

Dyostoses Mandibulofaciales

Projet de Recherches

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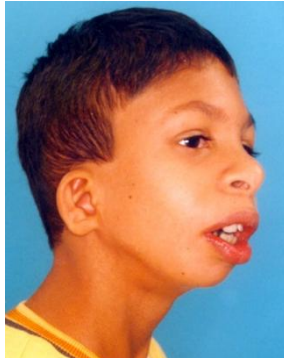
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**MANDIBULOFACIAL DYSOSTOSIS
WITH MICROCEPHALY
SYNDROME (MFDM, MIM610536)**

Mandibulofacial Dysostosis Guion-Almeida type (MIM610536)



Spectre des signes observés par ordre décroissant

- Pre and/or post natal growth retardation
- Microcephaly, ID +/- epilepsy
- MFD with dysplastic external ears +/- tags
- Sensorineural hearing loss
- Semicircular canal dysplasia
- Congenital cardiac defect
- **Oesophageal atresia**
- Choanal atresia
- Radial ray defect
- Vertebral malformation / skoliosis
- Renal malformation
- Olfactory bulb agenesis

Diagnostics différentiels

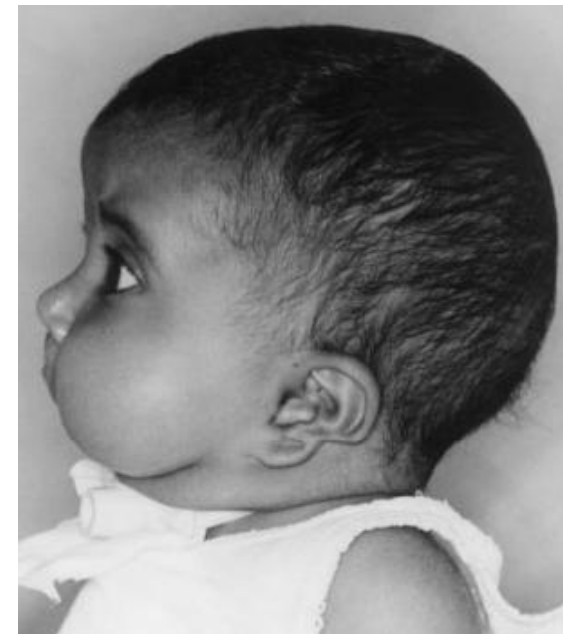
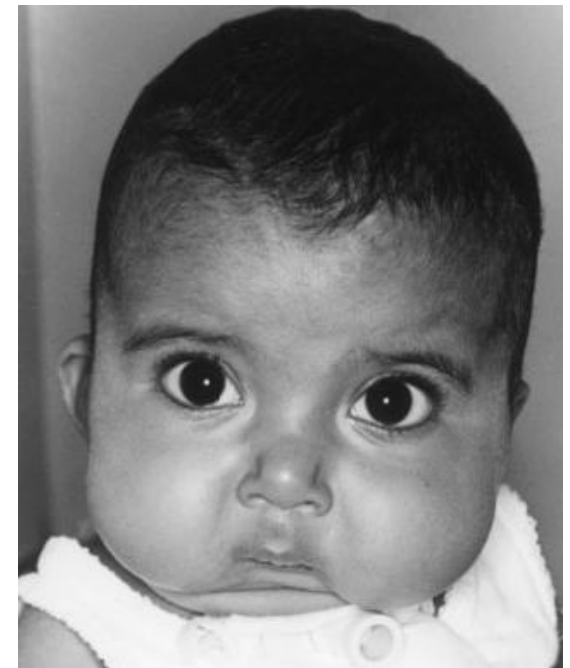
- **VACTERL ?**
- **OAVS-AO**
- **Anémie de Blakfan-Diamond**

- **Feingold Syndrome ?**
 - Microcephaly
 - Growth retardation
 - Esophageal atresia
 - Radial ray defect
 - Toe syndactyly
 - Congenital cardiac defect
 - Deafness
 - ~~Brachymesophalangy~~

- **CHARGE**
 - Dysplastic ears
 - Facial asymmetry
 - Choanal atresia
 - Sensorineural hearing loss
 - Semicircular canal dysplasia
 - Congenital cardiac defect
 - Olfactory bulb agenesis
 - Esophageal atresia
 - ~~HUGR and primary microcephaly~~

**AURICULOCONDYLAR
SYNDROME (MIM602483)**

Clinical signs (N=24)	Frequency (%)
Question mark ear(s)	100
Temporomandibular joint anomaly	100
Mandibular condyle anomaly	93
Malocclusion	93
Mandibular hypoplasia	78
Microstomia	78
Round face	78
Prominent cheeks	74
earing loss	56
abnormal palate	55
Facial asymmetry	44
Glossoptosis	35
Hypoplastic tongue	17
Apneas	48
Feeding difficulties	25
Pre / Postauricular tags	20
Hypotonia / mild ID	< 10

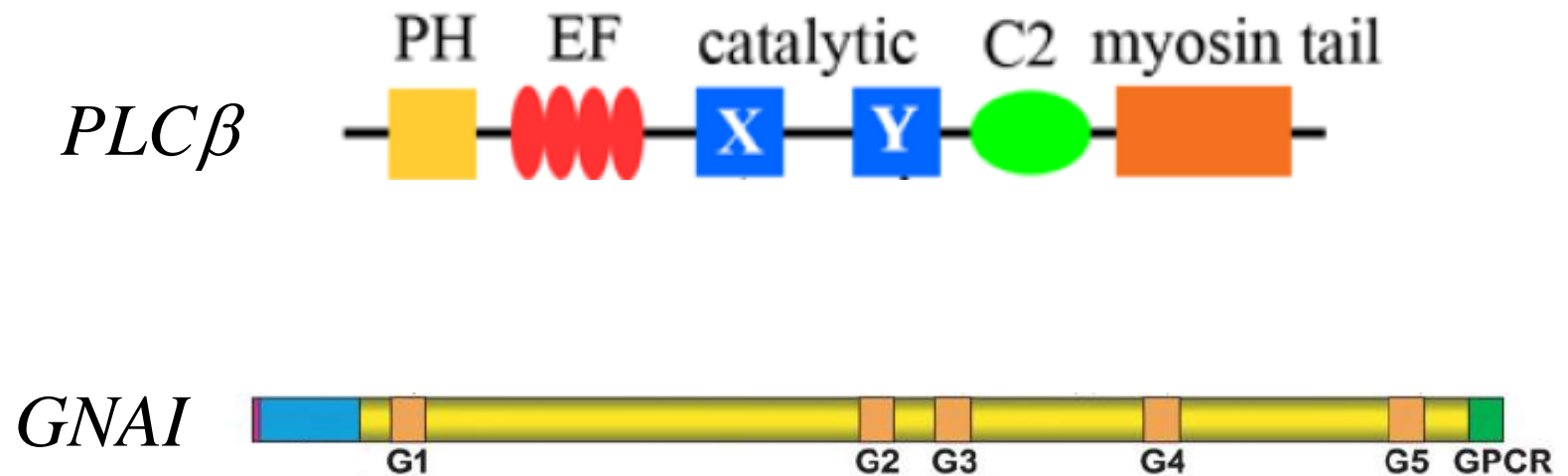


Adapted from Kokitsu-Nakata et al. *AJMG* 2011

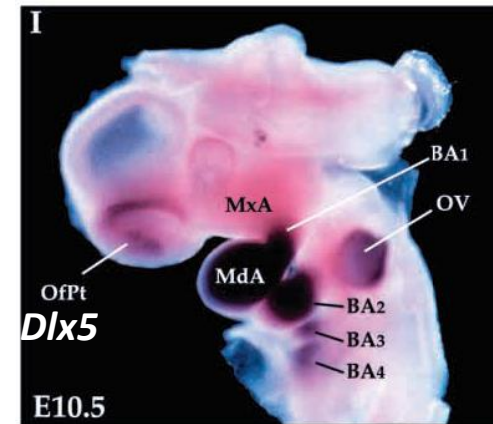
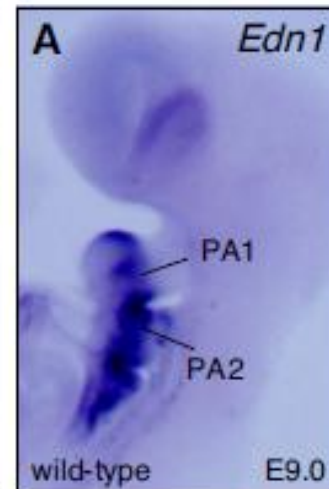
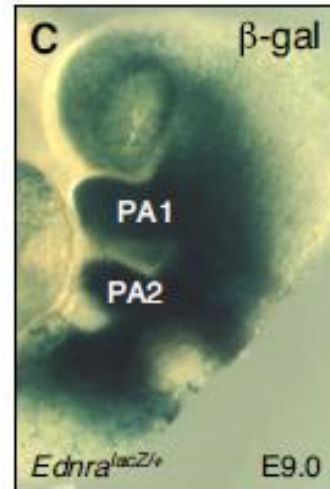
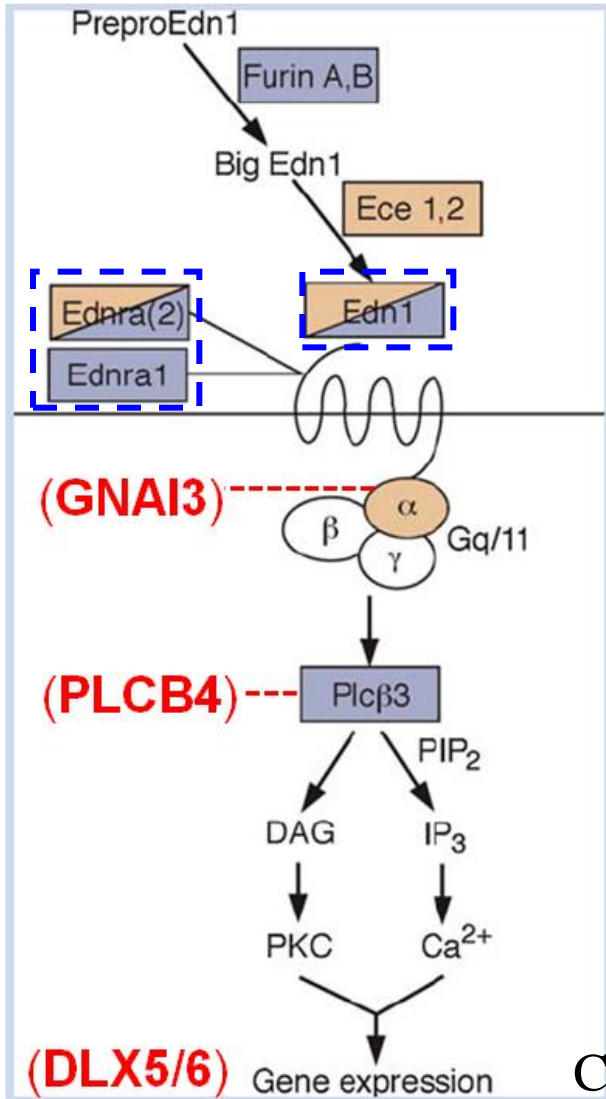
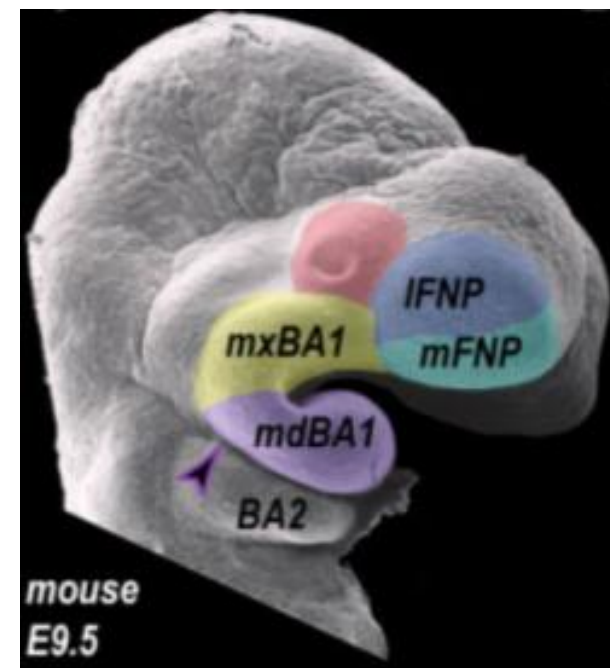
Guion-Almeida et al. *AJMG* 2002

A Human Homeotic Transformation Resulting from Mutations in *PLCB4* and *GNAI3* Causes Auriculocondylar Syndrome

Mark J. Rieder,^{1,*} Glenn E. Green,² Sarah S. Park,³ Brendan D. Stamper,³ Christopher T. Gordon,^{4,5} Jason M. Johnson,⁶ Christopher M. Cunniff,⁷ Joshua D. Smith,¹ Sarah B. Emery,² Stanislas Lyonnet,^{4,5,8} Jeanne Amiel,^{4,5,8} Muriel Holder,⁹ Andrew A. Heggie,¹⁰ Michael J. Bamshad,^{1,11} Deborah A. Nickerson,¹ Timothy C. Cox,^{3,11,12,13} Anne V. Hing,^{3,11,12} Jeremy A. Horst,¹⁴ and Michael L. Cunningham^{3,11,12}



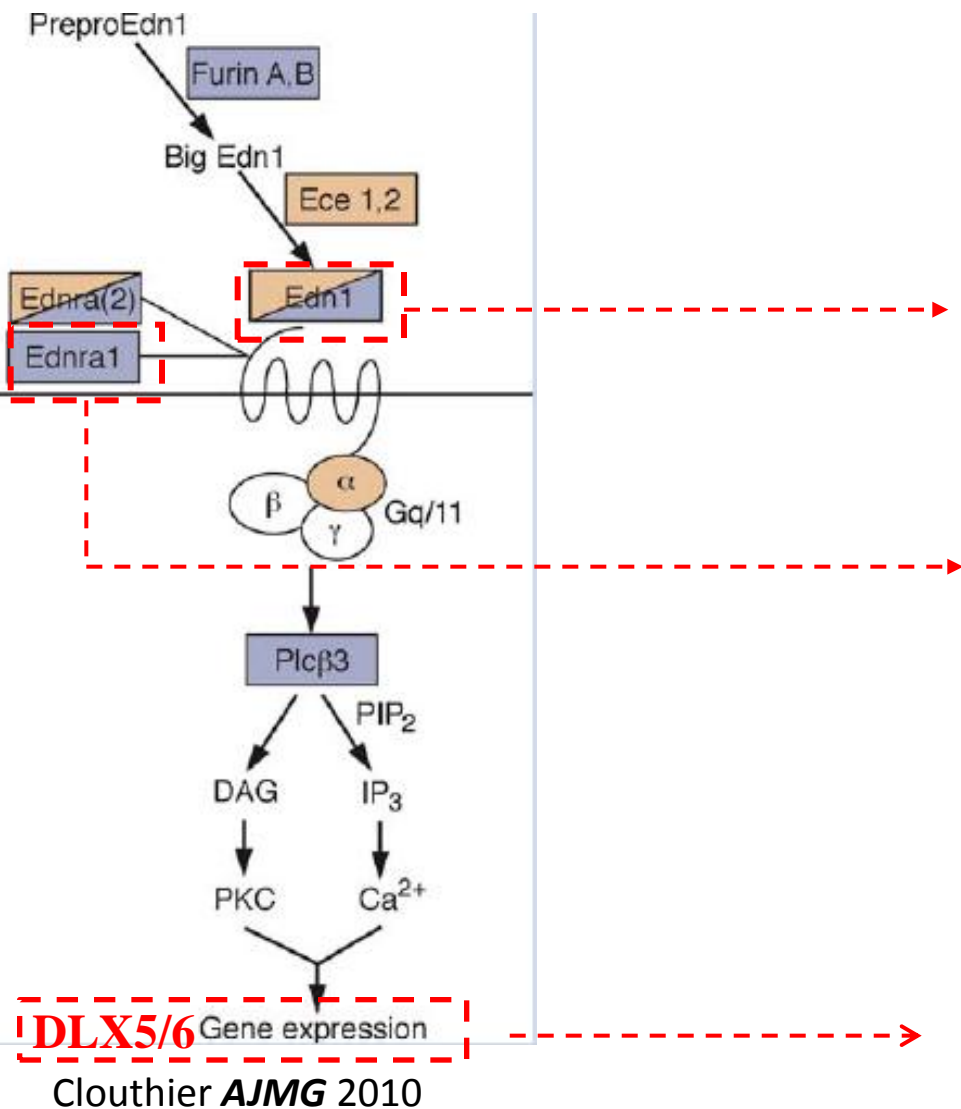
The Endothelin Pathway Drives the First Pharyngeal Arch Development



Mandible-specific pathway

Clouthier *AJMG* 2010, Depew *Dev* 1999, Sato *PNAS* 2008

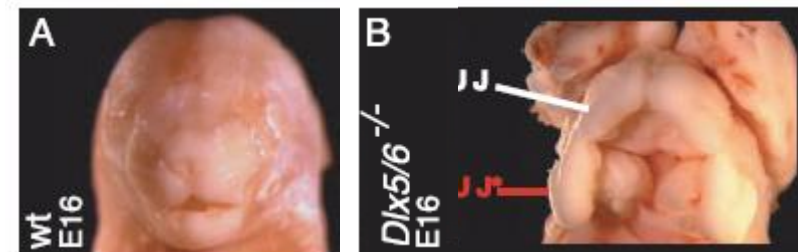
The Endothelin Pathway Drives the First PA Development



Ozeki et al. *Mech Dev* 2004



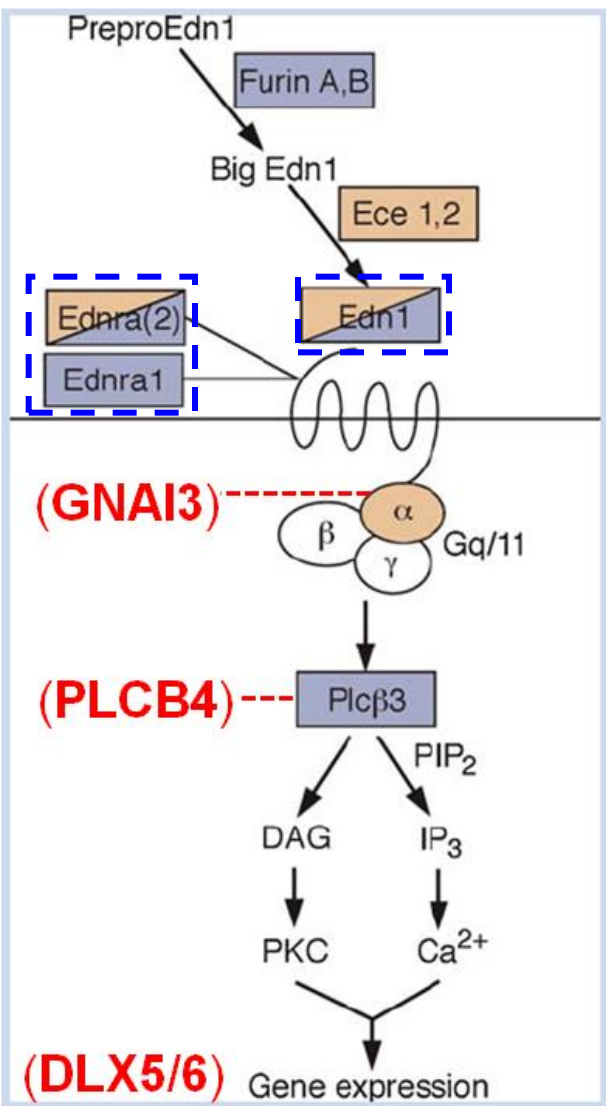
Clouthier et al. *Development* 1998



Depew et al. *Science* 2002

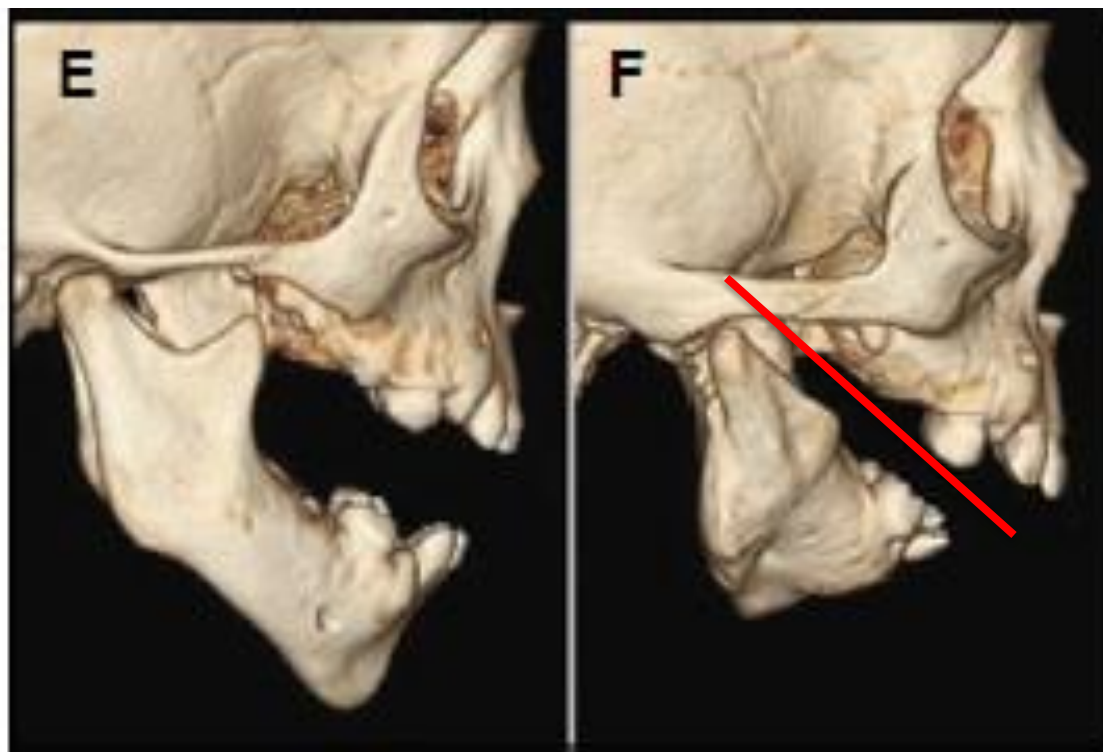
Knockouts of the Edn1/Ednra/Dlx Pathway in Mice Result in Mandibular to Maxillary Transformation

Mandible to Maxillary Transformation in ACS



Normal

ACS



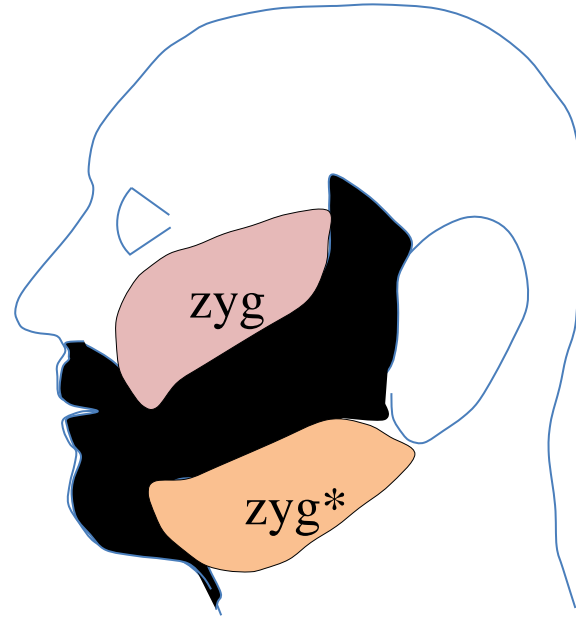
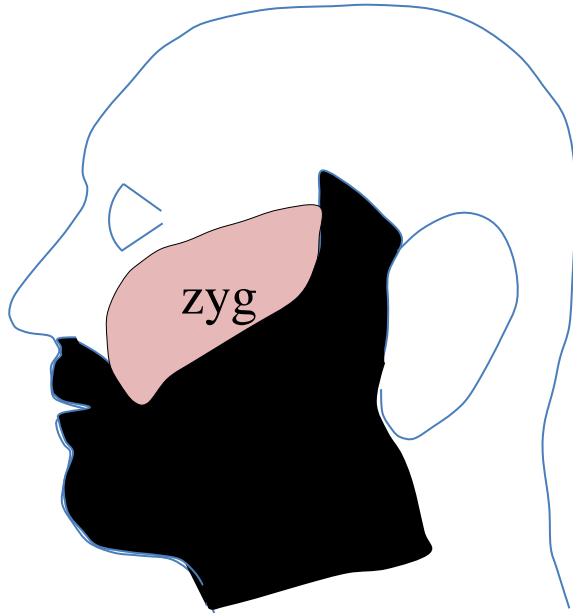
Regions of Absent Facial Hair on Jaw-Line of ACS males



Phenotype

Normal

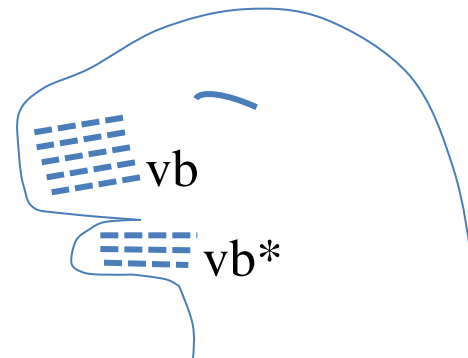
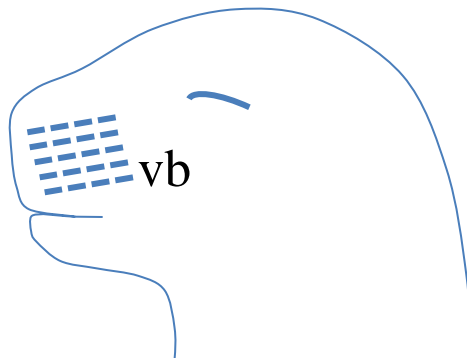
Mandibular to maxillary transformation



Genotype

Wildtype

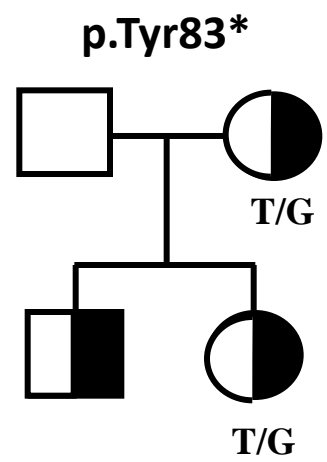
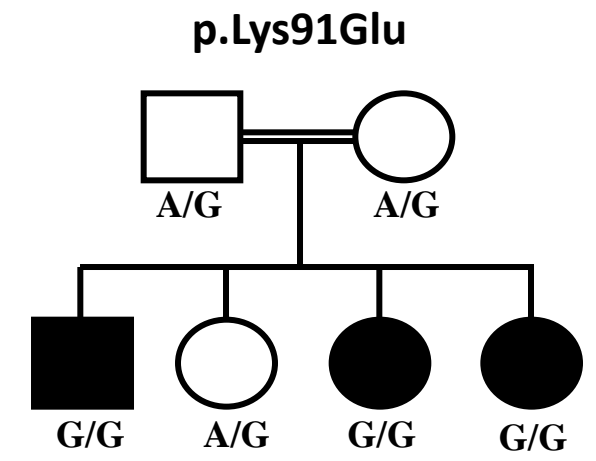
PLCB4/GNAI3 missense mutation



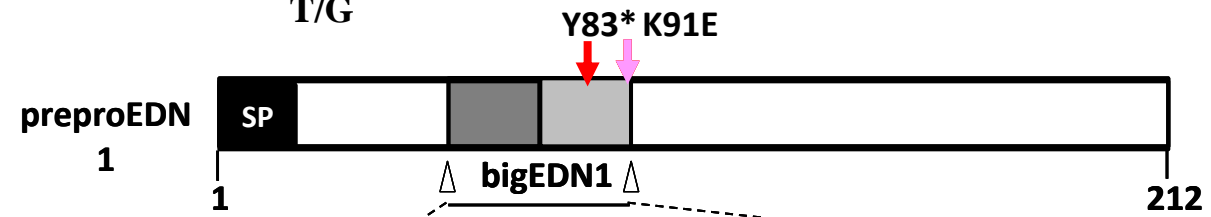
Genotype

Wildtype

Edn1/Ednra/Dlx5+6 knockout



Mutations de EDN1 dans l'ACS et l'oreille en point d'interrogation isolée



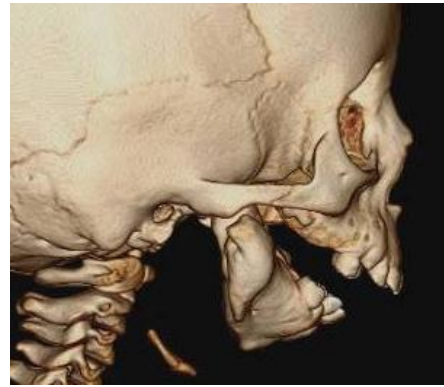
human_EDN1	LRRSKRCSCSSLMDKECVYFCHLDIIWVNTPEHVVPYGL---GSPRSKRAL
mouse_Edn1	PRRSKRCSCSSLMDKECVYFCHLDIIWVNTPERVVPYGLG---GSSRSKRSL
zebrafish_edn1	HSRNKRCSCASFLDKECVYFCHLDIIWVNTPERTVSYGLGN---APRKKRSV
human_EDN3	HHRSRRCTCFITYKDKECVYYCHLDIIWINTPECTVYGLSNYRGSFRGKRSA
mouse_Edn3	HHRPRRCTCFITYKDKECVYYCHLDIIWINTPECTVYGLSNYRESLRGKRSL

EDNRA Signalling in ACS

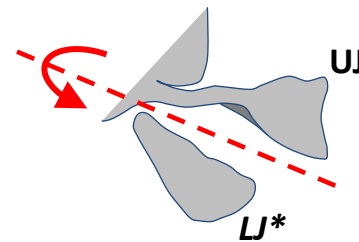
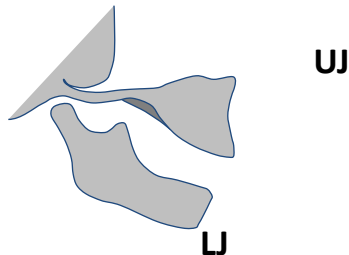
Down-regulation of the
EDNRA pathway
in the lower jaw



Normal



ACS



Lower jaw
transformed
into upper
jaw-like
structure

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