FaceBase Annual Meeting at USC
June 24-26, 2012

Center for Craniofacial Molecular Biology

FaceBase
A Resource For Craniofacial Researchers

Research on functional genomics, image analysis and rescue of cleft palate

Our USC Team: Yang Chai (PI), Junichi Iwata, Carolina Parada, Joe Hacia, Pedro Sanchez, Richard Pelican, and Thach-Vu Ho

Collaborators: Scott Fraser, Mike Dixon, Steve Potter, David Clouthier, Axel Visel

Specific Aims:

1. We will carry out sophisticated imaging and gene expression profile analysis to build a comprehensive data base for the investigation of the regulatory mechanism of palatogenesis.

2. To use mouse palatal explant culture model to perform high-throughput analysis of Tgf-β downstream target genes that have specific functions in regulating the fate of CNC cells during palatogenesis and to test whether manipulation of altered Tgf-β downstream signaling molecule(s) offers the opportunity to rescue cleft palate in vivo.

3. We will investigate gene expression profiles in the palatal mesenchyme of *Msx1* and *K14-Cre;Fgfr2*$^{fl/fl}$ mutant models and to identify the point(s) of intersection where multiple signaling pathways converge in order to develop therapeutic strategies to prevent or restore palate formation.

Micro-CT scan inventory as of 2/2012

Green cells are submitted scans to HUB. Yellow cells are goals in 6 months. Grey cells are goals achieved or will complete by next report.

Wildtype C57BL6J bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	2	1	1	2
17.5	1	2	1	1	2
18.5	1	2	1	1	2
P0	1	2	2		2

Wildtype C57BL6J tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5		2		1	2
14.5		1		1	2
15.5					2
16.5	1	2	1	1	2
17.5	1	2	1	1	2
18.5	1	7	1	1	2
P0	1	2	2		2

K14-Cre;Fgfr2fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0	1				2

K14-Cre;Fgfr2fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0	1				2

Fgfr2fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0	1				2

Fgfr2fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0	1				2

CTGF KO -/- bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0		21		10	2

CTGF KO -/- tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0		5		2	2

CTGF control +/+ bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0		21		10	2

CTGF control +/+ tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0	3	6		3	2

Msx1-/- bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0	1	2	1	1	2

Msx1-/- tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0	1				2

K14-Cre; Tgfbr2fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1				2
17.5	1				2
18.5		4		2	2
P0		2		2	2

K14-Cre; Tgfbr2fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1				2
17.5	1				2
18.5		3		2	2
P0	1	1	1		2

Tgfbr2 fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	1	1		2
17.5					2
18.5		7		3	2
P0	1	2		1	2

Tgfbr2 fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1	1	1		2
17.5					2
18.5		2		2	2
P0	1	1	1		2

Msx1+/+ bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1				2
P0	1	2	1	1	2

Msx1+/+ tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1				2
P0	1				2

Wnt1-Cre; Tgfbr2fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Wnt1-Cre; Tgfbr2fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1	1	1		2
P0	1				2

Myf5-Cre;Smad4fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	2	2		2
17.5	1				2
18.5		2		2	2
P0	1	2	1	1	2

Myf5-Cre;Smad4fl/fl Tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1	1	1		2
17.5	1				2
18.5	1	2	1	1	2
P0	1				2

Smad4fl/fl bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	2	1	1	2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Smad4fl/fl tissue

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1	2	1	1	2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Wnt1-Cre;Tgfbr2fl/fl;Alk5fl/+ bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	1	1		2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Wnt1-Cre;Tgfbr2fl/fl;Alk5fl/+ tiss

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1	1	1		2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Wnt1-Cre;Tgfbr2fl/fl;Tak1fl/+ bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5					2
17.5					2
18.5	1	2	1	1	2
P0	1				2

Wnt1-Cre;Tgfbr2fl/fl;Tak1fl/+ tiss

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5					2
17.5					2
18.5	1	4	1	1	2
P0					2

Wnt1-Cre;Tgfbr2fl/fl;Tgfb2+/- bone

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					N/A
14.5					N/A
15.5					N/A
16.5	1	1	1		2
17.5					2
18.5	1	2	2		2
P0	1				2

Wnt1-Cre;Tgfbr2fl/fl;Tgfb2+/- tiss

Age	Goals in 6 months	Scanned	Cue for HUB	Submitted	Final Goal
13.5					2
14.5					2
15.5					2
16.5	1	1	1		2
17.5					2
18.5	1	2	2		2
P0	1				2

FaceBase

Search Msx1

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Tissues:
Epithelium
Oral epithelium
Nasal epithelium
Midline epithelium
Basal epithelium
Peridermal cells

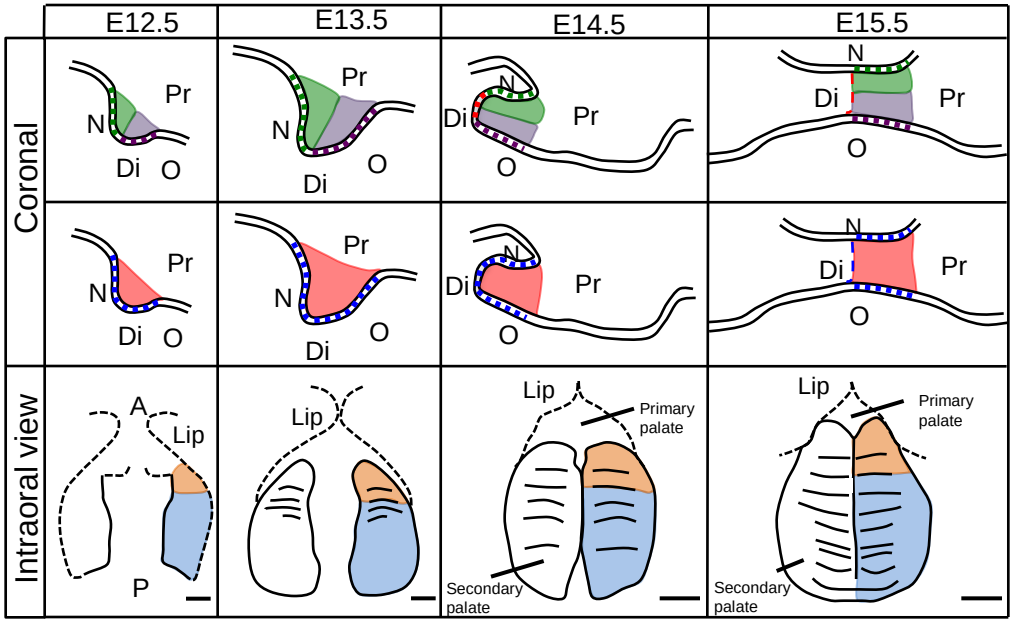
Mesenchyme
Nasal region
Oral region
Anterior region
Posterior region
Palatal bone primordium

Muscles of the soft palate
Levator
Tensor
Palatoglossus
Palatopharyngeous
Uvula

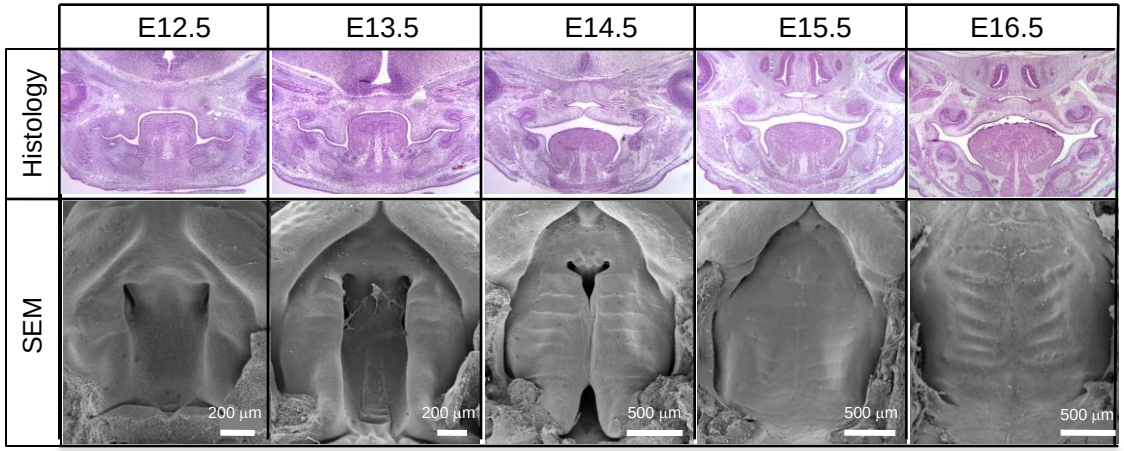
Species:
Mouse
Rat
Human
Other

Gene expression in the secondary palate

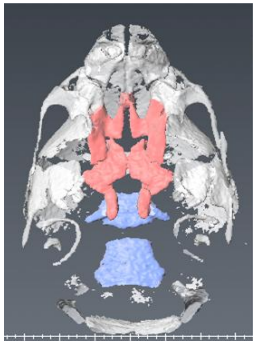
Select the tissue of interest (click at the tissue of interest to get a list of the genes expressed in that tissue)



Color code:
- Nasal mesenchyme
- Oral mesenchyme
- All mesenchyme
- Anterior mesenchyme
- Posterior mesenchyme
- Nasal epithelium
- Midline epithelium
- Oral epithelium
- All epithelium



3D images
µCT scans



FaceBase

Search Msx1

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Tissues:
Epithelium
Oral epithelium
Nasal epithelium
Midline epithelium
Basal epithelium
Peridermal cells

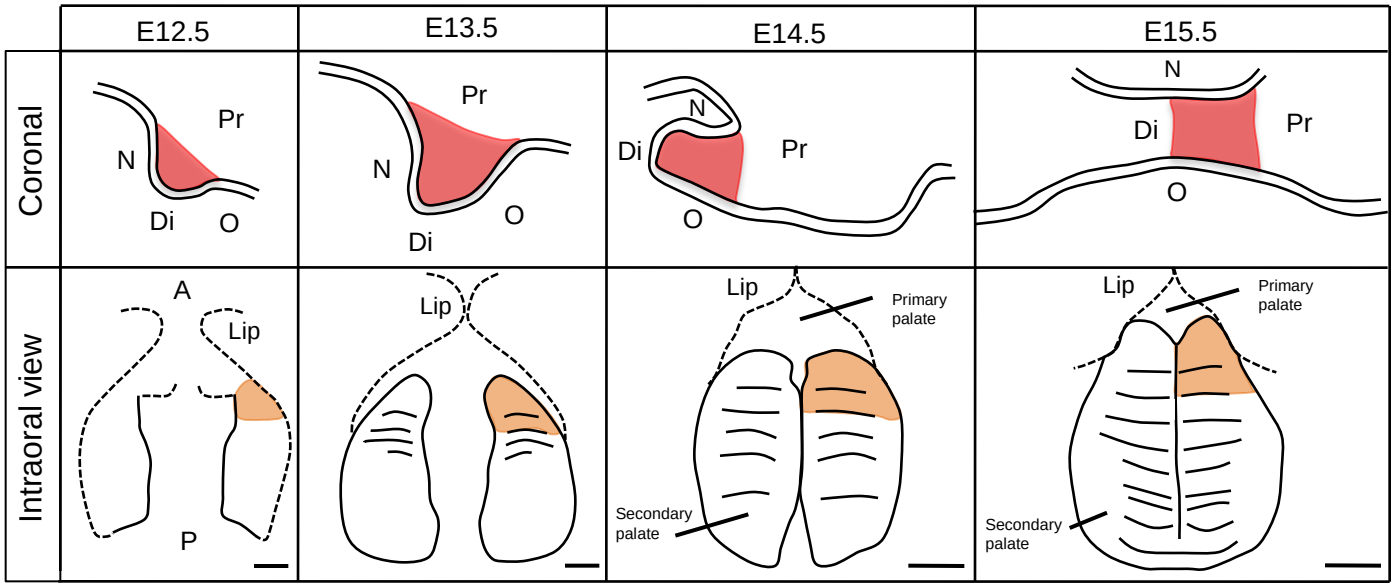
Mesenchyme
Nasal region
Oral region
Anterior region
Posterior region
Palatal bone primordium

Muscles of the soft palate
Levator
Tensor
Palatoglossus
Palatopharyngeous
Uvula

Species:
Mouse
Rat
Human
Other

Gene expression in the secondary palate

***Msx1* (Msh homeobox 1)**



Color code: All mesenchyme (ON axis) Anterior mesenchyme (AP axis)

Description: *Msx1* is expressed in the mesenchyme of the anterior region of the developing palate in both nasal and oral sides

Zhang *et al*. (2002) Rescue of cleft palate in Msx1-deficient mice by transgenic Bmp4 reveals a network of BMP and Shh signaling in the regulation of mammalian palatogenesis. *Development*. Sep;129(17):4135-46.

Unpublished data. Chai's Lab.

FaceBase

Search epithelium

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Tissues:
Epithelium
Oral epithelium
Nasal epithelium
Midline epithelium
Basal epithelium
Peridermal cells

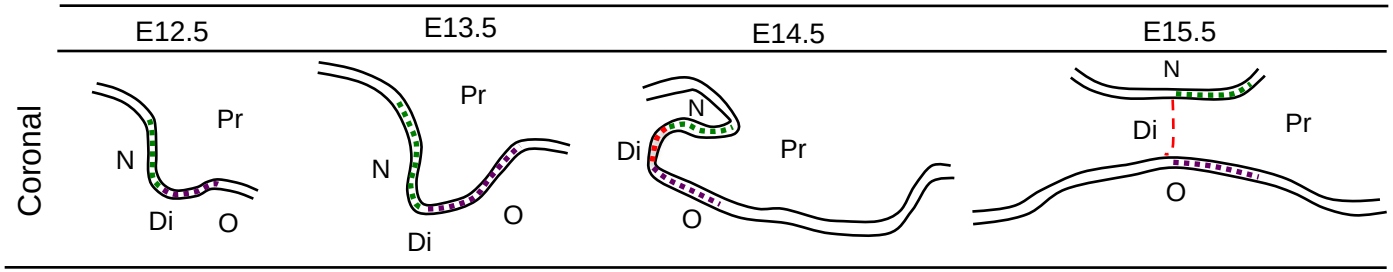
Mesenchyme
Nasal region
Oral region
Anterior region
Posterior region
Palatal bone primordium

Muscles of the soft palate
Levator
Tensor
Palatoglossus
Palatopharyngeous
Uvula

Species:
Mouse
Rat
Human
Other

Gene expression in the secondary palate

Select the area of interest (click at the area of interest to get a list of the genes expressed in that tissue)

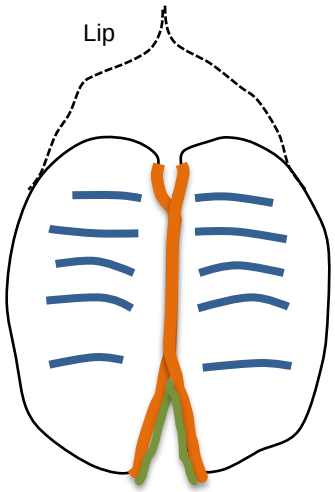


Color code:
Nasal epithelium
Midline epitheliu
Oral epithelium

Click

Click

E14.5



Rugae
Shh

Anterior - Posterior
Tgfb3
Irf6
p21
Mmp13
Lef1
Pitx2

Posterior
Hand2

FaceBase

Search Tgfbr2

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

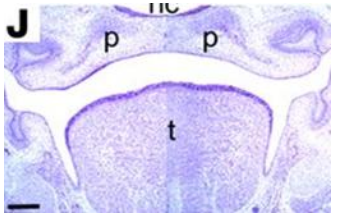
Genes:
A-E
F-J
K-O
P-S
T-Z

Classification of cleft palate in mutant mouse models:
Class I
Class II
Class III
Class IV

Human syndromes:
A-E
F-J
K-O
P-S
T-Z

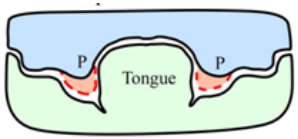
Normal palate

Newborn



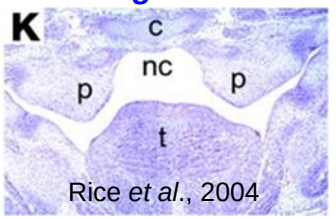
Classification of cleft palate in mutant mouse models

Class I: Palatal shelf hypoplasia



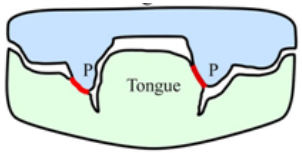
Fgfr2$^{-/-}$

Fgfr2$^{-/-}$



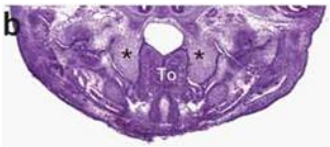
Rice *et al*., 2004

Class II: Palatal shelf fusion with the tongue or the mandible



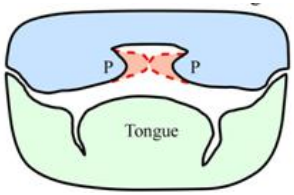
Irf6$^{-/-}$
Irf6$^{R84C/R84C}$

Irf6$^{-/-}$



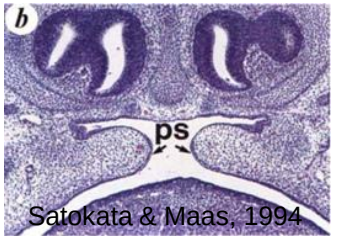
Richardson *et al*., 2006 Null

Class III: Palatal shelf fail to meet at the midline



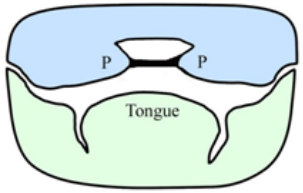
Tgfbr2$^{fl/fl}$*;Wnt1-Cre*
Alk5$^{fl/fl}$*;Wnt1-Cre*
Shh$^{fl/fl}$*;K14-Cre*
Ctgf$^{-/-}$
Msx1$^{-/-}$

Msx1$^{-/-}$



Satokata & Maas, 1994

Class IV: Submucosal cleft palate and/or persistence of medial edge epithelial cells



Tgfbr2$^{fl/fl}$*;K14-Cre*
Alk5$^{fl/fl}$*;K14-Cre*
Tbx1$^{-/-}$
Tbx22$^{-/-}$
Bmpr1$^{fl/fl}$*;Osr2-IresCre*

Tgfbr2$^{fl/fl}$*;K14-Cre*

Xu *et al*., 2006

FaceBase

Search submucous

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Genes:
A-E
F-J
K-O
P-S
T-Z

Classification of cleft palate in mutant mouse mod
Class I
Class II
Class III
- Complete cleft palate
- Anterior cleft palate
- Posterior cleft palate

Class IV

Click

Human syndromes:
A-E
F-J
K-O
P-S
T-Z

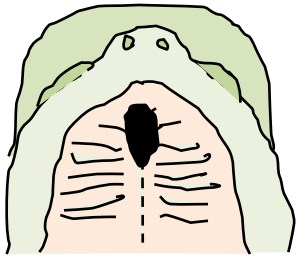
Class III Palatal shelf fail to meet at the midline

Complete cleft of secondary palate

Click

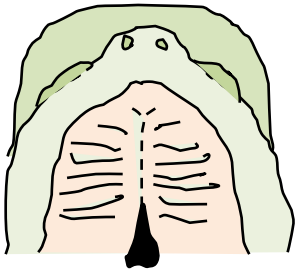
Tgfbr2$^{fl/fl}$;Wnt1-Cre
Alk5$^{fl/fl}$;Wnt1-Cre
Shh$^{fl/fl}$;K14-Cre
Ctgf$^{-/-}$

Partial cleft of secondary palate



Anterior

Tgfbr2$^{fl/fl}$;K14-Cre
Alk5$^{fl/fl}$;K14-Cre
Shox2$^{-/-}$
Shox2$^{fl/fl}$;Wnt1-Cre



Posterior/
Cleft soft palate

Tgfbr2$^{fl/fl}$;K14-Cre
Alk5$^{fl/fl}$;K14-Cre
Tbx1$^{-/-}$

FaceBase

Search Tgfbr2

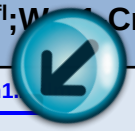
Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Mutation in:
Epithelium
Mesenchyme

Species:
Mouse
Rat
Human
Other

Craniofacial phenotype analysis of mutant animal models

Genotype	Tgfbr2$^{fl/fl}$;W[illegible]Cre
Symbol (MGI)	Tgfbr2^{tm1}[illegible] Tg(Wnt1-cre)11Rth
Known defects	Cleft palate, Bone defects, Small tongue
Known human diseases	Loeys-Dietz syndrome
Histology	E13.5, E14.5, E16.5, E18.5
SEM	E18.5
µCT	E18.5
3D µCT	E18.5
µMRI	E18.5
Gene expression analysis	E14.5
Protein expression analysis	E13.5, E14.5
References	Ito Y *et al.*, *Development* 2003 Sasaki T *et al.*, *Development* 2005 Oka K *et al.*, *Dev Biol* 2007 Oka K *et al.*, *Dev Biol* 2008 Iwata J *et al.*, *J Biol Chem* 2010 Iwata J *et al.*, *J Clin Invest* 2012 Iwata J *et al.*, *J Biol Chem* 2012



Tgfbr2$^{tm1.2Hlm}$

Targeted Allele Detail

Your Input Welcome

Nomenclature | Mutation origin | Mutation description | Find Mice (IMSR) | Phenotype summary | Phenotypes by genotype | Disease models | References

Nomenclature

Symbol: Tgfbr2$^{tm1.2Hlm}$

Name: transforming growth factor, beta receptor II; targeted mutation 1.2, Harold L Moses

MGI ID: MGI:2384513

Synonyms: +Exon2/-Neo^{r}, floxed-Tbr2, TbetaRII^{flox}, TbetaRII^{flox+}, Tbr2^{fl}, TGFbeta IIR^{fl}, TGFbetaRII^{f}, Tgfbr2^{E2flx}, Tgfbr2^{fl}, Tgfbr2^{floxE2}, Tgfbr2^{loxP}, Tgfbr^{floxE2}

Gene: Tgfbr2 *Location:* Chr9:115996813-116084481 bp, - strand *Genetic Position*: Chr9, 68.39 cM

Mutation origin

Germline Transmission: Earliest citation of germline transmission: J:75073

Parent Cell Line: TL1/TL-1 (ES Cell)

Strain of Origin: 129S6/SvEvTac

Mutation description

Allele Type: Targeted (Floxed/Frt)

Mutation: Insertion

This allele is derived from Tgfbr2^{tm1Hlm}. Expression of cre recombinase at the one cell stage resulted in the excision of the floxed region containing the neo transgene. Two single loxP sites were left flanking exon 2. (*J:75073*)

Find Mice (IMSR)

Mouse strains and cell lines available from the International Mouse Strain Resource (IMSR)

Carrying this Mutation: Mouse Strains: 0 strains available Cell Lines: 0 lines available

Carrying any Tgfbr2 Mutation: 5 strains or lines available

Phenotype summary

Phenotype Summary by Mammalian Phenotype terms

(show or hide all annotated terms)

Genotypes are listed in the next section.

Key: hm homozygous; ht heterozygous; cn conditional genotype; cx complex: > 1 genome feature; tg involves transgenes; ot other: hemizygous, indeterminate,...; N normal phenotype; ⊘ expected model not found

Affected Systems (Genotypes:)	hm1	cn2	cn3	cn4	cn5	cn6	cn7	cn8	cn9	cn10	cn11	cn12	cn13
behavior/neurological			√								√		
cardiovascular system			√			√						N	
cellular						√			√				
craniofacial						√					√		
digestive/alimentary system			√			√					√		
embryogenesis						√							
endocrine/exocrine glands			√		√								
growth/size			√										
hematopoietic system		√	√						√	√			
homeostasis/metabolism			√										
immune system		√	√				N	N	√	√			
liver/biliary system			√						√				
mortality/aging		√	√	√		√			√		√		√
nervous system						√							
respiratory system											√		√
skeleton						√							√
tumorigenesis	N	√	√	√									
normal phenotype	N											N	
Disease Models		√											

Phenotypic data by genotype

Phenotypic Data by Genotype

(show or hide all phenotypic details)

Genotype	Allelic Composition	Genetic Background
hm1	Tgfbr2$^{tm1.2Hlm}$/Tgfbr2$^{tm1.2Hlm}$	involves: 129S6/SvEvTac * C57BL/6
cn2 *Disease Model*	Kras^{tm4Tyj}/Kras^{+} Tgfbr2$^{tm1.2Hlm}$/Tgfbr2$^{tm1.2Hlm}$	B6.129-Kras^{tm4Tyj} Tgfbr2$^{tm1.2Hlm}$

FaceBase

Search μCT

Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Mutation in:
Epithelium
Mesenchyme
Mesoderm-derived cells
Cranial neural crest cells
Muscle

Species:
Mouse
Rat
Human
Other

Craniofacial phenotype analysis of mutant animal models

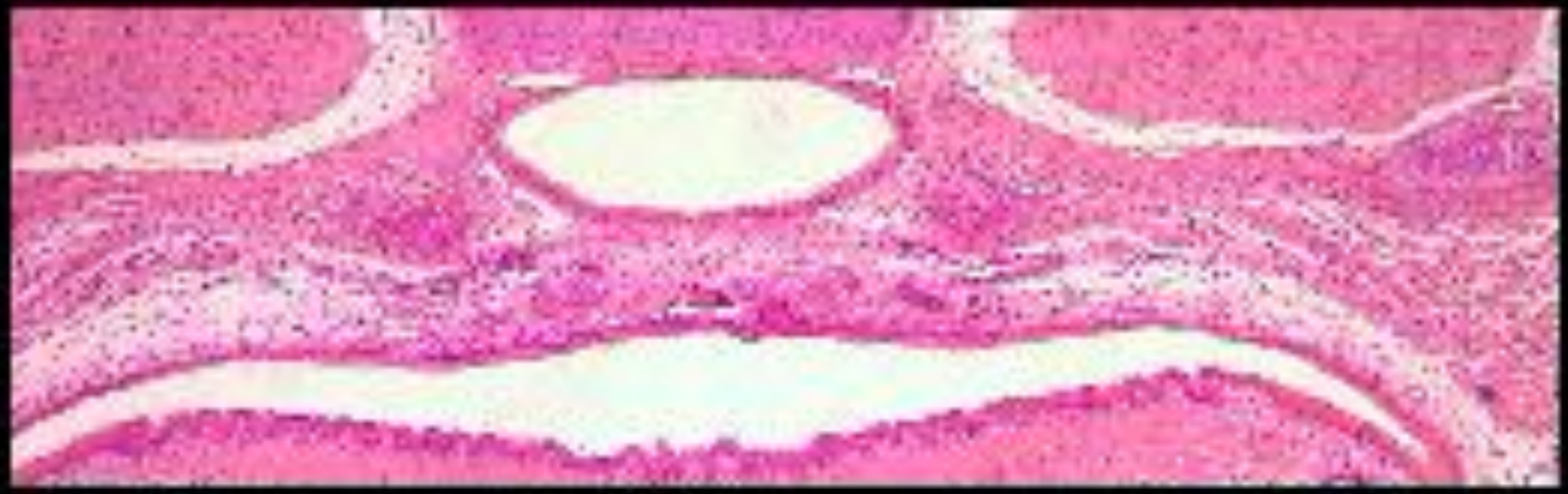
Genotype	Tgfbr2$^{fl/fl}$;Wnt1-Cre
Symbol (MGI)	Tgfbr2$^{tm1.2Hlm}$
Known defects	Cleft palate, Bone defects, Small tongue
Known human diseases	Loeys-Dietz syndrome
Histology	E13.5, E14.5, E16.5, E18.5
SEM	E18.5
μCT	E18.5
μMRI	E18.5
Gene expression analysis	E14.5
Protein expression analysis	E13.5, E14.5
References	Ito Y *et al.*, *Development* 2003 Sasaki T *et al.*, *Development* 2005 Oka K *et al.*, *Dev Biol* 2007 Oka K *et al.*, *Dev Biol* 2008 Iwata J *et al.*, *J Biol Chem* 2010 Iwata J *et al.*, *J Clin Invest* 2012 Iwata J *et al.*, *J Biol Chem* 2012

Click

Click

FaceBase

Wild type



E18.5

FaceBase

Search Tgfbr2

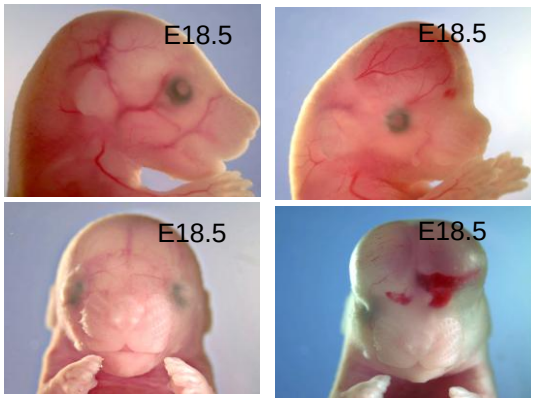
Molecules:
Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules
miRNA
Enhancers

Mutation in:
Epithelium
Mesenchyme
Mesoderm-derived cells
Cranial neural crest cells
Muscle

Species:
Mouse
Rat
Human
Other

Gross picture

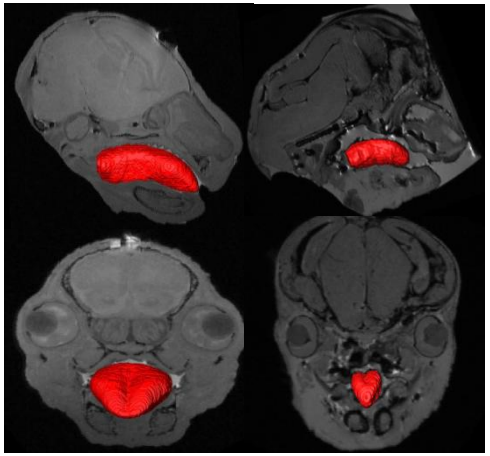
Control	*Tgfbr2$^{fl/fl}$; Wnt1-Cre*
E18.5	E18.5
E18.5	E18.5



microMRI

Control	*Tgfbr2$^{fl/fl}$; Wnt1-Cre*

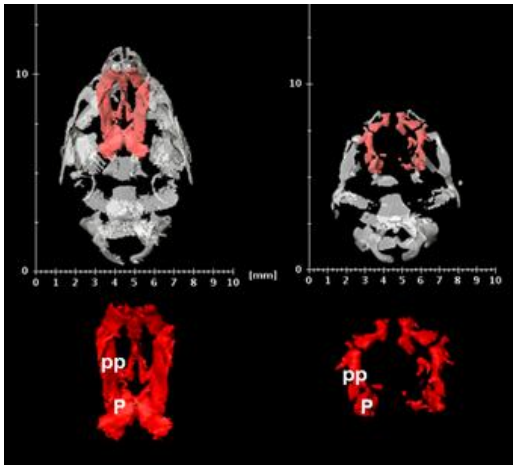
Sagital
Frontal



microCT (Hard tissue)

Control	*Tgfbr2$^{fl/fl}$; Wnt1-Cre*

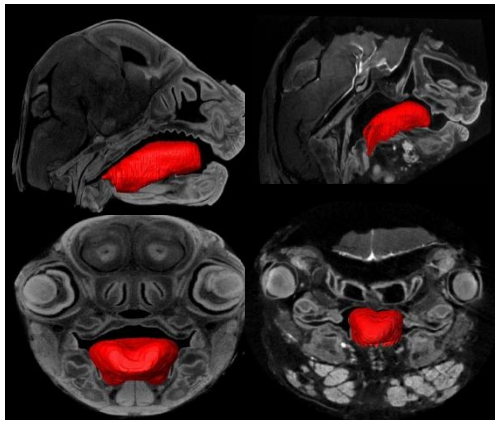
Maxilla
Palate



microCT (Soft tissue)

Control	*Tgfbr2$^{fl/fl}$; Wnt1-Cre*

Sagital
Frontal



3D

Collaboration

Foroud, Schutte

Shapiro

Satya/Hub

Admin Supplement Submitted

Weinberg/ Marazita

Jeff Murray/ Mary Marazita/ David FitzPatrick

CIDR Application

Spritz

Visel

Donahue/ Murray

Beaty

Potter

Clouthier/ Artinger/ Postlethwaite

Mike Dixon

Chai

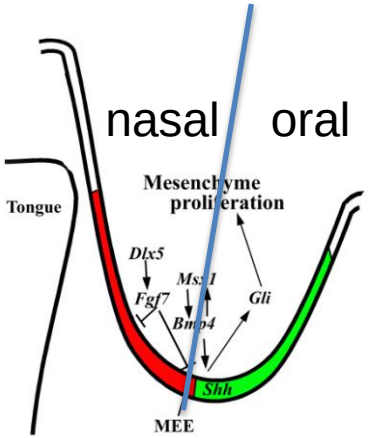
Regional specific gene expression analysis

TGF-β/IRF6

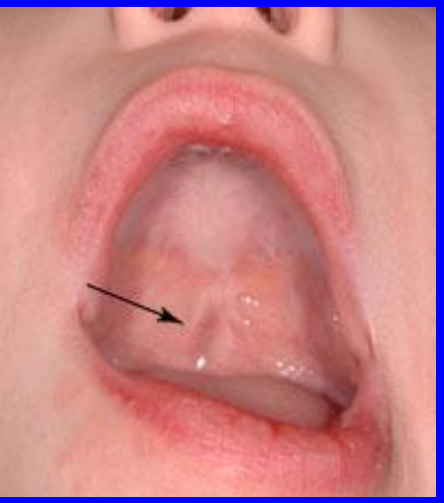
Fraser

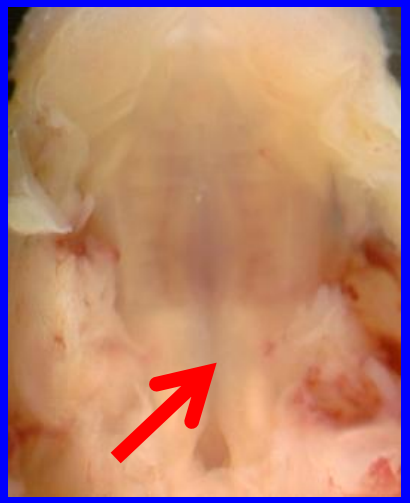
Proposal Submitted

3D imaging



Submucosal cleft palate model

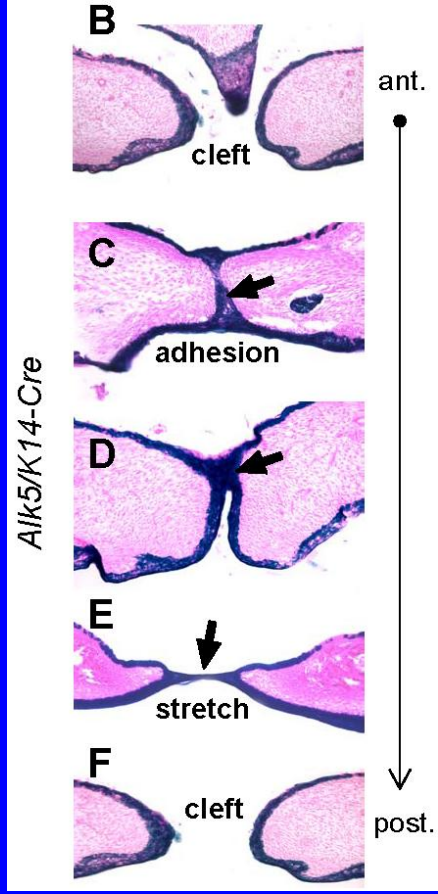




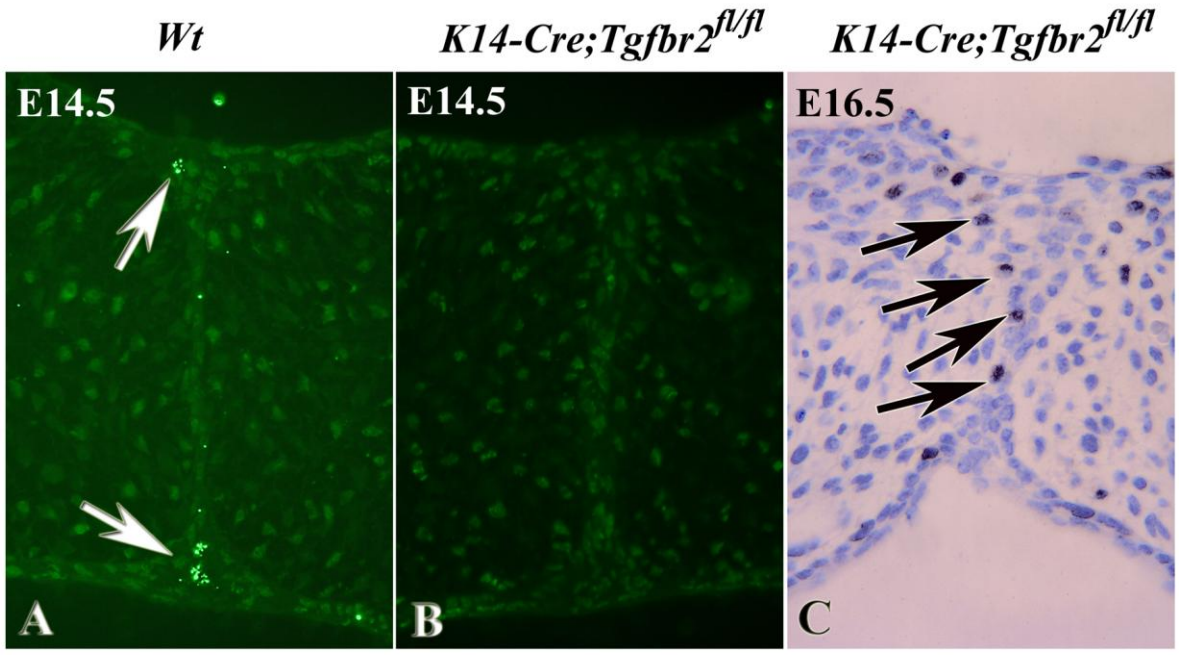
K14-Cre;Tgfbr2$^{fl/fl}$

K14-Cre;Tgfbr1$^{fl/fl}$

NB

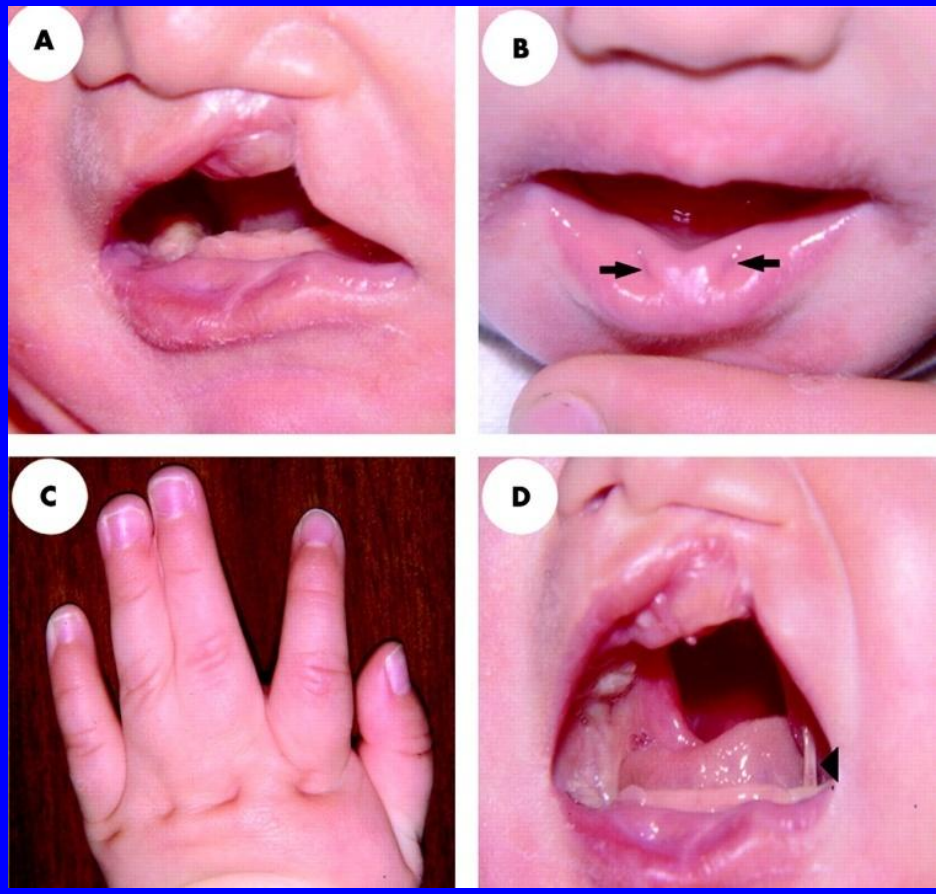


Tgfbr1=Alk5



Mutations in *IRF6* underlie Van der Woude syndrome (VWS) and popliteal pterygium syndrome (PPS)

VWS and PPS are allelic variants of the same condition; that is, they are caused by different mutations of the same gene. PPS includes all the features of VWS, plus popliteal pterygium, syngnathia, distinct toe/nail abnormality, syndactyly, and genito-urinary malformations.

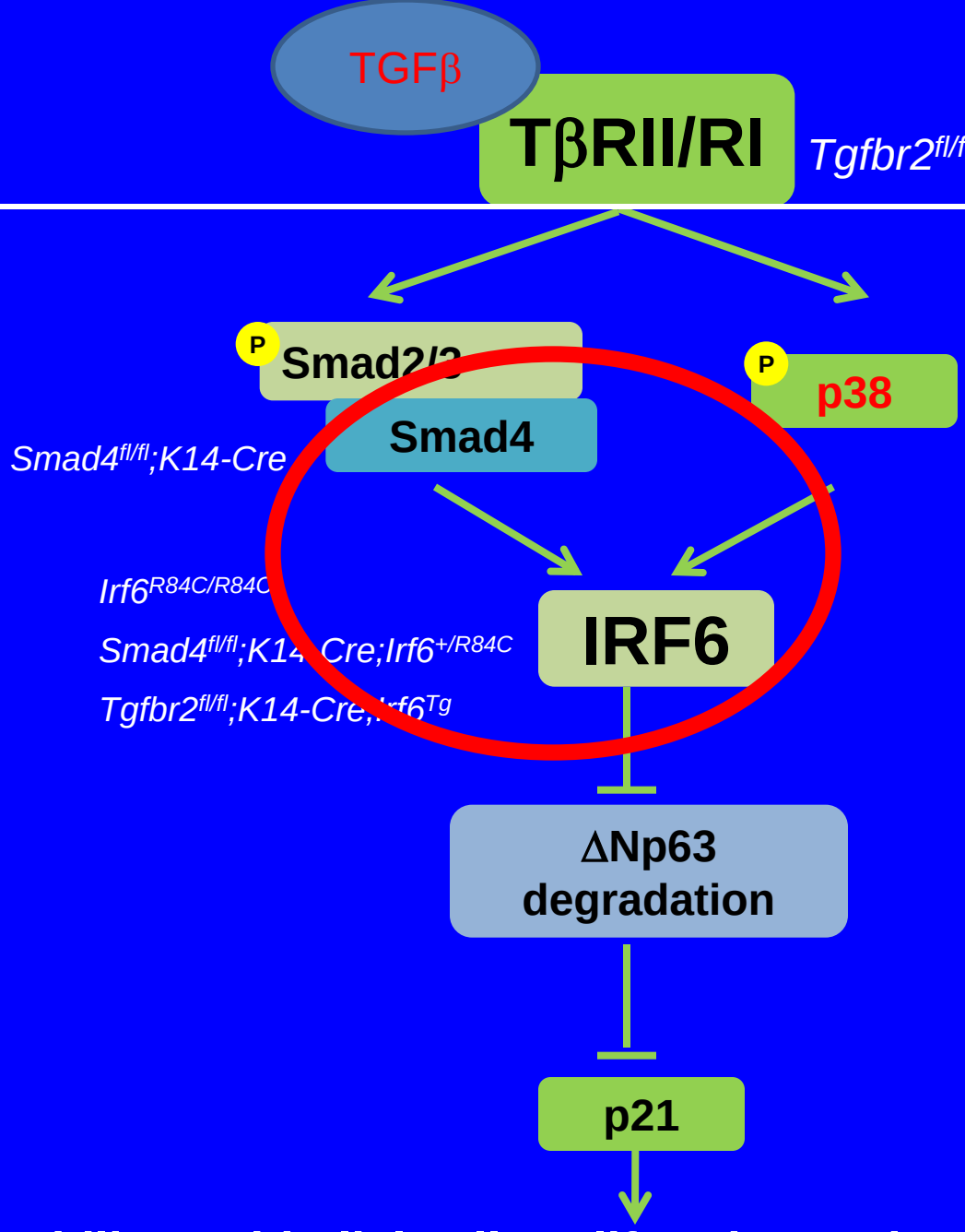


Genetics

VWS and PPS are inherited in an autosomal dominant manner and are **due to mutation of the *IRF6* gene**. Most reported cases are sporadic; advanced parental age is found in a number of these cases, suggesting new mutations.

Kondo et al. (2002) Nature Genetic

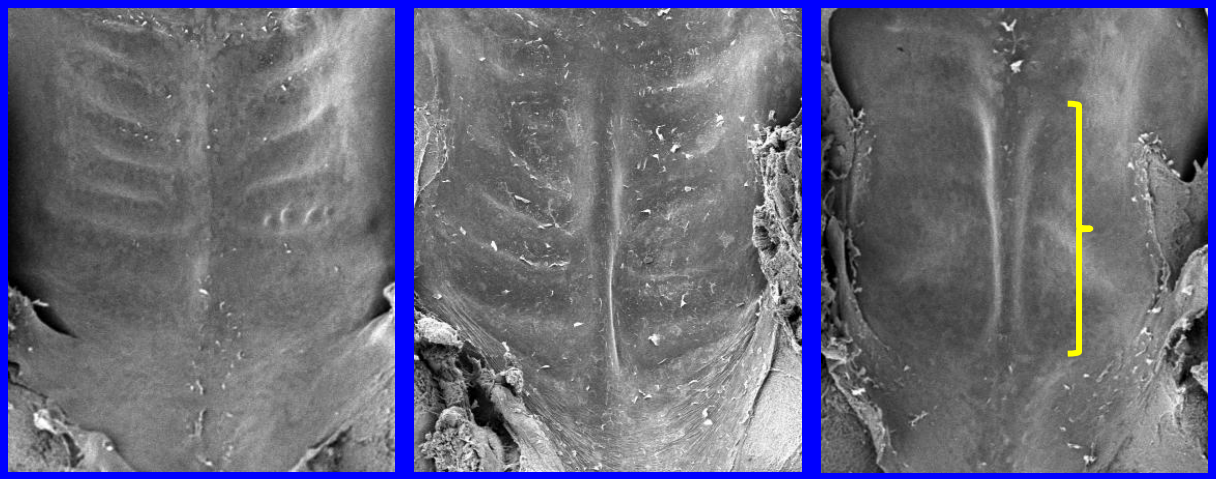
Proposed model



Midline epithelial cell proliferation and apoptosis during palatal fusion

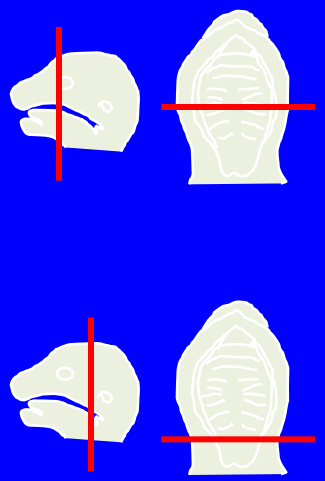
A haploinsufficiency of *Irf6* in *Smad4$^{fl/fl}$;K14-Cre* mice cause submucosal cleft palate

Control | *K14-Cre;Smad4$^{fl/fl}$* | *K14-Cre;Smad4$^{fl/fl}$;Irf6$^{R84C/+}$*



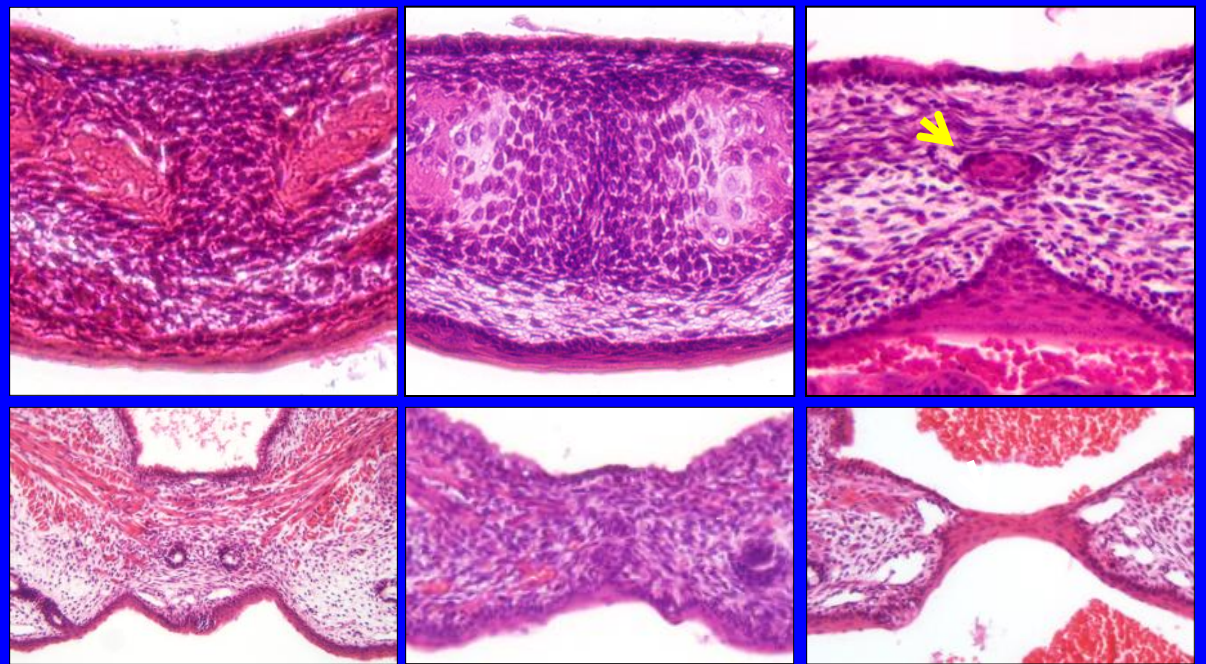
Control | *K14-Cre;Smad4$^{fl/fl}$* | *K14-Cre;Smad4$^{fl/fl}$;Irf6$^{R84C/+}$*

E18.5

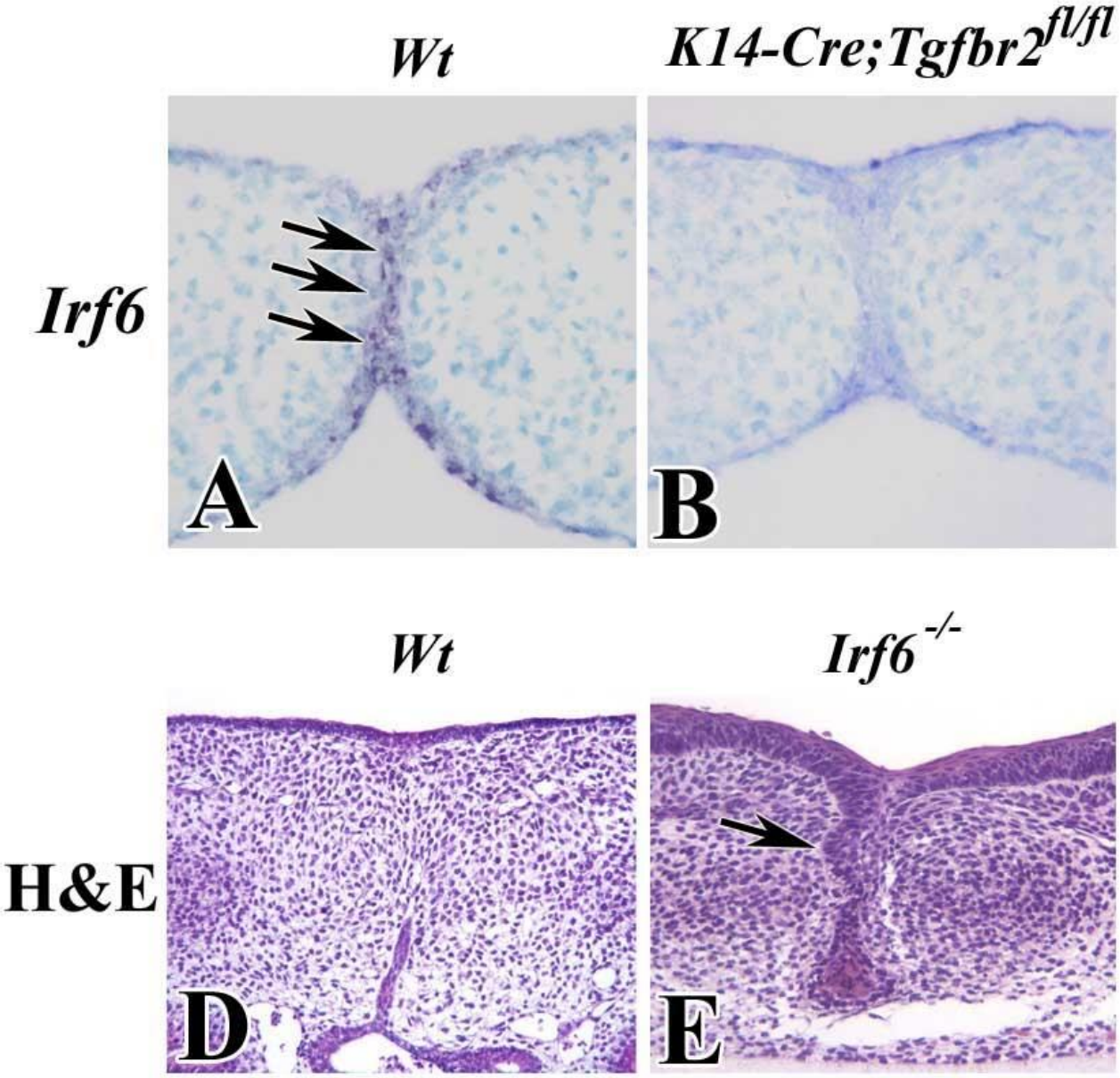


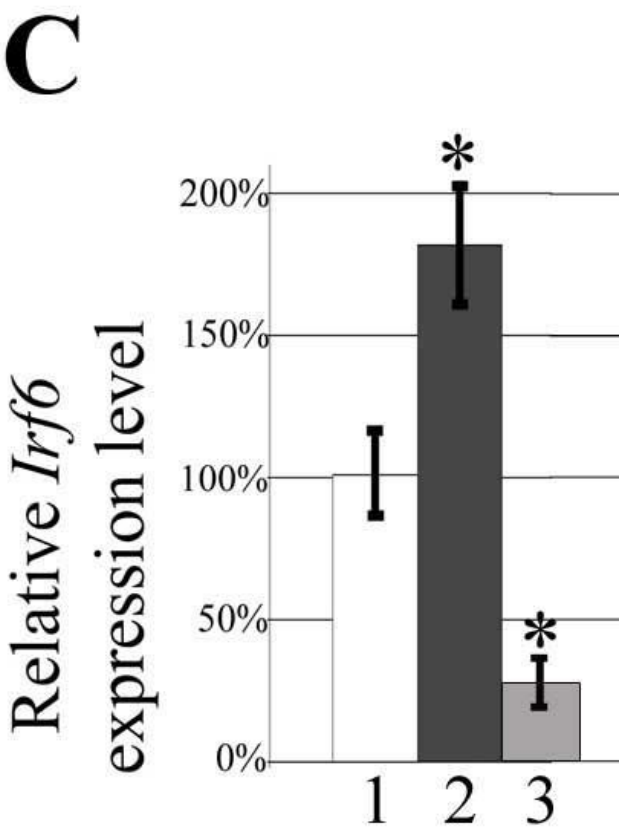
Hard palate

Soft palate



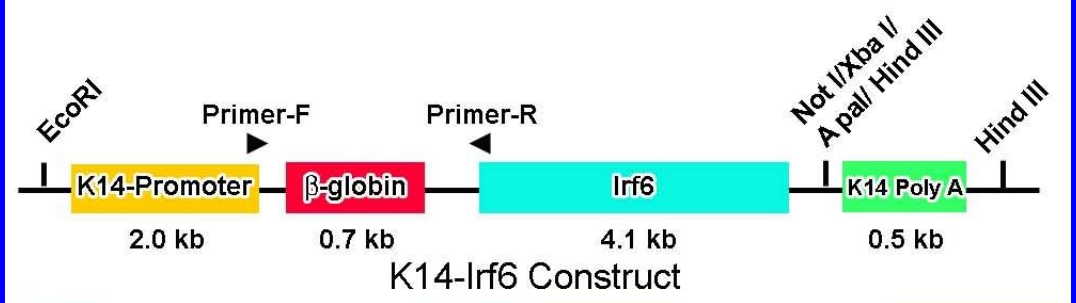
TGF-β mediated Irf6 expression is crucial for the disappearance of MEE cells during palatogenesis

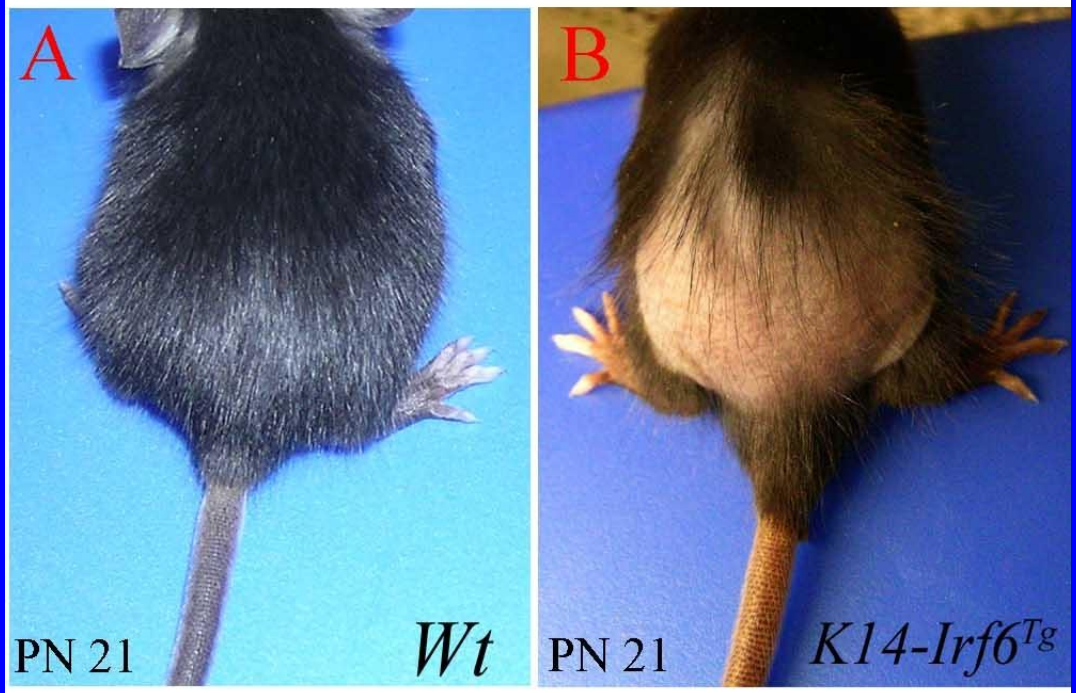


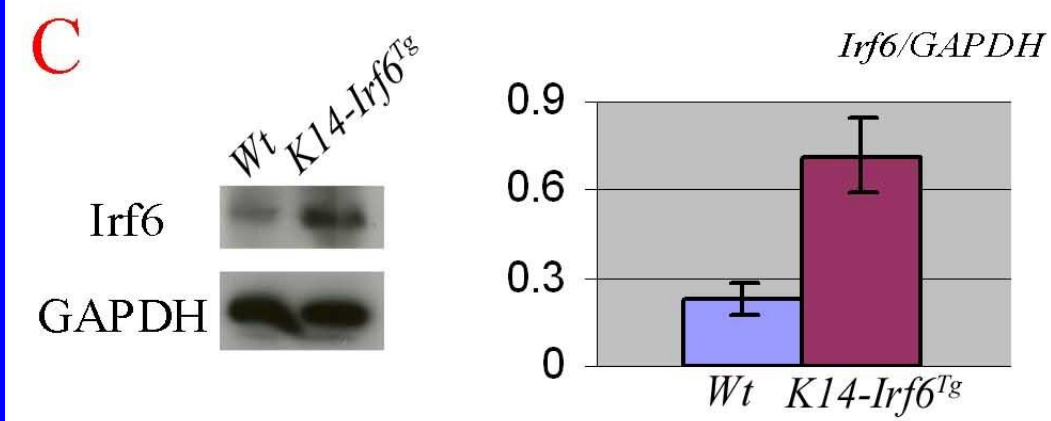


1. Wt
2. Wt plus TGF-β3 Tx
3. K14-Cre;Tgfbr2$^{fl/fl}$ plus TGF-β3 Tx

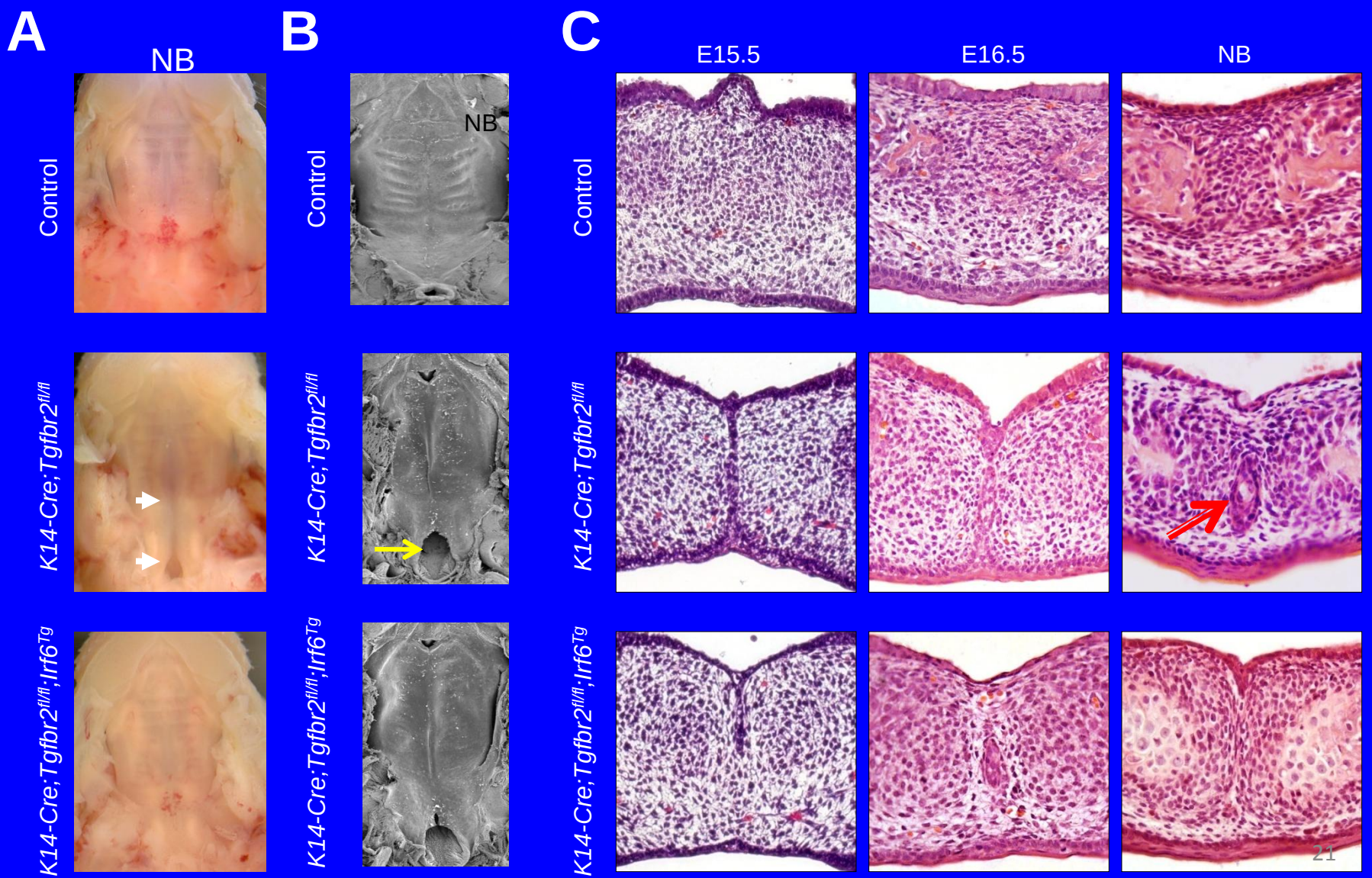
Generation of *K14-Irf6^{Tg}* line to overexpress IRF6 in epithelial cells







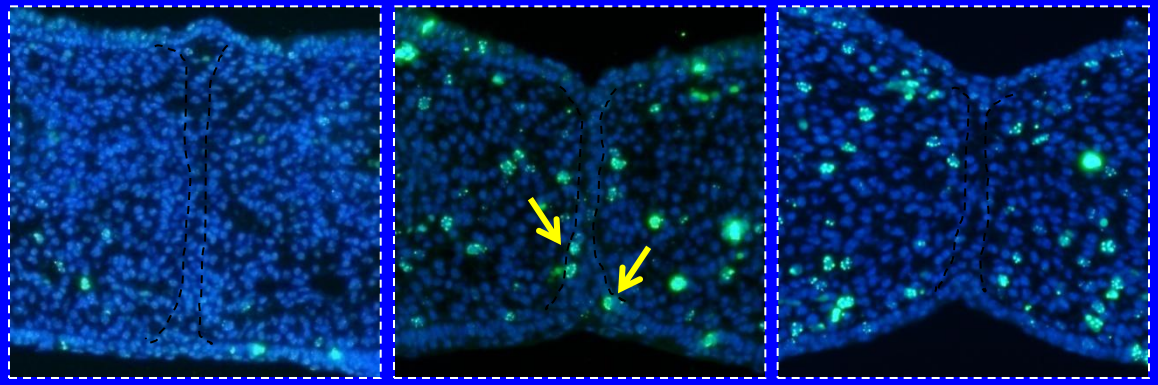
Over-expression of *Irf6* results in disappearance of MEE in *Tgfbr2$^{fl/fl}$;K14-Cre* mice

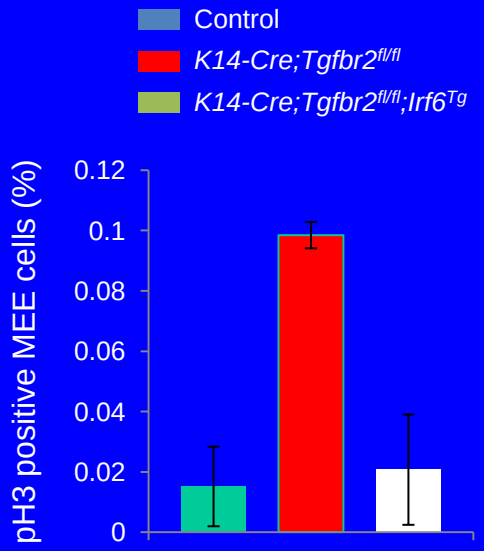


Disappearance of MEE cells in *Tgfbr2$^{fl/fl}$;K14-Cre* mice following over-expression of *Irf6*

Cell proliferation analysis

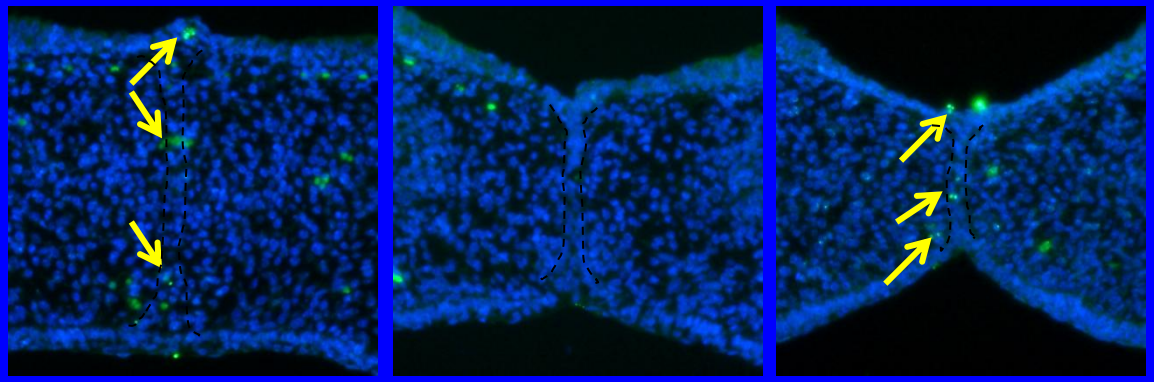
Control | *K14-Cre;Tgfbr2$^{fl/fl}$* | *K14-Cre;Tgfbr2$^{fl/fl}$;Irf6^{Tg}*

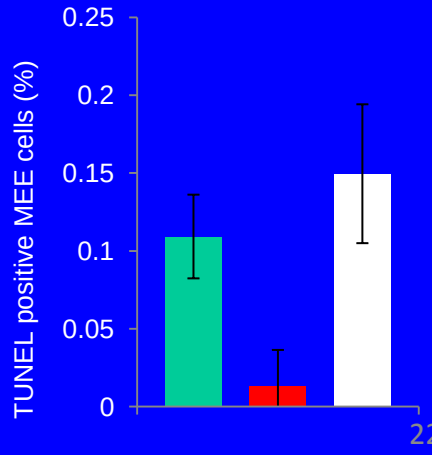




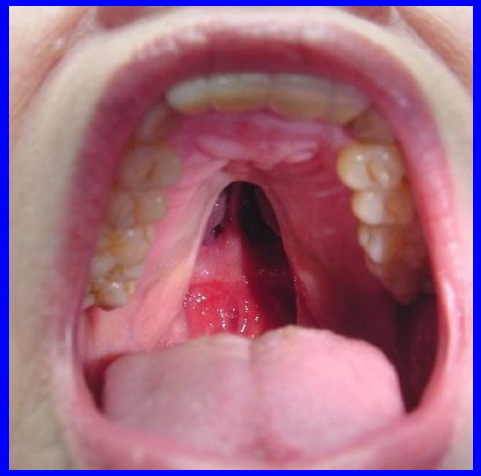
TUNEL assay

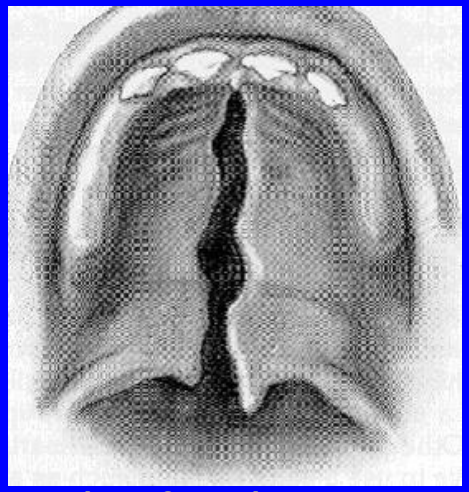
Control | *K14-Cre;Tgfbr2$^{fl/fl}$* | *K14-Cre;Tgfbr2$^{fl/fl}$;Irf6^{Tg}*



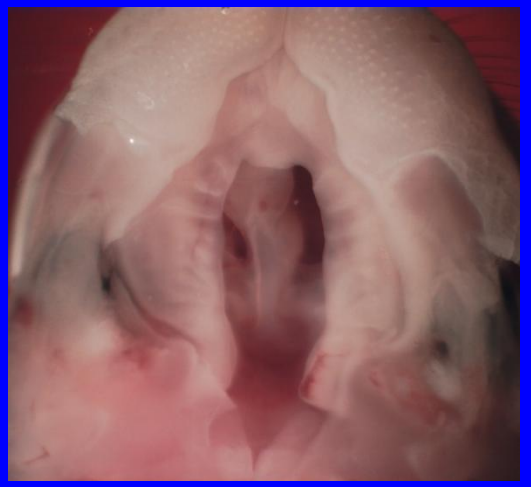


Cleft palate in Animal models

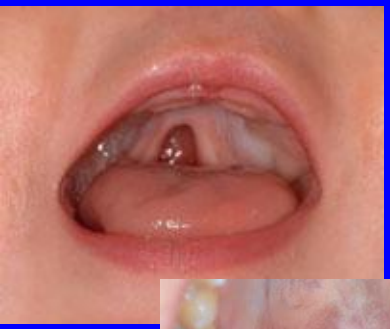


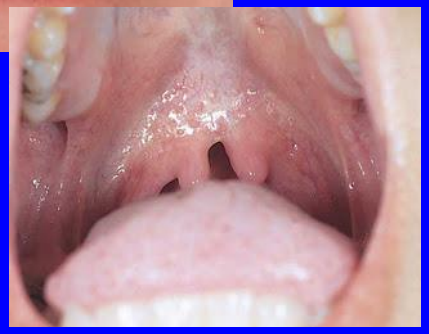


Complete cleft of hard and soft palate

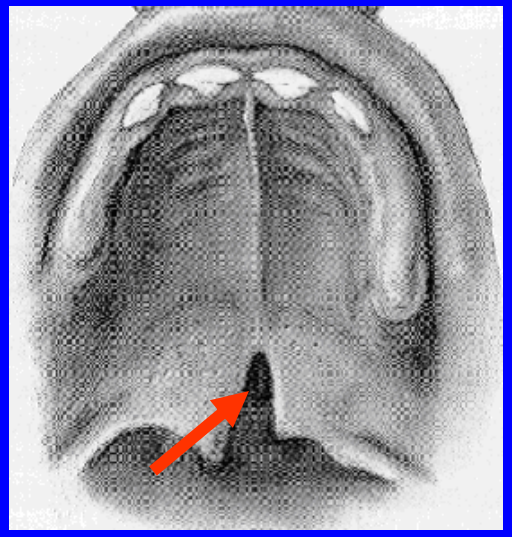


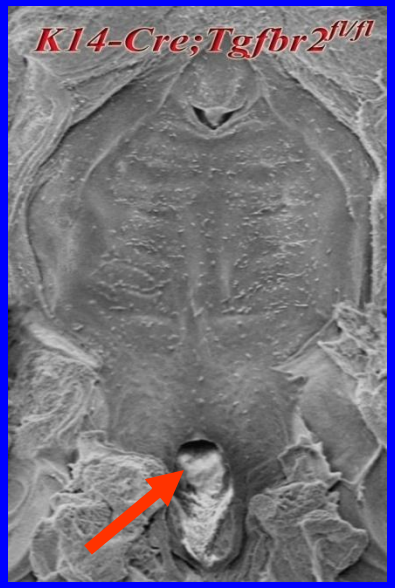
Wnt1-Cre;Tgfbr2$^{fl/fl}$





Cleft of soft palate





K14-Cre;Tgfbr2$^{fl/fl}$

Summary and discussion:

1. TGF-β mediated *Irf6* expression is crucial for midline epithelial cells (MEE) to undergo apoptosis during palatal fusion. The connection between TGF-β and Irf6 signaling in the mouse model advocates for a closer examination of associated TGF-β and IRF6 mutations in human clefting cases. Smad4 and IRF6 interaction plays an important role in MEE cell fate determination. Compound mutations of Smad4 and IRF as well as their implications in submucosal cleft palate.

2. What is the best way to present our data at the hub? How do people search our data?

Poster presentations from Yang Chai's group

Junichi Iwata: TGF-β-mediated IRF6 activity is crucial for disappearance of the medial edge epithelium during palate formation in mice.

Carolina Parada: Crucial role for Erk2 signaling in palate development

Richard Pelican: Identification of Novel Candidate Pathways Contributing to Cleft Palate Formation in Tgfbr2 Mutant mice

Pedro Sanchez: Validation and reproducibility of three-dimensional craniofacial volume and anatomy using micro-CT and micro-MRI modalities in wild type and mutant mouse embryos