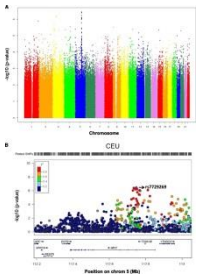
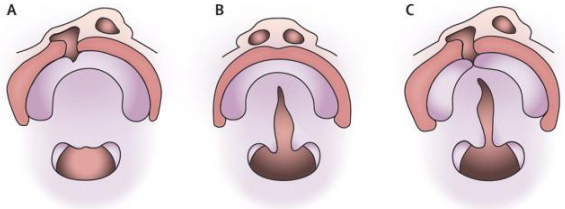
Cleft Lip and Palate: Genetic aspects and phenotypic aspects of syndromic forms

DEVELOPMENTAL, GENETIC AND MOLECULAR ASPECTS

PR FRANÇOIS CLAUSS



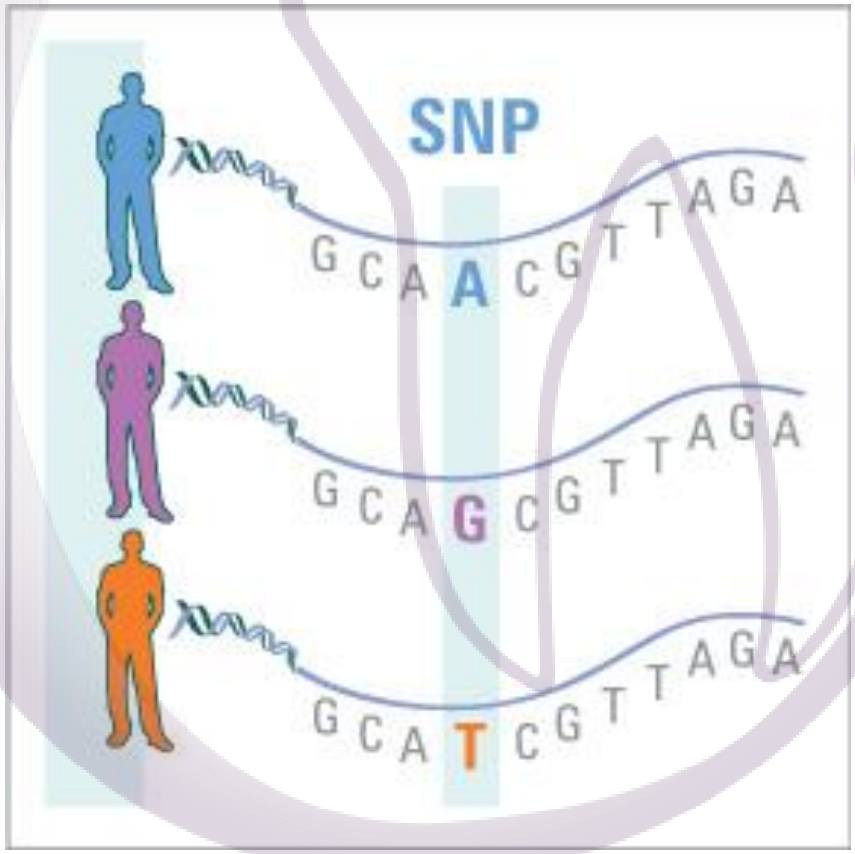


ORares
MANIFESTATIONS ORALES ET DENTAIRES DES MALADIES RARES STRASBOURG

Faculté de chirurgie dentaire
UNIVERSITÉ DE STRASBOURG

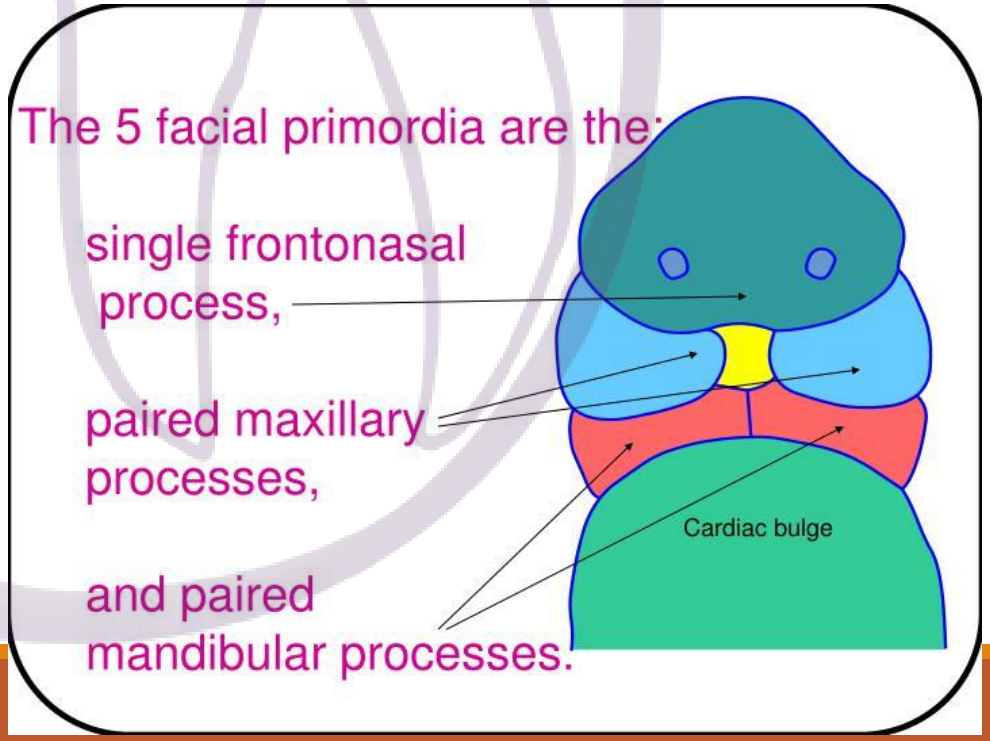
Les Hôpitaux Universitaires de STRASBOURG

Pathogenesis and genetic analysis in the field of cleft lip palate



Aetiological mechanisms of clefts

- Differentiation and fusion of the different facial primordia : complex mechanisms with molecular regulation begin in the 4th week of embryonic development (ED) : formation of **single frontonasal, maxillary and mandibular processes**
- Spatial and temporal regulation by environmental and genetical factors : **genome-environement interactions**
- Underlying cellular and molecular mechanisms: cellular proliferation, neural crest cells migration, fusion, apoptosis

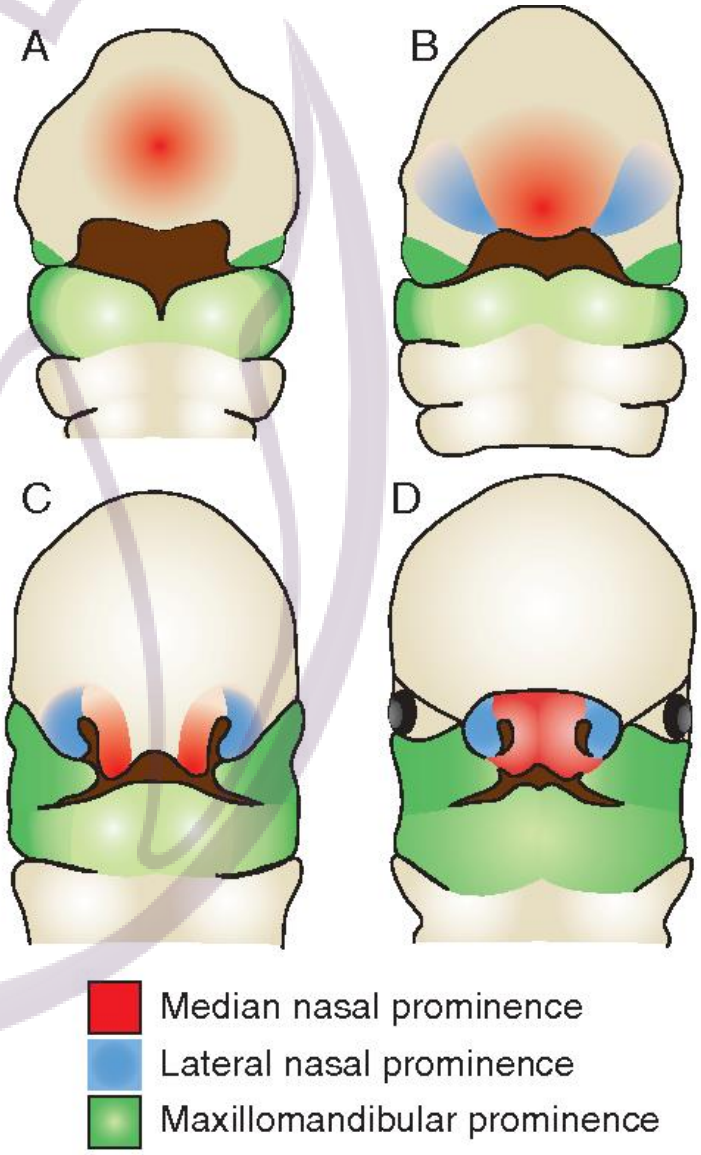


Aetiological mechanisms of clefts

- **6th-7th week of ED**: fusion of maxillary process-lateral and median nasal processes
  Defect at this stage: **labio-alveolar cleft with or without cleft palate**

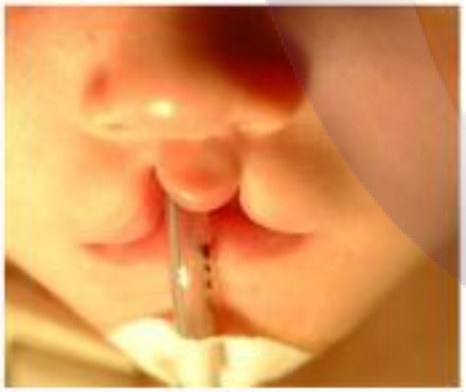
- **7th week of ED:** palatogenesis with development of palatal processes from the maxillary process and fusion on the median line (**MEE**: medial edge epithelia)

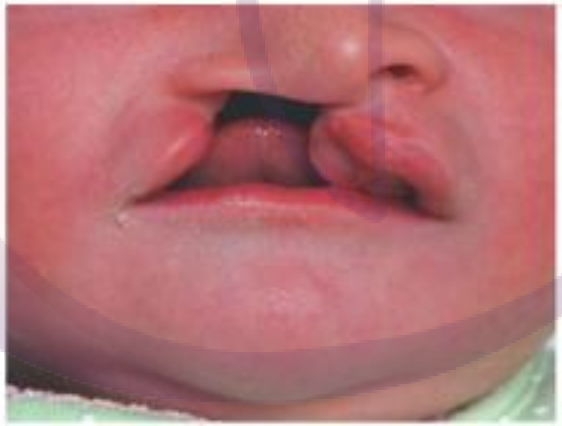
- Defects in development or elevation of the palatal processes : **secondary palatal cleft**

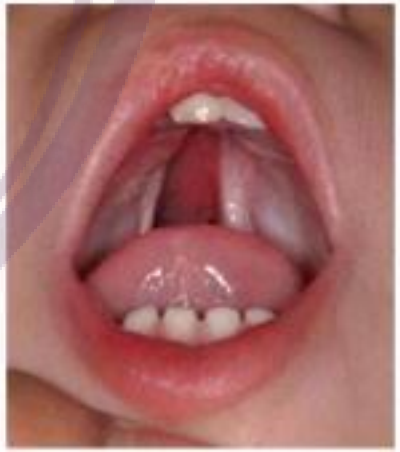


Aetiological mechanisms of clefts

- Strong clinical variability and genetic heterogeneity of clefts
- Early defects : lip of primary palate cleft
- Late defect of palatogenesis: secondary palate cleft







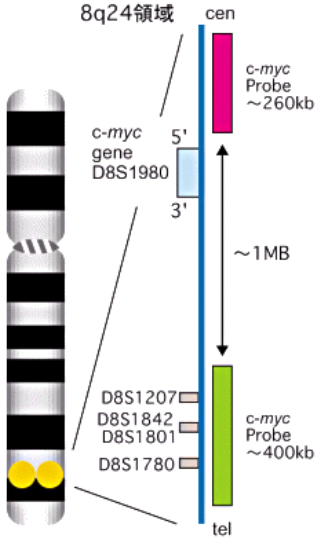
Leslie et al., 2013

Genome Wide Association Studies (GWAS) analysis : Application to CLP molecular pathogenesis

- SNP analysis for potentially pathogenic variants identification in families with affected individuals

- 3 major international GWAS case-control studies and one case-parent study on CLP genetic ethiologies

- Birnbaum et coll., **Key susceptibility locus for non syndromic cleft lip with or without cleft palate on chromosome 8q24**. Nature Genetics 2009.



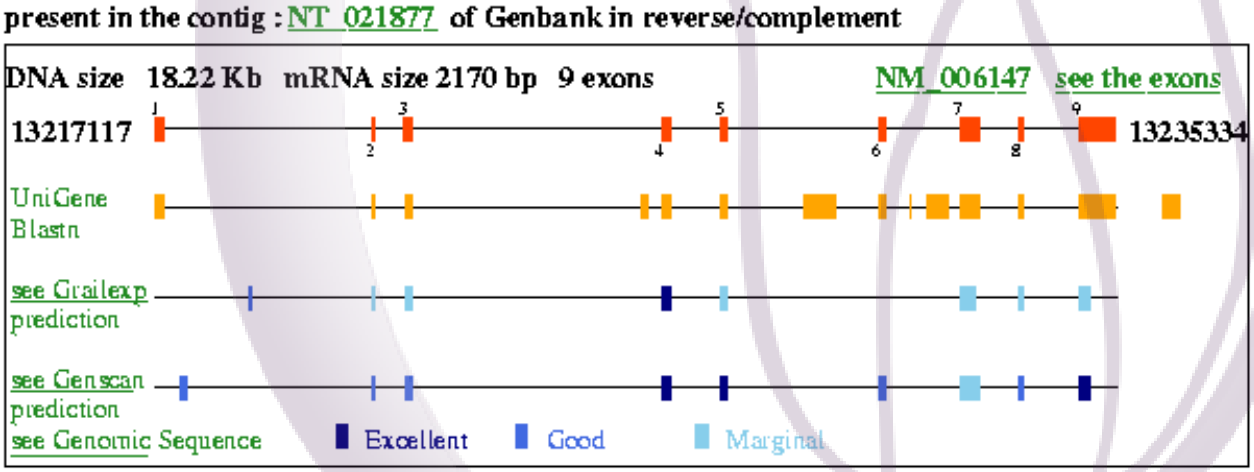
GWAS analysis : Application to CLP molecular pathogenesis

- Grant et coll., **Genome-wide association study identifies a locus for non syndromic cleft lip with or without cleft palate on 8q24**. J Pediatr 2009.
- Mangold et coll. **Genome-wide association study identifies two susceptibility loci for cleft lip with or without cleft palate**. Nature genetics 2010. locus 10q25 (*VAX1*) et 17q22 (*NOG*)
- Beaty et coll. **A genome association study of cleft lip with or without cleft palate identifies risk variants near *MAFB* and *ABCA4*.** Nature Genetics 2010.

Genetic heterogeneity of individuals affected by CLP

Major involvement of *IRF6* gene, 8q24 locus and *ABCA4-MAFB locus*

Main genes involved in CLP molecular etiology



Gene *IRF6*: gene atlas sheet

Genetic analysis in familial forms of CLP : ethical aspects

Problematics of pertinence, diagnosis interest, tiling and psychological impact of genetic analysis in the field of CLP

Main ethical and psychological aspects :

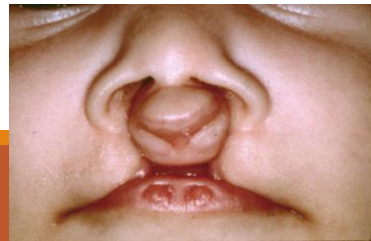
- Modalities for the transfer to a medical genetics department
- Transmission of informations related to genetic diagnosis: genomic uncertainty, psychological impact
- Ethical aspects

Eur J Hum Genet. 2019 Jan 25. Delivering effective genetic services for patients and families affected by cleft lip and/or palate. Stock NM, MacLeod R, Clayton-Smith J

IRF6 gene and CLP molecular pathogenesis

- **Interferon Regulatory Factor 6**: transcriptional factor involved in embryonic development of the face, skin and genitals
- **Central gene in syndromic and isolated CLP**
- *IRF6* gene also mutated in Popliteal Pterygium syndrome and van der Woude syndrome
- Initial Identification of IRF6 mutation in a syndromic form of CLP: **van der Woude syndrome** (CLP-labial pits)
- GWAS analysis identified also *IRF6* mutations in non-syndromic forms of CLP

CLP and labial pits seen in van der Woude syndrome



Other genes involved in non-syndromic CLP

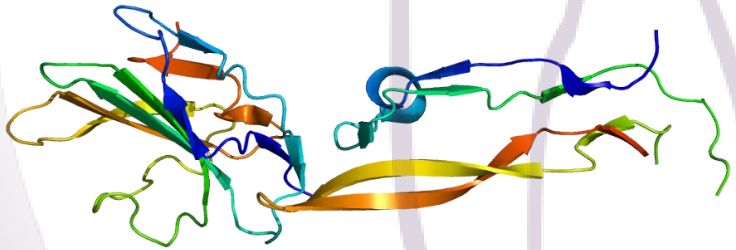
- ***IFT88 gene***: intra-flagellar Transport 88
- Polymorphism of ***MTHFR*** gene coding for 5,10-methylenetetrahydrofolate reductase involved in non-syndromic CLP
- ***RAX*** mutations in Human (homozygous or heterozygous): microphtalmia/anophtalmia, hypopituitarism and CLP
- ***MFAB*** SNP identification in a large cohort of 1149 patients presenting non-syndromic CLP

Other genes involved in non-syndromic CLP

- GWAS analysis showed associations with ***ABCA4*** *mutations*: SNP identified in an asian cohort of CLP patients
- GWAS analysis showed SNP on 10q25 locus in ***VAX1*** gene *:* non-syndromic CLP
- Involvement *of* ***TBX22*** in non-syndromic CLP : GWAS analysis on monozygotic twins

Other genes involved in non-syndromic CLP

- Association between pathogenic variant of ***TGFA*** and environmental factors (smoking): increase of CLP risk by a factor 6-8
- Pathogenic variant of TGF-β3(IVS5+104 A>G) **increase the CLP risk by a factor 16**



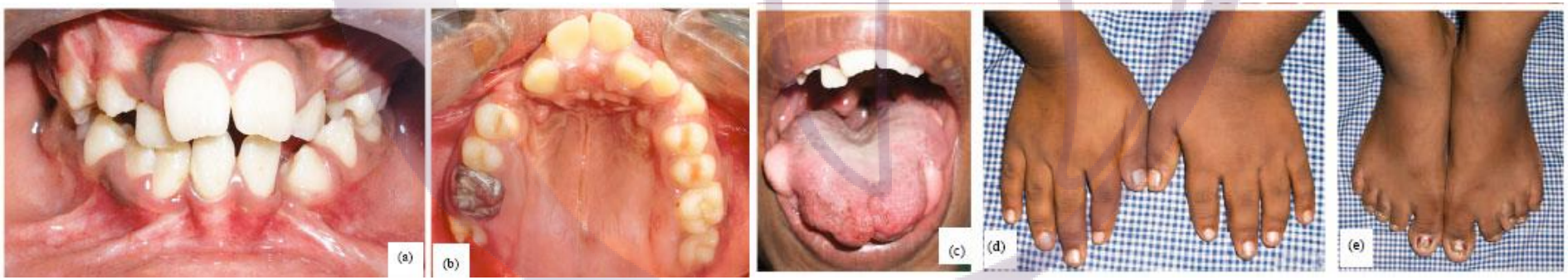
Syndromic forms of CLP

Syndromic forms of CLP

Syndrome	Gene	Type of cleft
AEC, EEC	*TP63*	CLP
Apert-Crouzon Craniosynostosis	*FGFR2*	CP
Branchio-oculo-facial Syndrome	*TFAP2A*	CLP
Kallmann Syndrome	*FGFR1*	CLP
OFD Syndrome	*Gli3*	CLP
Oto-palato-digital OFD type I and II	*FLNA*	CP
Pierre Robin Sequence	*SOX9*	CP
X-linked cleft and ankyloglossia	*TBX22*	CP
Stickler Diasease	*COL2A1*	CP
Tetra amelia syndrome with cleft	*Wnt3*	CLP
Miller Syndrome	*DHODH*	CP

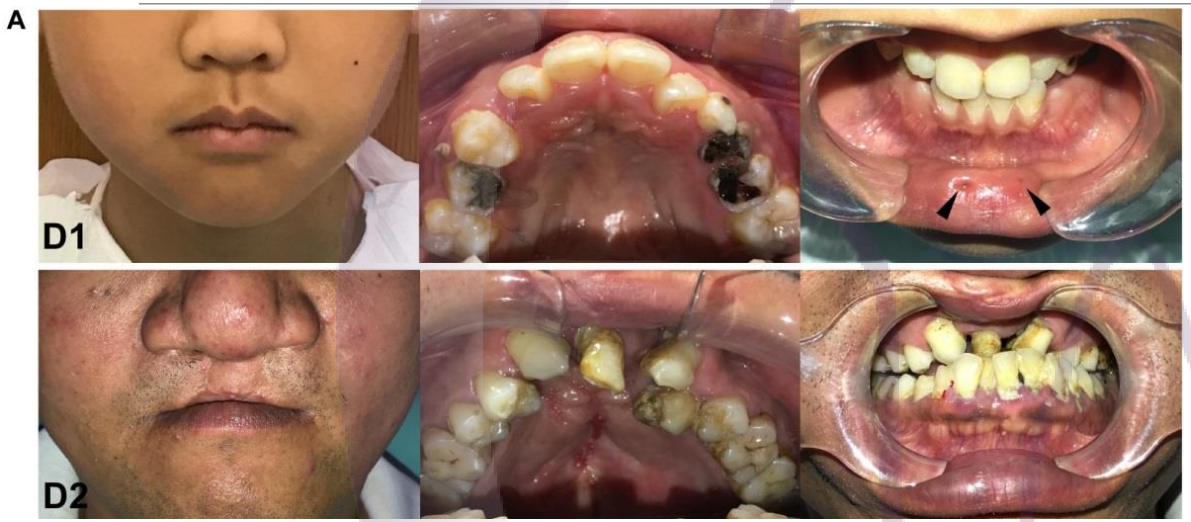
CLP and Van der Woude syndrome: congenital labial pits and *IRF6 mutations*

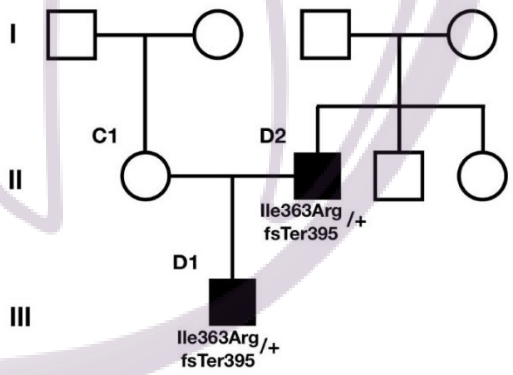
- Most prevalent form of syndromic CLP : prevalence of 1/60,000
- Associated anomalies in VDW syndrome : hypodontia, cognitive delay
- Genetic heterogeneity with more of 70 mutations in *IRF6* gene
- Alterations of IRF6 transcriptional factor biological activities
- **Differential diagnosis** : facio-genito-popliteal syndrome and oro-facio-digital syndrome

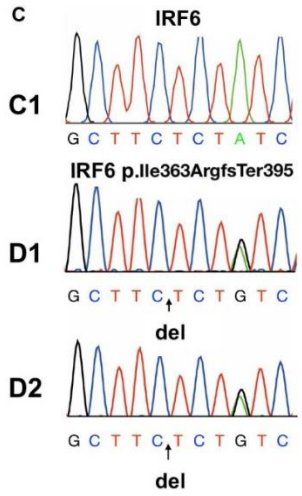


Arun et al., 2011

IRF6 gene and Van der Woude syndrome



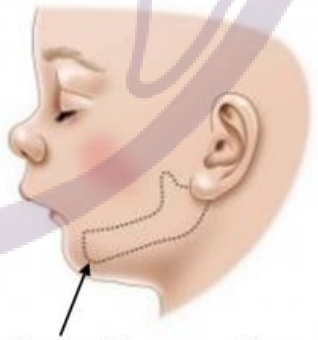




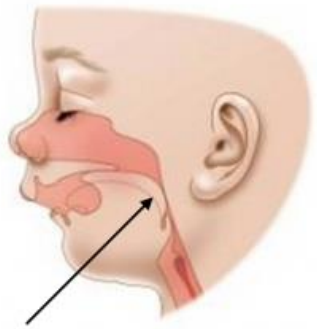
Zhang et al., 2020

CLP associated to Pierre Robin sequence

- Congenital anomaly associating mandibular micrognathia, glossoptosis and CLP
- CLP not systematically associated to isolated Pierre-Robin
- Early respiratory distress
- Swallowing anomalies
- Isolated form of Pierre Robin sequence in 20-40% of cases
- Syndromic forms associated with other systemic pathologies



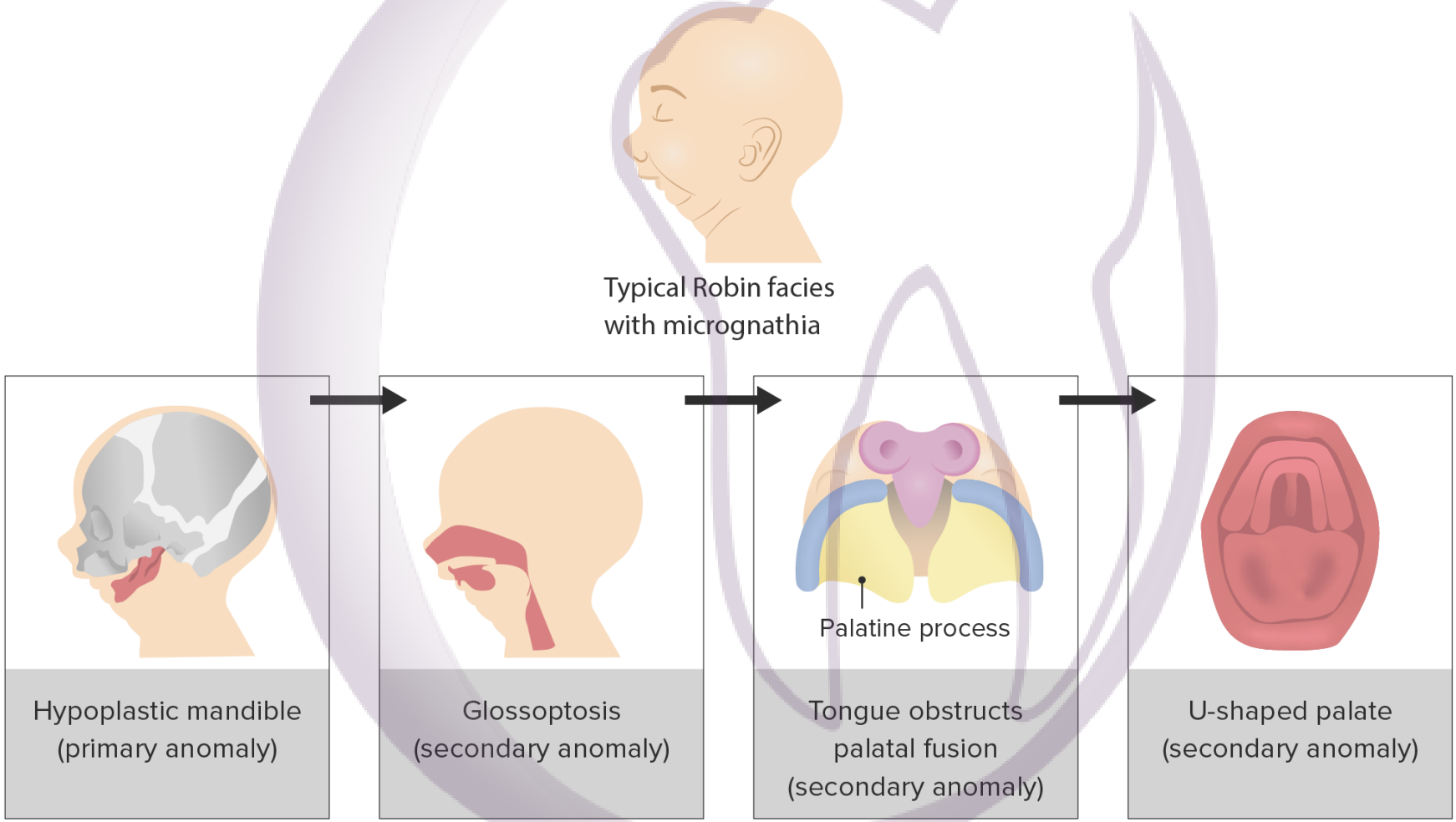
Micrognathia - a small jaw with a receding chin



Tongue that is large compared to the jaw, resulting in airway obstruction

https://www.craniofacialteamtexas.com/pierre-robin-sequence-prs/

Physiopathology of Pierre-Robin sequence

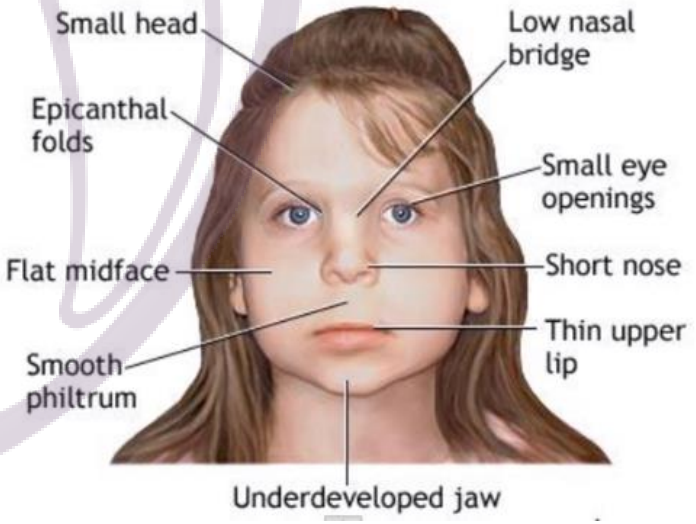


Syndromic form of CLP: CHARGE syndrome

C oloboma (80%)
H eart defect (75 - 80%)
A tresia choanae (70%)
R etarded growth and development (80%)
G enital hypoplasia (80%)
E ar anomalies / deafness (95 – 100%)

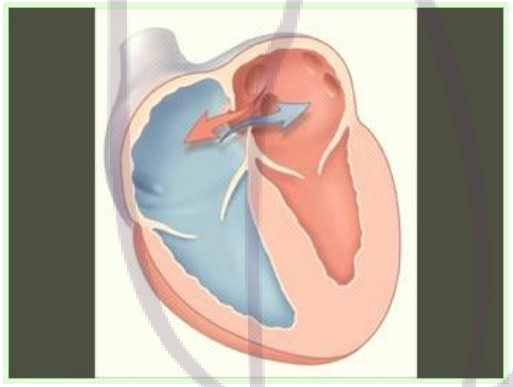
Syndromic form of CLP: Wolf-Hirschorn syndrome

- Neuro-developemental disease non-systematically associated with CLP, prevalence : 1/50.000
- Facial dysmorphysm –growth delay-microcephaly-hypertelorism
- CLP or CP associated to oligodontia-micrognathia
- Neurological pathologies: seizures-cognitive and motor delay
- Congenital heart disease-eyes disease-renal hypoplasia



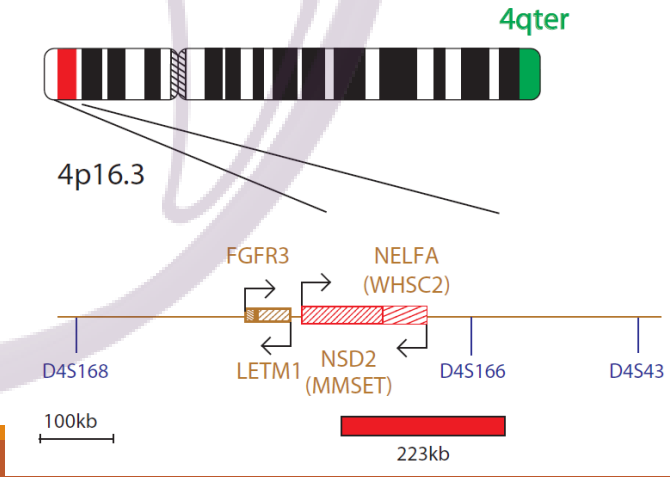
Syndromic form of CLP: Wolf-Hirschorn syndrome

- CLP in a **context of general closure process defect** : coloboma-heart septal defect



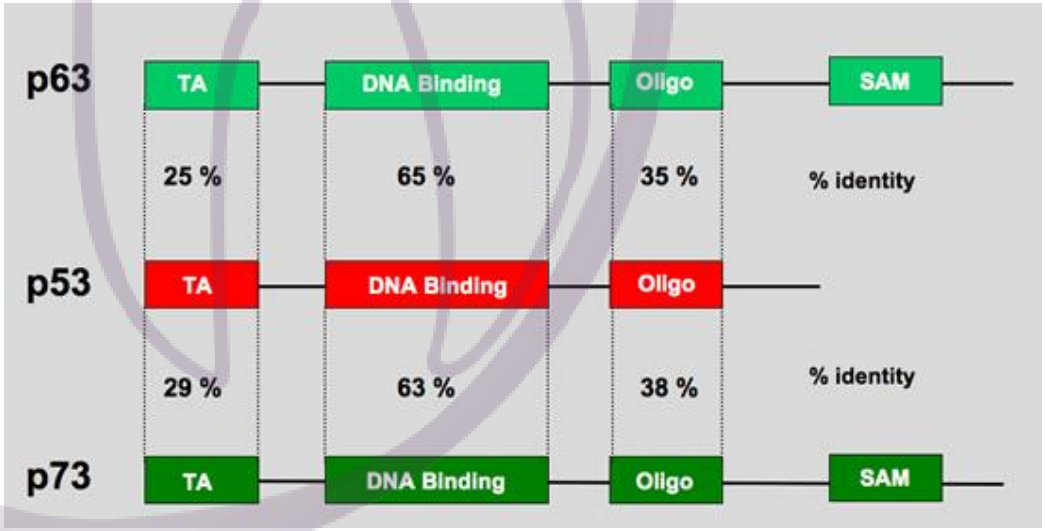
Syndromic form of CLP: Wolf-Hirschorn syndrome

- 4p16.3 deletion
- Deletion in **WHSCR**: Wolf-Hirschorn Syndrome Critical Region
- Chromosomal deletions of various size : genotype-phenotype correlations : most severe forms associated to large deletions
- Deletions of *MSX1*, *NSD2, LETM1* genes
- *LETM1:* involvement *in* neuronal development-deletion responsible for neurological diseases
- *MSX1: C*LP-dental anomalies



Syndromic forms of CLP associated to *P63* mutations

- Family of complex ectodermal dysplasia **: *P63* mutation**
- Family of p53: proto-oncogenic involved in cell cycle regulation
- EEC: ectrodactyly(*), ectodermal dysplasia, cleft lip palate
- AEC: ankyloblepharon, ectodermal dysplasia, cleft lip palate
- Rapp-Hodgkin Syndrome



(*) ***Ectrodactyly*** (a.k.a. *split hand-split foot malformation/ cleft hand / lobster claw hand*) is a **skeletal anomaly predominantly affecting the hands** (but the feet can also be affected).