agenesis, a decrease of Nkx2.1 expression and a ventral expansion of Sox2 and Trp63 expression. Subsequent activation of Wnt signaling did not promote respiratory differentiation. Deletion of Sox2 in the Bmpr1a/b deficient mouse rescued the foregut separation defect, showing that Sox2 is downstream of Bmp signaling[[87](#_ENREF_87)]. Ectopic expression of Sox2 in the distal lung buds showed that Fgf-Erk signaling was abrogated at the expense of Bmp-Smad signaling[[39](#_ENREF_39)].

**RELATIONSHIP BETWEEN SOX 2 AND CONGENITAL DEFECTS OF THE FOREGUT**

Congenital malformations of the lung constitute a spectrum of lesions that originate during the embryonic period. Incidences of congenital defects of the foregut are in the range of 1:11.000-35.000 pregnancies (WHO). Patients present a broad range of clinical manifestations ranging from intra uterine death to significant illnesses at birth with a variable severity of respiratory symptoms and later on distress and repeated chest infections. However a number, although impressive at repeated prenatal ultrasound or MRI may remain asymptomatic for long periods and significantly regress in the course of pregnancy. Congenital defects of the foregut occur either in isolated cases or as part of a complex syndrome[[88](#_ENREF_88)]. The causes of most of these malformations as well as their molecular genetic background are still unknown. Different types of congenital lung malformations can be distinguished, which will be briefly discussed.

***Congenital pulmonary and airway malformations***

Congenital pulmonary and airway malformations (CPAM) constitute a spectrum of lesions that originate during the embryonic period. The prevalence of congenital lung malformations has seemingly increased over the last decade probably due to better antenatal ultrasound screening and is estimated at 1 in 3000 pregnancies[[89](#_ENREF_89)]. Although most newborns with antenatally diagnosed congenital lung malformations are asymptomatic at birth, approximately 10% show respiratory insufficiency. Secondary infections of these lesions occur in approximately 5% of unoperated children.

The different types of congenital pulmonary and airway malformations are classified in bronchopulmonary malformations, pulmonary hyperplasia, congenital lobar overinflation and other cystic lesions[[90](#_ENREF_90)].

**Bronchogenic cyst:** A bronchogenic cyst is often a solitary cyst in the mediastinum or in the lung parenchyma filled with fluid. Their structural lining resembles that of the bronchus, cartilage and bronchial-type glands included. Symptoms at birth are mostly due to compression of surrounding structures, especially bronchial structures resulting in hyperinflation of lung parenchyma distal to the obstruction. Symptoms at later age are mainly due to infection. Etiology is probably similar to other duplication cysts as aberrant bud formation from the foregut structures. The molecular biology has not been studied so far.

**Bronchial atresia:** Bronchial atresia, mostly asymptomatic often results in overinflation of a lobe, segment or even smaller part of the lung depending on the level of bronchus being atretic. Symptoms are rare. Etiology is unknown and may be similar to the reasons of bronchial blockage in congenital lobar overinflation.

**Cystic adenomatoid malformation Stocker type 1 and type 2:** Although CCAM pathogenesis is unknown, several authors have hypothesized that different types of CCAM originate at different stages of lung development. Abnormal airway development during branching morphogenesis probably results in specific areas of the lung where terminal bronchioles overgrow and alveolar formations are absent[[88](#_ENREF_88)]. Another hypothesis postulates that CCAM originate as a result of imbalance between cell proliferation and apoptosis during airway branching[[62](#_ENREF_62),[91](#_ENREF_91),[92](#_ENREF_92)]. Type 1 CCAM consists of a few large cysts with bronchiolar configuration and a lining of respiratory epithelium overlying fibroelastic tissue and small amounts of smooth muscles. It may have a systemic arterial supply. Type 2 CCAM are multicystic lesions (cysts < 2 cm) often localized in one lobe, although multiple lobes can be affected.

Aberrant expression of genes involved in lung development has been shown to result in CCAM-like phenotypes. Transiently induced overexpression of Sox2[[39](#_ENREF_39),[62](#_ENREF_62)], Fgf10[[93](#_ENREF_93)], orthotopic overexpression of Fgf 9 and heterotopic overexpression of Fgf7 show perturbations of lung morphogenesis some mimicking CCAM type 1 and 2 depending on the time of overexpression.

In human resection specimens increased levels of the transcription factors HOXB5, TTF1, FGF9[[94](#_ENREF_94),[95](#_ENREF_95)] as well as changed expression patterns of the adhesion molecules α-2 integrins and E-cadherin, increased levels of Clara cell marker CC-10 and reduced expression of Fatty acid binding protein-7 have been described[[96](#_ENREF_96)]. Moreover, microarray data revealed a 6 fold up-regulation of SOX2 in CCAM tissue compared with controls[[96](#_ENREF_96)]. These findings correspond with recently published data, describing the generation of CCAM–like phenotype by overexpressing Sox2 in mouse. In a comparative study, expression of SOX2 in human CCAM tissue was identified[[62](#_ENREF_62)]. Different etiology for type 1 and type 2 may be supported by recent findings that SOX2 is expressed in epithelial lining of cystic lesions in CCAM type 2, but not in CCAM type 1. Moreover, TRP63 was co-expression in SOX2 positive cells, suggesting that the epithelium had proximal characteristics (Ochieng *et al*[62], 2014).

**Extralobar sequestration:** Extralobar sequestration (ELS) are characterized by normal, non-functioning lung tissue without connection with the bronchial tree and often receive blood supply from the systemic circulation. Mainly found in the left lower chest, these lesions can also be found in or below the diaphragm. In contrast to CCAM, associated anomalies like vertebral and chest wall deformities and congenital heart disease are described. In 5%-15% of patients with congenital diaphragmatic hernia an ELS is found at operation. Although often asymptomatic, antenatal diagnosis can be very helpful to detect congestive heart failure caused by the arteriovenous shunting through the anomalous systemic blood supply. Late symptoms are mainly infectious. One of the genes that is thought to be involved in the pathogenesis of this anomaly is the HOXB5 gene. It is previously shown that this gene is involved in airway branching[[97](#_ENREF_97),[98](#_ENREF_98)].

***Pulmonary hyperplasia and related lesions***

**Laryngeal atresia:** Laryngeal atresia causes congenital high airway obstruction syndrome (CHAOS) at birth in the absence of a tracheoesophageal fistula. Prenatally, a polyhydramnios, large lung volume and inverted diaphragm are associated with fetal hydrops. Survivors are only described in those patients who have a tracheoesophageal fistula or a pinpoint laryngeal connection to relieve pressure from the lungs. Still, these patients may suffer from tracheobronchomalacia and diaphragmatic dysfunction due to increased lung extension during pregnancy. CHAOS can be associated with Fraser syndrome[[99](#_ENREF_99)]. If a bigger tracheoesophageal connection exists, prenatal diagnosis is difficult and diagnosis is only made at birth due to severe dyspnea. As a cause of laryngeal atresia, failure of recanalization of the laryngeal membrane is described. No detailed molecular analysis of lungs of laryngeal atresia, either pre- or postnatally, has been reported.

**Solid or cystic adenomatoid malformation, Stocker type 3:** The type 3 lesion, which accounts for 5%-10% of cases, occurs almost exclusively in males, and is associated with maternal polyhydramnios in nearly 80% of the cases. These are large, non-cystic bulky lesions, compressing the adjacent lung and mediastinum. Microscopically, randomly scattered bronchiolar/alveolar duct-like structures are lined by low cuboidal epithelium and surrounded by “alveoli” also lined by cuboidal epithelium. The virtual absence of any small, medium, or large pulmonary arteries in this type of lesion is remarkable.

***Congenital Iobar overinflation***

Congenital Iobar overinflation, or Congenital lobar emphysema (CLE), is a rare lung malformation with an incidence ranging from 1:20000 births to 1:30000 births[[100-102](#_ENREF_100)]. CLE is characterised by distended alveoli distal to the terminal bronchiole with destruction of the lining of the lobes, in contrast to a polyalveolar lobe where the number of alveoli is increased. CLE usually affects the left upper or right middle lobe[[103](#_ENREF_103)]. Prenatal diagnosis can be made when a hyperechogenic lung is seen, but discrimination with CCAM and ELS is difficult at that point. Although respiratory failure can be present at birth due to compression of normal lung and displacement of the heart, many patients are asymptomatic. As a cause of CLE, a disruption of normal bronchopulmonary tree development is described with dysplastic cartilage, mucosal overgrowth, main stem bronchial atresia or external compression from abnormal cardiovascular structures. No specific genetic anomalies have been linked to this anomaly so far.

***Bochdalek type of Congenital diaphragmatic hernia***

Bochdalek type of Congenital diaphragmatic hernia (CDH) is characterized by a posterolateral defect mostly in the left diaphragm, which results in herniation of the abdominal organs into the chest[[104](#_ENREF_104),[105](#_ENREF_105)]. Subsequent pulmonary hypoplasia and pulmonary hypertension cause severe respiratory failure at birth. Lung hypoplasia is characterized by reduced alveolar air spaces lacking secondary septae, thickened alveolar walls and increased interstitial tissue. In the pulmonary vessels hyperplasia of the median and increased adventitial layer of the arterial wall is well described. The incidence of CDH is approximately one in 2500 births and the underlying cause of CDH is still unknown in a large number of patients.

Several links to gene loci have been found partly based on animal experiments[[106](#_ENREF_106)] and several members of the vitamin A-RA pathway have been implicated in the occurrence of CDH, such as vitamin A deficiency, STRA6 and RALDH2[[104](#_ENREF_104),[105](#_ENREF_105),[107](#_ENREF_107)]. Moreover, some genes that are downstream of this pathway, like COUP-TFII, FOG2, GATA4 and GATA6, have also been found to be associated with CDH (review, see[[107](#_ENREF_107),[108](#_ENREF_108)]. Recent exome sequencing identified a novel candidate gene, PIGN, aside from the known FOG2 involvement[[109](#_ENREF_109),[110](#_ENREF_110)].A direct link of CDH and SOX2 has not been described.

***Esophageal atresia***

Esophageal atresia with or without tracheaesophageal fistulas (TEF) has an incidence ranging between one in 2500 to one in 4500 births[[111](#_ENREF_111)]. In EA, the proximal esophagus is blunt-ended, while the distal part is connected to the trachea. This connection and the position of the atresia varies between patients and leads to the classification of five subtypes[[112](#_ENREF_112)]. In 85% of cases the esophageal atresia (EA) is accompanied by a distal tracheoesophageal fistula. Approximately half of the patients suffer from associated anomalies, as recently been reviewed[[113](#_ENREF_113)].

The genetics of EA/TEF is complex, and several studies have indicated putative factors associated with either the multifactorial syndromes, or with EA/TEF. Based on murine models of this anomaly, several candidate genes and pathways have been identified, such as the receptors of the RA pathway (RARα/RARβ), members of the SHH-PTC-GLI pathway (Shh, Gli2/3, Foxf1), BMP signaling (Noggin) and some transcription factors (Hoxc4, Ttf-1, Pcsk5, Tbx4, Sox2)[[113](#_ENREF_113)].

Some of these candidate genes seem to be associated with human EA/TEF, such as FOXF1, PCSK5, SHH, NOG and SOX2. Moreover, other human genes have been associated with EA/TEF as part of several syndromes, such as Feingold (MYCN), Opitz G (MID1), Fanconi anemia (FANCA/C/D/G) and CHARGE (CHD7). Recently, CHD7 was shown to directly associate with SOX2, thereby linking CHARGE syndrome with AEG[[65](#_ENREF_65)]. Moreover, it was shown that these two proteins activated the transcription of a number of genes that are implicated in related syndromes, like Shh, Gli2/3, Mycn.

***Alveolar capillary dysplasia***

Although alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a very rare condition without known incidence it has a dismal prognosis. The diagnosis is most likely underreported because it can only be made by histological examination of lung tissue. Newborn patients present with respiratory failure, hypoxemia, metabolic acidosis, pulmonary hypertension and right ventricular failure. Chest X-ray can be interpreted as normal but might show diffuse haziness or ground-glass opacities. Associated congenital anomalies may be present, especially of the genitourinary, gastrointestinal and cardiovascular system. Histologically, a decreased number of pulmonary capillaries is observed, distantly from the alveolar epithelium and thickened septae with a malposition of pulmonary veins close to pulmonary arteries. Often lymphangiectases are seen. Pulmonary arteries show medial hypertrophy with muscularization of distal arterioles. Although treatment response especially to therapy relieving pulmonary hypertension has been described, effects are transient. Late presenters and long-term survivors very rarely have been described and might be due to a lesser degree of histological changes.

Deletions in chromosomal region 16q24.1q24.2 have been described. The smallest region of overlap in these deletions contains the FOX transcription factor gene cluster, including FOXF1, FOXC2 and FOXL1. Findings in the mouse model with heterozygous deficiency of FOXF1 are similar to those in humans with ACD/MPV whereas mouse embryos with homozygous deficiency die at E9,5 due to pulmonary vascular abnormalities. A relationship with SOX2 never has been described[[114-116](#_ENREF_114)].

**CONCULUSION**

SOX2 has only been found to be associated with a limited number of specific subsets of congenital anomalies. Modulating the expression levels of Sox2 during trachea and lung development in mice have led to abnormalities which relate to human conditions, such as CPAM and EA/TEF[[39](#_ENREF_39),[58](#_ENREF_58),[62](#_ENREF_62)]. Interestingly, CHD7, which is linked to CHARGE syndrome, was recently shown to be a binding partner of SOX2[[65](#_ENREF_65)]. SOX2 is linked to AEG syndrome, which is clinically related to CHARGE syndrome. In fact, in some the diagnosis of AEG or CHARGE is hard to distinguish from each other[[57](#_ENREF_57),[58](#_ENREF_58)]. Thus, some of the congenital pulmonary abnormalities may be part of very complex syndromes, and it may be that the interactions between SOX2 and CHD7, or other proteins, may result in combinations of different clinical parameters. Therefore, mutations that change the interactions between SOX2 and other proteins, like CHD7, may result in the various clinical manifestations observed in syndromes.

**REFERENCES**

1 **Wells JM**, Melton DA. Vertebrate endoderm development. *Annu Rev Cell Dev Biol* 1999; **15**: 393-410 [PMID: 10611967 DOI: 10.1146/annurev.cellbio.15.1.393]

2 **Chamberlain CE**, Jeong J, Guo C, Allen BL, McMahon AP. Notochord-derived Shh concentrates in close association with the apically positioned basal body in neural target cells and forms a dynamic gradient during neural patterning. *Development* 2008; **135**: 1097-1106 [PMID: 18272593 DOI: 10.1242/dev.013086]

3 **Serls AE**, Doherty S, Parvatiyar P, Wells JM, Deutsch GH. Different thresholds of fibroblast growth factors pattern the ventral foregut into liver and lung. *Development* 2005; **132**: 35-47 [PMID: 15576401 DOI: 10.1242/dev.01570]

4 **Desai TJ**, Chen F, Lü J, Qian J, Niederreither K, Dollé P, Chambon P, Cardoso WV. Distinct roles for retinoic acid receptors alpha and beta in early lung morphogenesis. *Dev Biol* 2006; **291**: 12-24 [PMID: 16427040 DOI: 10.1016/j.ydbio.2005.10.045]

5 **Chen F**, Cao Y, Qian J, Shao F, Niederreither K, Cardoso WV. A retinoic acid-dependent network in the foregut controls formation of the mouse lung primordium. *J Clin Invest* 2010; **120**: 2040-2048 [PMID: 20484817]

6 **Morrisey EE**, Hogan BL. Preparing for the first breath: genetic and cellular mechanisms in lung development. *Dev Cell* 2010; **18**: 8-23 [PMID: 20152174 DOI: 10.1016/j.devcel.2009.12.010]

7 **Herriges M**, Morrisey EE. Lung development: orchestrating the generation and regeneration of a complex organ. *Development* 2014; **141**: 502-513 [PMID: 24449833 DOI: 10.1242/dev.098186]

8 **Warburton D**, El-Hashash A, Carraro G, Tiozzo C, Sala F, Rogers O, De Langhe S, Kemp PJ, Riccardi D, Torday J, Bellusci S, Shi W, Lubkin SR, Jesudason E. Lung organogenesis. *Curr Top Dev Biol* 2010; **90**: 73-158 [PMID: 20691848 DOI: 10.1016/S0070-2153(10)90003-3]

9 **Wells JM**, Melton DA. Early mouse endoderm is patterned by soluble factors from adjacent germ layers. *Development* 2000; **127**: 1563-1572 [PMID: 10725233]

10 **Rackley CR**, Stripp BR. Building and maintaining the epithelium of the lung. *J Clin Invest* 2012; **122**: 2724-2730 [PMID: 22850882 DOI: 10.1172/JCI60519]

11 **Burri PH**. Structural aspects of postnatal lung development - alveolar formation and growth. *Biol Neonate* 2006; **89**: 313-322 [PMID: 16770071 DOI: 10.1159/000092868]

12 **Jacobs IJ**, Ku WY, Que J. Genetic and cellular mechanisms regulating anterior foregut and esophageal development. *Dev Biol* 2012; **369**: 54-64 [PMID: 22750256 DOI: 10.1016/j.ydbio.2012.06.016]

13 **Roberts DJ**, Johnson RL, Burke AC, Nelson CE, Morgan BA, Tabin C. Sonic hedgehog is an endodermal signal inducing Bmp-4 and Hox genes during induction and regionalization of the chick hindgut. *Development* 1995; **121**: 3163-3174 [PMID: 7588051]

14 **de Santa Barbara P**, Roberts DJ. Tail gut endoderm and gut/genitourinary/tail development: a new tissue-specific role for Hoxa13. *Development* 2002; **129**: 551-561 [PMID: 11830557]

15 **Litingtung Y**, Lei L, Westphal H, Chiang C. Sonic hedgehog is essential to foregut development. *Nat Genet* 1998; **20**: 58-61 [PMID: 9731532 DOI: 10.1038/1717]

16 **McMahon AP**, Ingham PW, Tabin CJ. Developmental roles and clinical significance of hedgehog signaling. *Curr Top Dev Biol* 2003; **53**: 1-114 [PMID: 12509125 DOI: 10.1016/S0070-2153(03)53002-2]

17 **Moniot B**, Biau S, Faure S, Nielsen CM, Berta P, Roberts DJ, de Santa Barbara P. SOX9 specifies the pyloric sphincter epithelium through mesenchymal-epithelial signals. *Development* 2004; **131**: 3795-3804 [PMID: 15240557 DOI: 10.1242/dev.01259]

18 **de Santa Barbara P**, van den Brink GR, Roberts DJ. Development and differentiation of the intestinal epithelium. *Cell Mol Life Sci* 2003; **60**: 1322-1332 [PMID: 12943221 DOI: 10.1007/s00018-003-2289-3]

19 **Gubbay J**, Collignon J, Koopman P, Capel B, Economou A, Münsterberg A, Vivian N, Goodfellow P, Lovell-Badge R. A gene mapping to the sex-determining region of the mouse Y chromosome is a member of a novel family of embryonically expressed genes. *Nature* 1990; **346**: 245-250 [PMID: 2374589]

20 **Sinclair AH**, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf AM, Lovell-Badge R, Goodfellow PN. A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* 1990; **346**: 240-244 [PMID: 1695712]

21 **Pevny L**, Placzek M. SOX genes and neural progenitor identity. *Curr Opin Neurobiol* 2005; **15**: 7-13 [PMID: 15721738]

22 **Wegner M**. From head to toes: the multiple facets of Sox proteins. *Nucleic Acids Res* 1999; **27**: 1409-1420 [PMID: 10037800]

23 **Harley VR**, Lovell-Badge R, Goodfellow PN. Definition of a consensus DNA binding site for SRY. *Nucleic Acids Res* 1994; **22**: 1500-1501 [PMID: 8190643]

24 **Lefebvre V**, Dumitriu B, Penzo-Méndez A, Han Y, Pallavi B. Control of cell fate and differentiation by Sry-related high-mobility-group box (Sox) transcription factors. *Int J Biochem Cell Biol* 2007; **39**: 2195-2214 [PMID: 17625949]

25 **Werner MH**, Burley SK. Architectural transcription factors: proteins that remodel DNA. *Cell* 1997; **88**: 733-736 [PMID: 9118214]

26 **Wolffe AP**. Architectural transcription factors. *Science* 1994; **264**: 1100-1101 [PMID: 8178167]

27 **Pevny LH**, Lovell-Badge R. Sox genes find their feet. *Curr Opin Genet Dev* 1997; **7**: 338-344 [PMID: 9229109]

28 **Wilson M**, Koopman P. Matching SOX: partner proteins and co-factors of the SOX family of transcriptional regulators. *Curr Opin Genet Dev* 2002; **12**: 441-446 [PMID: 12100890]

29 **Sarkar A**, Hochedlinger K. The sox family of transcription factors: versatile regulators of stem and progenitor cell fate. *Cell Stem Cell* 2013; **12**: 15-30 [PMID: 23290134 DOI: 10.1016/j.stem.2012.12.007]

30 **Kamachi Y**, Kondoh H. Sox proteins: regulators of cell fate specification and differentiation. *Development* 2013; **140**: 4129-4144 [PMID: 24086078 DOI: 10.1242/dev.091793]

31 **Goodfellow PN**, Lovell-Badge R. SRY and sex determination in mammals. *Annu Rev Genet* 1993; **27**: 71-92 [PMID: 8122913]

32 **Hacker A**, Capel B, Goodfellow P, Lovell-Badge R. Expression of Sry, the mouse sex determining gene. *Development* 1995; **121**: 1603-1614 [PMID: 7600978]

33 **Koopman P**, Münsterberg A, Capel B, Vivian N, Lovell-Badge R. Expression of a candidate sex-determining gene during mouse testis differentiation. *Nature* 1990; **348**: 450-452 [PMID: 2247150]

34 **Kaplan F**. Molecular determinants of fetal lung organogenesis. *Mol Genet Metab* 2000; **71**: 321-341 [PMID: 11001825 DOI: 10.1006/mgme.2000.3040]

35 **Sock E**, Rettig SD, Enderich J, Bösl MR, Tamm ER, Wegner M. Gene targeting reveals a widespread role for the high-mobility-group transcription factor Sox11 in tissue remodeling. *Mol Cell Biol* 2004; **24**: 6635-6644 [PMID: 15254231 DOI: 10.1128/MCB.24.15.6635-6644.2004]

36 **Lange AW**, Keiser AR, Wells JM, Zorn AM, Whitsett JA. Sox17 promotes cell cycle progression and inhibits TGF-beta/Smad3 signaling to initiate progenitor cell behavior in the respiratory epithelium. *PLoS One* 2009; **4**: e5711 [PMID: 19479035 DOI: 10.1371/journal.pone.0005711]

37 **Tompkins DH**, Besnard V, Lange AW, Keiser AR, Wert SE, Bruno MD, Whitsett JA. Sox2 activates cell proliferation and differentiation in the respiratory epithelium. *Am J Respir Cell Mol Biol* 2011; **45**: 101-110 [PMID: 20855650]

38 **Park KS**, Wells JM, Zorn AM, Wert SE, Whitsett JA. Sox17 influences the differentiation of respiratory epithelial cells. *Dev Biol* 2006; **294**: 192-202 [PMID: 16574095 DOI: 10.1016/j.ydbio.2006.02.038]

39 **Gontan C**, de Munck A, Vermeij M, Grosveld F, Tibboel D, Rottier R. Sox2 is important for two crucial processes in lung development: branching morphogenesis and epithelial cell differentiation. *Dev Biol* 2008; **317**: 296-309 [PMID: 18374910 DOI: 10.1016/j.ydbio.2008.02.035]

40 **Rockich BE**, Hrycaj SM, Shih HP, Nagy MS, Ferguson MA, Kopp JL, Sander M, Wellik DM, Spence JR. Sox9 plays multiple roles in the lung epithelium during branching morphogenesis. *Proc Natl Acad Sci U S A* 2013; **110**: E4456-E4464 [PMID: 24191021 DOI: 10.1073/pnas.1311847110]

41 **Turcatel G**, Rubin N, Menke DB, Martin G, Shi W, Warburton D. Lung mesenchymal expression of Sox9 plays a critical role in tracheal development. *BMC Biol* 2013; **11**: 117 [PMID: 24274029 DOI: 10.1186/1741-7007-11-117]

42 **Park J**, Zhang JJ, Moro A, Kushida M, Wegner M, Kim PC. Regulation of Sox9 by Sonic Hedgehog (Shh) is essential for patterning and formation of tracheal cartilage. *Dev Dyn* 2010; **239**: 514-526 [PMID: 20034104 DOI: 10.1002/dvdy.22192]

43 **Elluru RG**, Thompson F, Reece A. Fibroblast growth factor 18 gives growth and directional cues to airway cartilage. *Laryngoscope* 2009; **119**: 1153-1165 [PMID: 19358209 DOI: 10.1002/lary.20157]

44 **Kanai-Azuma M**, Kanai Y, Gad JM, Tajima Y, Taya C, Kurohmaru M, Sanai Y, Yonekawa H, Yazaki K, Tam PP, Hayashi Y. Depletion of definitive gut endoderm in Sox17-null mutant mice. *Development* 2002; **129**: 2367-2379 [PMID: 11973269]

45 **Dong S**, Leung KK, Pelling AL, Lee PY, Tang AS, Heng HH, Tsui LC, Tease C, Fisher G, Steel KP, Cheah KS. Circling, deafness, and yellow coat displayed by yellow submarine (ysb) and light coat and circling (lcc) mice with mutations on chromosome 3. *Genomics* 2002; **79**: 777-784 [PMID: 12036291]

46 **Liu K**, Lin B, Zhao M, Yang X, Chen M, Gao A, Liu F, Que J, Lan X. The multiple roles for Sox2 in stem cell maintenance and tumorigenesis. *Cell Signal* 2013; **25**: 1264-1271 [PMID: 23416461 DOI: 10.1016/j.cellsig.2013.02.013]

47 **Avilion AA**, Nicolis SK, Pevny LH, Perez L, Vivian N, Lovell-Badge R. Multipotent cell lineages in early mouse development depend on SOX2 function. *Genes Dev* 2003; **17**: 126-140 [PMID: 12514105 DOI: 10.1101/gad.224503]

48 **Wood HB**, Episkopou V. Comparative expression of the mouse Sox1, Sox2 and Sox3 genes from pre-gastrulation to early somite stages. *Mech Dev* 1999; **86**: 197-201 [PMID: 10446282]

49 **Papanayotou C**, Mey A, Birot AM, Saka Y, Boast S, Smith JC, Samarut J, Stern CD. A mechanism regulating the onset of Sox2 expression in the embryonic neural plate. *PLoS Biol* 2008; **6**: e2 [PMID: 18184035]

50 **Ishii Y**, Rex M, Scotting PJ, Yasugi S. Region-specific expression of chicken Sox2 in the developing gut and lung epithelium: regulation by epithelial-mesenchymal interactions. *Dev Dyn* 1998; **213**: 464-475 [PMID: 9853967]

51 **Donner AL**, Episkopou V, Maas RL. Sox2 and Pou2f1 interact to control lens and olfactory placode development. *Dev Biol* 2007; **303**: 784-799 [PMID: 17140559]

52 **Schlosser G**, Ahrens K. Molecular anatomy of placode development in Xenopus laevis. *Dev Biol* 2004; **271**: 439-466 [PMID: 15223346]

53 **Uchikawa M**, Ishida Y, Takemoto T, Kamachi Y, Kondoh H. Functional analysis of chicken Sox2 enhancers highlights an array of diverse regulatory elements that are conserved in mammals. *Dev Cell* 2003; **4**: 509-519 [PMID: 12689590]

54 **Taranova OV**, Magness ST, Fagan BM, Wu Y, Surzenko N, Hutton SR, Pevny LH. SOX2 is a dose-dependent regulator of retinal neural progenitor competence. *Genes Dev* 2006; **20**: 1187-1202 [PMID: 16651659]

55 **Pan W**, Jin Y, Chen J, Rottier RJ, Steel KP, Kiernan AE. Ectopic expression of activated notch or SOX2 reveals similar and unique roles in the development of the sensory cell progenitors in the mammalian inner ear. *J Neurosci* 2013; **33**: 16146-16157 [PMID: 24107947 DOI: 10.1523/Jneurosci.3150-12.2013]

56 **Okubo T**, Pevny LH, Hogan BL. Sox2 is required for development of taste bud sensory cells. *Genes Dev* 2006; **20**: 2654-2659 [PMID: 17015430]

57 **Williamson KA**, Hever AM, Rainger J, Rogers RC, Magee A, Fiedler Z, Keng WT, Sharkey FH, McGill N, Hill CJ, Schneider A, Messina M, Turnpenny PD, Fantes JA, van Heyningen V, FitzPatrick DR. Mutations in SOX2 cause anophthalmia-esophageal-genital (AEG) syndrome. *Hum Mol Genet* 2006; **15**: 1413-1422 [PMID: 16543359]

58 **Que J**, Okubo T, Goldenring JR, Nam KT, Kurotani R, Morrisey EE, Taranova O, Pevny LH, Hogan BL. Multiple dose-dependent roles for Sox2 in the patterning and differentiation of anterior foregut endoderm. *Development* 2007; **134**: 2521-2531 [PMID: 17522155 DOI: 10.1242/dev.003855]

59 **Fantes J**, Ragge NK, Lynch SA, McGill NI, Collin JR, Howard-Peebles PN, Hayward C, Vivian AJ, Williamson K, van Heyningen V, FitzPatrick DR. Mutations in SOX2 cause anophthalmia. *Nat Genet* 2003; **33**: 461-463 [PMID: 12612584]

60 **Hagstrom SA**, Pauer GJ, Reid J, Simpson E, Crowe S, Maumenee IH, Traboulsi EI. SOX2 mutation causes anophthalmia, hearing loss, and brain anomalies. *Am J Med Genet A* 2005; **138A**: 95-98 [PMID: 16145681]

61 **Harris-Johnson KS**, Domyan ET, Vezina CM, Sun X. beta-Catenin promotes respiratory progenitor identity in mouse foregut. *Proc Natl Acad Sci U S A* 2009; **106**: 16287-16292 [PMID: 19805295 DOI: 10.1073/pnas.0902274106]

62 **Ochieng JK**, Schilders K, Kool H, Boerema-De Munck A, Buscop-Van Kempen M, Gontan C, Smits R, Grosveld FG, Wijnen RM, Tibboel D, Rottier RJ. Sox2 regulates the emergence of lung Basal cells by directly activating the transcription of trp63. *Am J Respir Cell Mol Biol* 2014; **51**: 311-322 [PMID: 24669837 DOI: 10.1165/rcmb.2013-0419OC]

63 **Minoo P**, Su G, Drum H, Bringas P, Kimura S. Defects in tracheoesophageal and lung morphogenesis in Nkx2.1(-/-) mouse embryos. *Dev Biol* 1999; **209**: 60-71 [PMID: 10208743 DOI: 10.1006/dbio.1999.9234]

64 **Boyer LA**, Lee TI, Cole MF, Johnstone SE, Levine SS, Zucker JP, Guenther MG, Kumar RM, Murray HL, Jenner RG, Gifford DK, Melton DA, Jaenisch R, Young RA. Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell* 2005; **122**: 947-956 [PMID: 16153702 DOI: 10.1016/j.cell.2005.08.020]

65 **Engelen E**, Akinci U, Bryne JC, Hou J, Gontan C, Moen M, Szumska D, Kockx C, van Ijcken W, Dekkers DH, Demmers J, Rijkers EJ, Bhattacharya S, Philipsen S, Pevny LH, Grosveld FG, Rottier RJ, Lenhard B, Poot RA. Sox2 cooperates with Chd7 to regulate genes that are mutated in human syndromes. *Nat Genet* 2011; **43**: 607-611 [PMID: 21532573 DOI: 10.1038/Ng.825]

66 **Gontan C**, Güttler T, Engelen E, Demmers J, Fornerod M, Grosveld FG, Tibboel D, Görlich D, Poot RA, Rottier RJ. Exportin 4 mediates a novel nuclear import pathway for Sox family transcription factors. *J Cell Biol* 2009; **185**: 27-34 [PMID: 19349578 DOI: 10.1016/j.ydbio.2008.05.306]

67 **Bellusci S**, Grindley J, Emoto H, Itoh N, Hogan BL. Fibroblast growth factor 10 (FGF10) and branching morphogenesis in the embryonic mouse lung. *Development* 1997; **124**: 4867-4878 [PMID: 9428423]

68 **Park WY**, Miranda B, Lebeche D, Hashimoto G, Cardoso WV. FGF-10 is a chemotactic factor for distal epithelial buds during lung development. *Dev Biol* 1998; **201**: 125-134 [PMID: 9740653]

69 **Sekine K**, Ohuchi H, Fujiwara M, Yamasaki M, Yoshizawa T, Sato T, Yagishita N, Matsui D, Koga Y, Itoh N, Kato S. Fgf10 is essential for limb and lung formation. *Nat Genet* 1999; **21**: 138-141 [PMID: 9916808 DOI: 10.1038/5096]

70 **Kato S**, Sekine K. [FGF10, a key factor for limb and lung formation]. *Seikagaku* 2000; **72**: 288-291 [PMID: 10853366]

71 **Colvin JS**, White AC, Pratt SJ, Ornitz DM. Lung hypoplasia and neonatal death in Fgf9-null mice identify this gene as an essential regulator of lung mesenchyme. *Development* 2001; **128**: 2095-2106 [PMID: 11493531]

72 **Abler LL**, Mansour SL, Sun X. Conditional gene inactivation reveals roles for Fgf10 and Fgfr2 in establishing a normal pattern of epithelial branching in the mouse lung. *Dev Dyn* 2009; **238**: 1999-2013 [PMID: 19618463 DOI: 10.1002/dvdy.22032]

73 **Krejci P**, Aklian A, Kaucka M, Sevcikova E, Prochazkova J, Masek JK, Mikolka P, Pospisilova T, Spoustova T, Weis M, Paznekas WA, Wolf JH, Gutkind JS, Wilcox WR, Kozubik A, Jabs EW, Bryja V, Salazar L, Vesela I, Balek L. Receptor tyrosine kinases activate canonical WNT/β-catenin signaling via MAP kinase/LRP6 pathway and direct β-catenin phosphorylation. *PLoS One* 2012; **7**: e35826 [PMID: 22558232 DOI: 10.1371/journal.pone.0035826]

74 **Shu W**, Guttentag S, Wang Z, Andl T, Ballard P, Lu MM, Piccolo S, Birchmeier W, Whitsett JA, Millar SE, Morrisey EE. Wnt/beta-catenin signaling acts upstream of N-myc, BMP4, and FGF signaling to regulate proximal-distal patterning in the lung. *Dev Biol* 2005; **283**: 226-239 [PMID: 15907834 DOI: 10.1016/j.ydbio.2005.04.014]

75 **Cornett B**, Snowball J, Varisco BM, Lang R, Whitsett J, Sinner D. Wntless is required for peripheral lung differentiation and pulmonary vascular development. *Dev Biol* 2013; **379**: 38-52 [PMID: 23523683 DOI: 10.1016/j.ydbio.2013.03.010]

76 **Goss AM**, Tian Y, Tsukiyama T, Cohen ED, Zhou D, Lu MM, Yamaguchi TP, Morrisey EE. Wnt2/2b and beta-catenin signaling are necessary and sufficient to specify lung progenitors in the foregut. *Dev Cell* 2009; **17**: 290-298 [PMID: 19686689 DOI: 10.1016/j.devcel.2009.06.005]

77 **Shu W**, Jiang YQ, Lu MM, Morrisey EE. Wnt7b regulates mesenchymal proliferation and vascular development in the lung. *Development* 2002; **129**: 4831-4842 [PMID: 12361974]

78 **Miller MF**, Cohen ED, Baggs JE, Lu MM, Hogenesch JB, Morrisey EE. Wnt ligands signal in a cooperative manner to promote foregut organogenesis. *Proc Natl Acad Sci U S A* 2012; **109**: 15348-15353 [PMID: 22949635 DOI: 10.1073/pnas.1201583109]

79 **Hashimoto S**, Chen H, Que J, Brockway BL, Drake JA, Snyder JC, Randell SH, Stripp BR. β-Catenin-SOX2 signaling regulates the fate of developing airway epithelium. *J Cell Sci* 2012; **125**: 932-942 [PMID: 22421361 DOI: 10.1242/jcs.092734]

80 **Mucenski ML**, Nation JM, Thitoff AR, Besnard V, Xu Y, Wert SE, Harada N, Taketo MM, Stahlman MT, Whitsett JA. Beta-catenin regulates differentiation of respiratory epithelial cells in vivo. *Am J Physiol Lung Cell Mol Physiol* 2005; **289**: L971-L979 [PMID: 16040629 DOI: 10.1152/ajplung.00172.2005]

81 **Li C**, Hu L, Xiao J, Chen H, Li JT, Bellusci S, Delanghe S, Minoo P. Wnt5a regulates Shh and Fgf10 signaling during lung development. *Dev Biol* 2005; **287**: 86-97 [PMID: 16169547]

82 **Sountoulidis A**, Stavropoulos A, Giaglis S, Apostolou E, Monteiro R, Chuva de Sousa Lopes SM, Chen H, Stripp BR, Mummery C, Andreakos E, Sideras P. Activation of the canonical bone morphogenetic protein (BMP) pathway during lung morphogenesis and adult lung tissue repair. *PLoS One* 2012; **7**: e41460 [PMID: 22916109 DOI: 10.1371/journal.pone.0041460]

83 **Que J**, Choi M, Ziel JW, Klingensmith J, Hogan BL. Morphogenesis of the trachea and esophagus: current players and new roles for noggin and Bmps. *Differentiation* 2006; **74**: 422-437 [PMID: 16916379 DOI: 10.1111/j.1432-0436.2006.00096.x]

84 **Li Y**, Litingtung Y, Ten Dijke P, Chiang C. Aberrant Bmp signaling and notochord delamination in the pathogenesis of esophageal atresia. *Dev Dyn* 2007; **236**: 746-754 [PMID: 17260385 DOI: 10.1002/dvdy.21075]

85 **Fausett SR**, Brunet LJ, Klingensmith J. BMP antagonism by Noggin is required in presumptive notochord cells for mammalian foregut morphogenesis. *Dev Biol* 2014; **391**: 111-124 [PMID: 24631216 DOI: 10.1016/j.ydbio.2014.02.008]

86 **Li Y**, Gordon J, Manley NR, Litingtung Y, Chiang C. Bmp4 is required for tracheal formation: a novel mouse model for tracheal agenesis. *Dev Biol* 2008; **322**: 145-155 [PMID: 18692041 DOI: 10.1016/j.ydbio.2008.07.021]

87 **Domyan ET**, Ferretti E, Throckmorton K, Mishina Y, Nicolis SK, Sun X. Signaling through BMP receptors promotes respiratory identity in the foregut via repression of Sox2. *Development* 2011; **138**: 971-981 [PMID: 21303850 DOI: 10.1242/dev.053694]

88 **Correia-Pinto J**, Gonzaga S, Huang Y, Rottier R. Congenital lung lesions--underlying molecular mechanisms. *Semin Pediatr Surg* 2010; **19**: 171-179 [PMID: 20610189 DOI: 10.1053/j.sempedsurg.2010.03.003]

89 **Ng C**, Stanwell J, Burge DM, Stanton MP. Conservative management of antenatally diagnosed cystic lung malformations. *Arch Dis Child* 2014; **99**: 432-437 [PMID: 24406806 DOI: 10.1136/archdischild-2013-304048]

90 **Langston C**. New concepts in the pathology of congenital lung malformations. *Semin Pediatr Surg* 2003; **12**: 17-37 [PMID: 12520470 DOI: 10.1053/spsu.2003.00001]

91 **Cass DL**, Quinn TM, Yang EY, Liechty KW, Crombleholme TM, Flake AW, Adzick NS. Increased cell proliferation and decreased apoptosis characterize congenital cystic adenomatoid malformation of the lung. *J Pediatr Surg* 1998; **33**: 1043-106; discussion 1047 [PMID: 9694091]

92 **Fromont-Hankard G**, Philippe-Chomette P, Delezoide AL, Nessmann C, Aigrain Y, Peuchmaur M. Glial cell-derived neurotrophic factor expression in normal human lung and congenital cystic adenomatoid malformation. *Arch Pathol Lab Med* 2002; **126**: 432-436 [PMID: 11900567 DOI: 10.1043/0003-9985(2002)126<0432: GCDNFE>2.0.CO; 2]

93 **Gonzaga S**, Henriques-Coelho T, Davey M, Zoltick PW, Leite-Moreira AF, Correia-Pinto J, Flake AW. Cystic adenomatoid malformations are induced by localized FGF10 overexpression in fetal rat lung. *Am J Respir Cell Mol Biol* 2008; **39**: 346-355 [PMID: 18421016 DOI: 10.1165/rcmb.2007-0290OC]

94 **Volpe MV**, Pham L, Lessin M, Ralston SJ, Bhan I, Cutz E, Nielsen HC. Expression of Hoxb-5 during human lung development and in congenital lung malformations. *Birth Defects Res A Clin Mol Teratol* 2003; **67**: 550-556 [PMID: 14632303 DOI: 10.1002/bdra.10086]

95 **Jancelewicz T**, Nobuhara K, Hawgood S. Laser microdissection allows detection of abnormal gene expression in cystic adenomatoid malformation of the lung. *J Pediatr Surg* 2008; **43**: 1044-1051 [PMID: 18558180 DOI: 10.1016/j.jpedsurg.2008.02.027]

96 **Wagner AJ**, Stumbaugh A, Tigue Z, Edmondson J, Paquet AC, Farmer DL, Hawgood S. Genetic analysis of congenital cystic adenomatoid malformation reveals a novel pulmonary gene: fatty acid binding protein-7 (brain type). *Pediatr Res* 2008; **64**: 11-16 [PMID: 18391847 DOI: 10.1203/PDR.0b013e318174eff8]

97 **Volpe MV**, Archavachotikul K, Bhan I, Lessin MS, Nielsen HC. Association of bronchopulmonary sequestration with expression of the homeobox protein Hoxb-5. *J Pediatr Surg* 2000; **35**: 1817-1819 [PMID: 11101743 DOI: 10.1053/jpsu.2000.19266]

98 **Volpe MV**, Vosatka RJ, Nielsen HC. Hoxb-5 control of early airway formation during branching morphogenesis in the developing mouse lung. *Biochim Biophys Acta* 2000; **1475**: 337-345 [PMID: 10913834]

99 **Berg C**, Geipel A, Germer U, Pertersen-Hansen A, Koch-Dörfler M, Gembruch U. Prenatal detection of Fraser syndrome without cryptophthalmos: case report and review of the literature. *Ultrasound Obstet Gynecol* 2001; **18**: 76-80 [PMID: 11489232 DOI: 10.1046/j.1469-0705.2001.00374.x]

100 **Epelman M**, Kreiger PA, Servaes S, Victoria T, Hellinger JC. Current imaging of prenatally diagnosed congenital lung lesions. *Semin Ultrasound CT MR* 2010; **31**: 141-157 [PMID: 20304322 DOI: 10.1053/j.sult.2010.01.002]

101 **Mei-Zahav M**, Konen O, Manson D, Langer JC. Is congenital lobar emphysema a surgical disease? *J Pediatr Surg* 2006; **41**: 1058-1061 [PMID: 16769334 DOI: 10.1016/j.jpedsurg.2006.02.011]

102 **Nayar PM**, Thakral CL, Sajwani MJ. Congenital lobar emphysema and sequestration--treatment by embolization. *Pediatr Surg Int* 2005; **21**: 727-729 [PMID: 15995872 DOI: 10.1007/s00383-005-1462-1]

103 **Kravitz RM**. Congenital malformations of the lung. *Pediatr Clin North Am* 1994; **41**: 453-472 [PMID: 8196988]

104 **Rottier R**, Tibboel D. Fetal lung and diaphragm development in congenital diaphragmatic hernia. *Semin Perinatol* 2005; **29**: 86-93 [PMID: 16050526]

105 **Klaassens M**, de Klein A, Tibboel D. The etiology of congenital diaphragmatic hernia: still largely unknown? *Eur J Med Genet* 2009; **52**: 281-286 [PMID: 19464395 DOI: 10.1016/j.ejmg.2009.05.005]

106 **Beurskens N**, Klaassens M, Rottier R, de Klein A, Tibboel D. Linking animal models to human congenital diaphragmatic hernia. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 565-572 [PMID: 17469205 DOI: 10.1002/bdra.20370]

107 **Veenma DC**, de Klein A, Tibboel D. Developmental and genetic aspects of congenital diaphragmatic hernia. *Pediatr Pulmonol* 2012; **47**: 534-545 [PMID: 22467525 DOI: 10.1002/ppul.22553]

108 **Leeuwen L,** Fitzgerald DA. Congenital diaphragmatic hernia. *J Paediatr Child Health* 2014 [PMID: 24528549 DOI: 10.1111/jpc.12508]

109 **Brady PD,** Moerman P, De Catte L, Deprest J, Devriendt K, Vermeesch JR. Exome sequencing identifies a recessive PIGN splice site mutation as a cause of syndromic Congenital Diaphragmatic Hernia. *Eur J Med Genet* 2014 [PMID: 24852103 DOI: 10.1016/j.ejmg.2014.05.001]

110 **Brady PD**, Van Houdt J, Callewaert B, Deprest J, Devriendt K, Vermeesch JR. Exome sequencing identifies ZFPM2 as a cause of familial isolated congenital diaphragmatic hernia and possibly cardiovascular malformations. *Eur J Med Genet* 2014; **57**: 247-252 [PMID: 24769157 DOI: 10.1016/j.ejmg.2014.04.006]

111 **Torfs CP**, Curry CJ, Bateson TF. Population-based study of tracheoesophageal fistula and esophageal atresia. *Teratology* 1995; **52**: 220-232 [PMID: 8838292 DOI: 10.1002/tera.1420520408]

112 **Spitz L**. Oesophageal atresia. *Orphanet J Rare Dis* 2007; **2**: 24 [PMID: 17498283 DOI: 10.1186/1750-1172-2-24]

113 **de Jong EM**, Felix JF, de Klein A, Tibboel D. Etiology of esophageal atresia and tracheoesophageal fistula: "mind the gap". *Curr Gastroenterol Rep* 2010; **12**: 215-222 [PMID: 20425471 DOI: 10.1007/s11894-010-0108-1]

114 **Bishop NB**, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. *Am J Respir Crit Care Med* 2011; **184**: 172-179 [PMID: 21471096 DOI: 10.1164/rccm.201010-1697CI]

115 **Kalinichenko VV**, Lim L, Shin B, Costa RH. Differential expression of forkhead box transcription factors following butylated hydroxytoluene lung injury. *Am J Physiol Lung Cell Mol Physiol* 2001; **280**: L695-L704 [PMID: 11238010]

116 **Mahlapuu M**, Enerbäck S, Carlsson P. Haploinsufficiency of the forkhead gene Foxf1, a target for sonic hedgehog signaling, causes lung and foregut malformations. *Development* 2001; **128**: 2397-2406 [PMID: 11493558]

117 **Kiefer JC**. Back to basics: Sox genes. *Dev Dyn* 2007; **236**: 2356-2366 [PMID: 17584862 DOI: 10.1002/dvdy.21218]

118 **Rainger JK**, Bhatia S, Bengani H, Gautier P, Rainger J, Pearson M, Ansari M, Crow J, Mehendale F, Palinkasova B, Dixon MJ, Thompson PJ, Matarin M, Sisodiya SM, Kleinjan DA, Fitzpatrick DR. Disruption of SATB2 or its long-range cis-regulation by SOX9 causes a syndromic form of Pierre Robin sequence. *Hum Mol Genet* 2014; **23**: 2569-2579 [PMID: 24363063 DOI: 10.1093/hmg/ddt647]

**P-Reviewer:** Gunther T **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Gestational ages in human and mouse during the five stages of lung development[**[**8**](#_ENREF_1)**]**

|  |  |
| --- | --- |
| **Phases of lung development** | **Gestational age** |
| *Human* | *Mouse* |
| Embryonic phase | Wk3-7 | E9-11.5 |
| Pseudoglandular phase | Wk5-17 | E9.5-16.6 |
| Canalicular phase | Wk16-25 | E16.6-17.4 |
| Saccular phase | Wk24-38 | E17.4-PN5 |
| Alveolar phase | Wk36 to maturity | PN5-30 |

Table 2 The role of *SOX* genes in diseases

|  |  |  |
| --- | --- | --- |
| ***SOX* gene** | **Chromosome location** | **Disease** |
| *SOX2* | [**3q26.3-q27**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6657) | Microphthalmia, syndromic 3 optic nerve hypoplasia, abnormalities of the central nervous system, CHARGE-syndrome[[65](#_ENREF_3)], AEG-syndrome[[57](#_ENREF_4)], EA/TEF[[58](#_ENREF_5)], CPAM[39,40] |
| *SOX3* | [**Xq27.1**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6658) | Mental retardation, X-linked with isolated growth hormone deficiency, infundibular hypoplasia, hypopituitarism[[117](#_ENREF_2)] |
| *SOX9* | [**17q23**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6662) | Campomelic dysplasia with autonomic XY sex reversal[[117](#_ENREF_2)], Pierre-Robin syndrome[11[8](#_ENREF_8)] |
| *SOX10* | [**22q13.1**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6663) | Waardenburg-Shah syndrome, Yemenite deaf-blind hypopigmentation syndrome, peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburgh syndrome, Hirschprung’s disease[[117](#_ENREF_2)] |
| *SOX11*  | [**2p25**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6664) | Unknown |
| *SOX17* | [**8q11.23**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=64321) | Unknown |
| *SOX18* | [**20q13.33**](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=54345) | Hypotrichosis-lymphedema-telangiectasia syndrome[[117](#_ENREF_2)] |