Cleft lip and palate

Nicole Revencu
16/04/2024

Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

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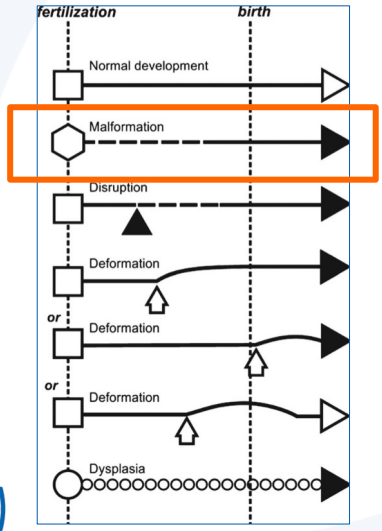
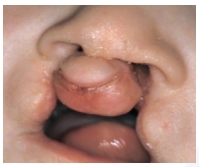
outline

- lip and palate embryological development
- characteristics – classification – prevalence
- clinical approach
- etiology of syndromic and non-syndromic cleft
- genetic testing
- genetic counselling

2

birth defects : mechanisms





Raoul C. Hennekam, AJMG, 2013

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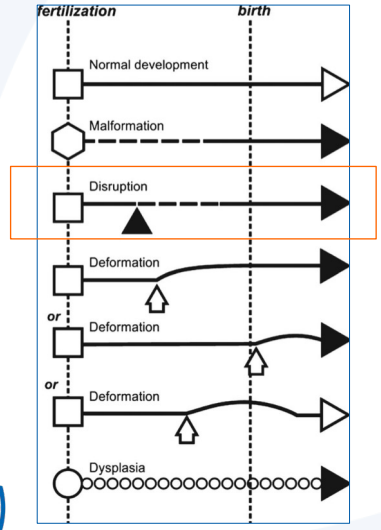
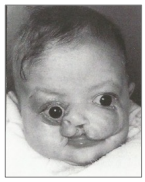
birth defects : mechanisms



secondary to amniotic bands (rare)



Human Malformations and Related Anomalies. 2nd Ed. Oxford Univ Press. 2006.

Raoul C. Hennekam, AJMG, 2013

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cleft lip and/or palate - general considerations

one of the most frequent birth defects

the most common craniofacial structural birth defect

group of disorders characterised by clinical and genetic heterogeneity

major problems : severe feeding problems, speech difficulties, frequent middle ear infections and dental defects

require long-term multidisciplinary treatments from the diagnosis (prenatal or postnatal) until the end of growth, around the age of 20 years

heavy burden for patients/families and the healthcare system

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lip and palate development

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lip and palate embryological development

derive from the cranial neuronal crest cells

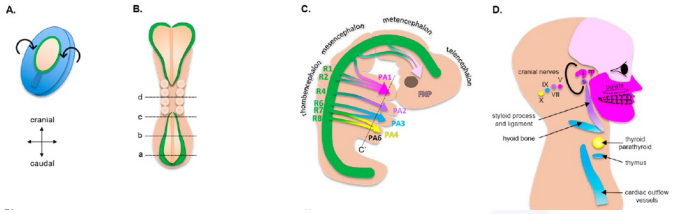
proliferation

migration

differentiation

apoptosis

fusion



morphogenesis of pharyngeal arches and their derivatives

Biology **2022**, *11*(2), 153; https://doi.org/10.3390/biology11020153

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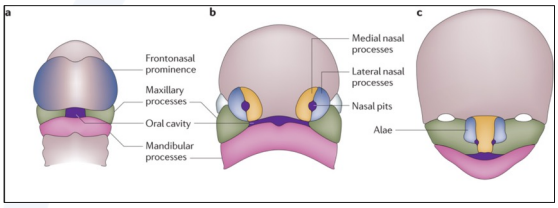
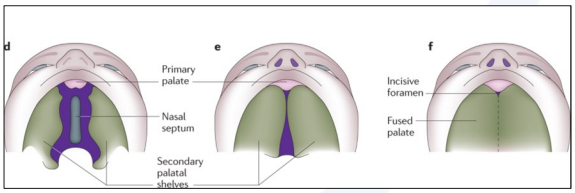
lip and palate embryological development

lip development



medial nasal processes form:
- upper lip philtrum
- the primary palate
- 4 incisory teeth

maxillary processes form
- remainder of the upper lip
- secondary palate



palate development

4 5 6 7 10

gestational weeks

Nat Rev Genet. 2011 Mar; 12(3): 167–178.

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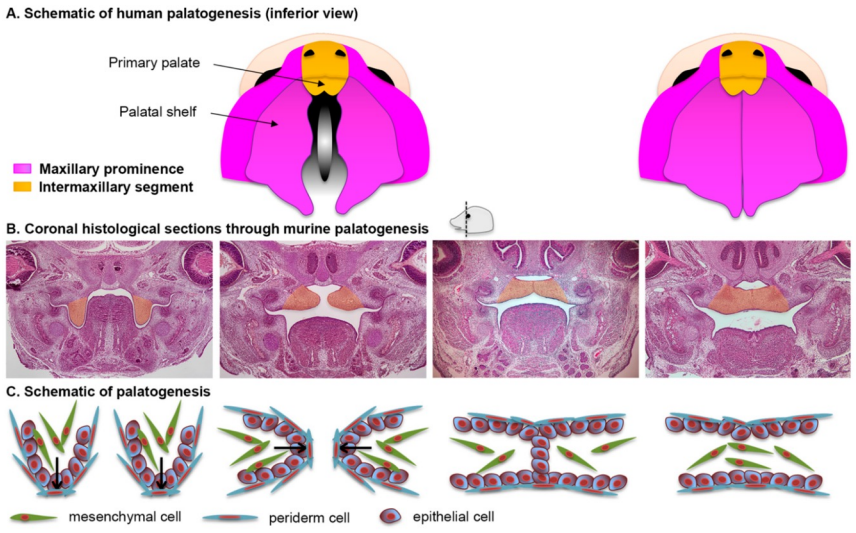
lip and palate embryological development



Biology **2022**, *11*(2), 153; https://doi.org/10.3390/biology11020153

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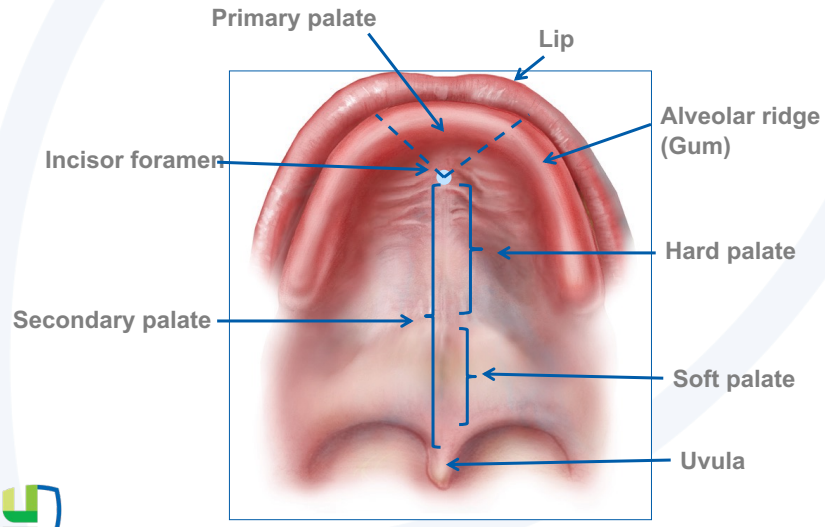
Anatomy of the palate



https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/quick-reference-handbook/cleft-palate.html

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pathways implicated in lip and palate formation

transcription factors

ligands

receptors

adhesion molecules

WNT

FGF

BMP

TGFβ

SHH

PDGF

NOTCH

proliferation, migration, differentiation, apoptosis, fusion, ….

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pathways implicated in lip and palate formation and disease

WNT

FGF

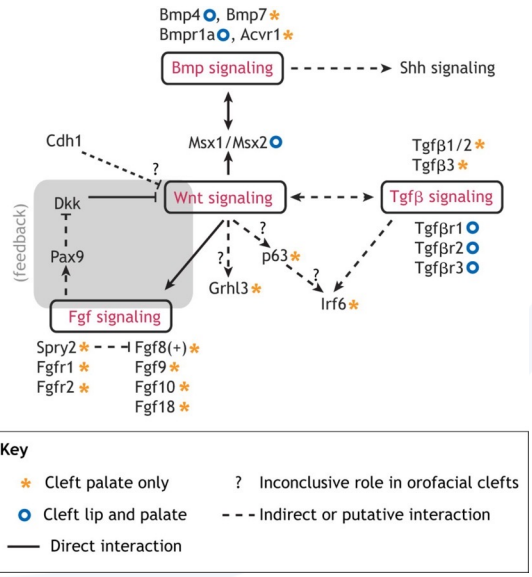
BMP

TGFβ

SHH

PDGF

NOTCH



Kurt Reynolds et al. Dis. Model. Mech. 2019;12:dmm037051

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characteristics – classification prevalence

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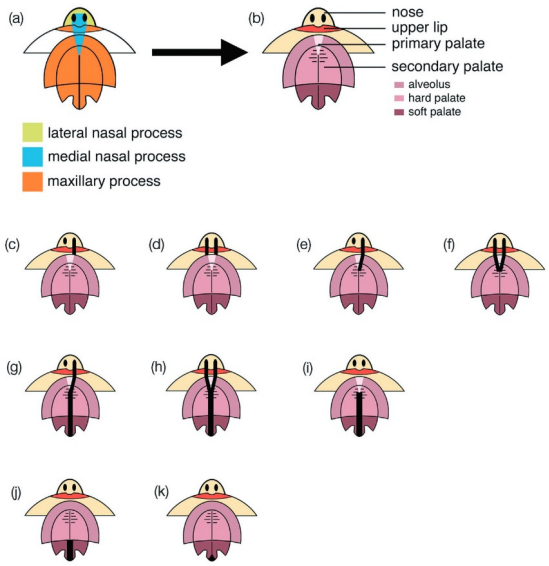
cleft types



European Journal of Orthodontics, 2004, 26, 7-16.

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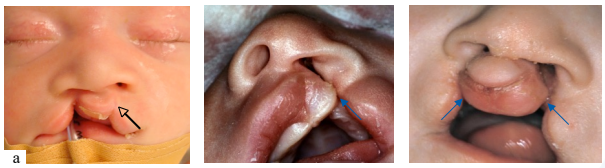
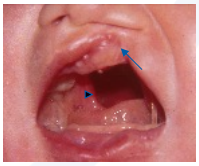
two major categories

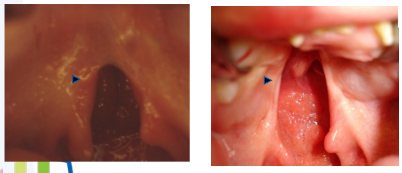


group 1: cleft lip and cleft lip and palate (CL/P)

epidemiological and embryological studies



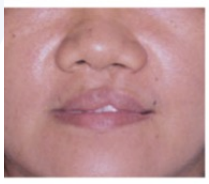
group 2: cleft palate only (CPO)



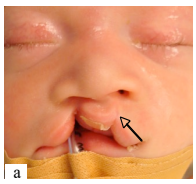
But some genes (*IRF6*, *GRHL3*, *TP63*, *MSX1*, *FGFR1*, …) are involved in both groups

Photos courtesy of Dr Bénédicte Bayet, Centre Labiopalatin, Cliniques universitaires Saint-Luc, Brussels, Belgium

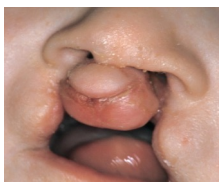
clinical spectrum : cleft lip or cleft lip and palate



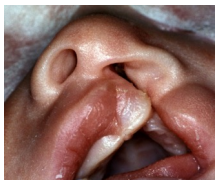
microform left cleft lip



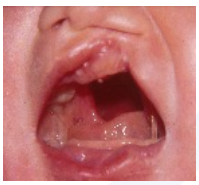
incomplete cleft lip



complete bilateral cleft lip (involves the nasal floor)



cleft lip and alveolus (gum)

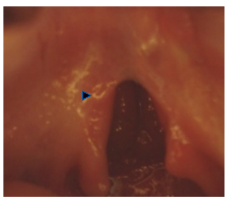


cleft lip and palate

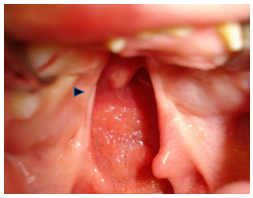
Nat Rev Genet. 2011 Mar; 12(3): 167–178.

Photos courtesy of Dr Bénédicte Bayet, Centre Labiopalatin, Cliniques universitaires Saint-Luc, Brussels, Belgium

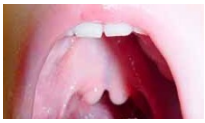
clinical spectrum : cleft palate



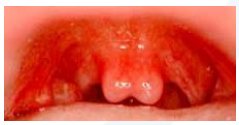
cleft of the soft palate



complete cleft palate



bifid uvula and submucosal cleft



bifid uvula

Photos courtesy of Dr Bénédicte Bayet, Centre Labiopalatin, Cliniques universitaires Saint-Luc, Brussels, Belgium

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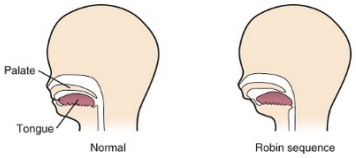
Pierre Robin sequence

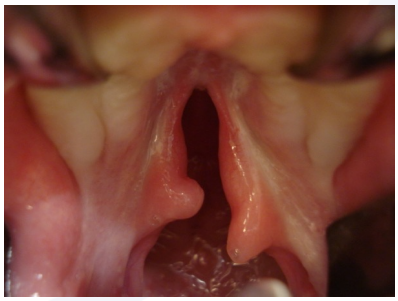
microretrognathia

glossoptosis

cleft palate

respiratory obstruction





Photos courtesy of Dr Bénédicte Bayet, Centre Labiopalatin, Cliniques universitaires Saint-Luc, Brussels, Belgium

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clinical spectrum

other rare forms :

median cleft (holoprosencephaly, frontonasal dysplasia, etc.)

lateral cleft (oro-auricular cleft) : incomplete merging of maxillary and mandibular processes (e.g. in craniofacial microsomia)

oblique-lateral cleft (oro-ocular cleft)

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epidemiology

most common craniofacial malformation

prevalence : 1/700 (frequent consultation in medical genetics)

220,000 babies per year worldwide

varies among populations

- 1/500 Asians
- 1/1000 Caucasians
- 1/2500 Africans

cleft lip only : 1/3000 (22%)

cleft lip and palate : 1/1500 (45%)

cleft palate : 1/2000 (33%)

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epidemiology

sex differences

- cleft lip +/- cleft palate : 2M/1F
- cleft palate : 1M/2F

cleft lip location

- unilateral 80%
- 2 left/1 right

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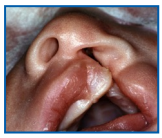
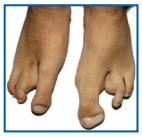
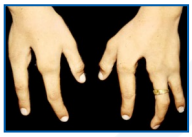
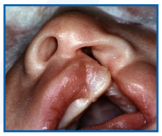
classification

isolated – cleft is the only feature
85% CL
70% CLP
50% CP



syndromic - additional physical / cognitive abnormalities
15% CL
30% CLP
50% CP

some patients have additional malformations that seem not to be related to a syndrome

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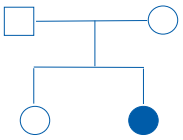
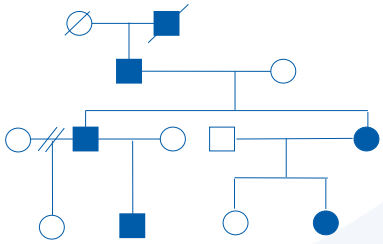
classification

- 80% sporadic



- 20% familial



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clinical approach

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clinical approach

questions :

- is the cleft isolated or syndromic ?
- is the cleft sporadic or familial ?

a precise diagnosis is necessary for :

- clinical follow up
- genetic counselling for the patient/parents and relatives

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clinical approach

is the cleft isolated or syndromic ?

- not always obvious at the time of diagnosis
- additional symptoms : can be mild or can develop later in life
- importance of the follow-up : propose to see the patient again

Rittler M et al. 2011 : 7 to 9% of the clefts that are initially thought to be isolated cases are found to have associated abnormalities

Rittler M et al. Am J Med Genet A. 2011 Jul;155A(7):1588-96.

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clinical approach

when is a cleft diagnosed :

- most of the cleft lip w/o palate are diagnosed prenatally
- cleft palate are usually diagnosed postnatally, in the first days of life

  (prenatally retro/micrognathia can be an indirect sign of CP)
- bifid uvula and submucosal cleft palate might not be diagnosed until later in life

family tree on 3 generations : cleft, other malformations, DD, miscarriages,

osteoarthritis, severe myopia, missing teeth, etc…

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clinical approach

pregnancy: maternal illnesses (hyperthermia, epilepsy, diabetes, etc…), tobacco, alcohol, drugs, periconceptinal vitamines, ...

personal history : growth, developmental milestones, other major anomalies, hearing, vision, immune deficiency, etc...

clinical examination :

type of cleft, unilateral or bilateral, complete or incomplete

growth : weight, height and OFC, dysproportion

facial asymmetry, dysmorphic features,

ectodermal anomalies : skin, hair, teeth, nails

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clinical approach

clinical examination :

- hands/feet : polydactyly, syndactyly, ectrodactyly ...
- minor features : preauricular pits, tags, lip pits, short lingual frenulum, ...
- cardiac examination
- anal anomaly, genital anomalies
- ....

examine the oral cavity of the parents : lip pits, bifid uvula, submucosal cleft, missing teeth, etc.

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clinical approach

if necessary, propose additional investigations based on your working hypotheses

- cardiac ultrasound
- renal ultrasound
- cerebral ultrasound / MRI
- vision (especially in case of CP/PR)
- ....

discuss :

- the option to perform a genetic testing
- that the result may depend on type of cleft/associated anomalies/family history
- the possibility of unclear results

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management : multidisciplinary team

- obstetrician
- pediatrician
- plastic surgeon and/or maxillofacial surgeon and/or ear, nose & throat surgeon
- ear, nose & throat specialist
- speech therapist
- pediatric dentist and orthodontist
- geneticist
- psychologist
- social worker
- ….

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etiology

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etiology of syndromic cleft

> 300 syndromes ; > 75% known etiology

chromosomal abnormalities : trisomy 13, trisomy 18, 22q11.2 deletion/duplication, 1p36 deletion, Wolf-Hirschhorn syndrome (4p16.3 deletion), etc…

monogenic disorders
147 genes on Genomics England PanelApp (AD, AR, X-linked)

teratogens (e.g. : methotrexate)

https://panelapp.genomicsengland.co.uk/panels/81/

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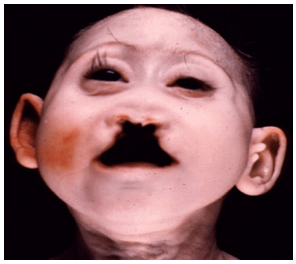
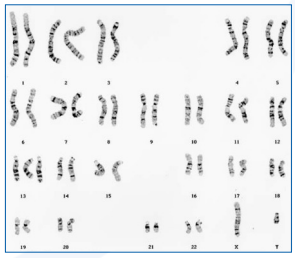
some diagnoses to consider : chromosomal abnormalities

Patau syndrome (trisomy 13)
in utero death > 95%
intrauterine growth retardation
cleft lip and palate
holoprosencephaly (70%)
congenital cardiac anomaly
facial dysmorphism
ocular anomalies
postaxial polydactyly
severe psychomotor retardation
……





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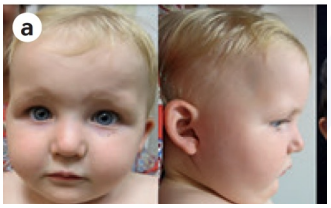
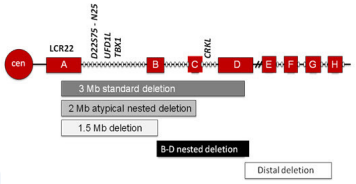
some diagnoses to consider : chromosomal abnormalities

22q11.2 deletion
prevalence : 1/6,000
palatal anomalies 75%
(the most common cause of syndromic palatal anomalies)
velopharyngeal insufficiency
submucosal cleft palate
bifid uvula, cleft palate
(CL/P)
congenital heart defects (75%) :
VSD, 4F, aortic arch anomalies, …
facial dysmorphism (hooded eyelids, ear anomalies, prominent nasal bridge, hypoplastic nasal alae, bulbous nasal tip,
thymic hypoplasia/aplasia (immune deficiency)
developmental delay
neuropsychiatric disorders
……





https://www.ncbi.nlm.nih.gov/books/NBK1523/; Nat Rev Dis Primers. 2015 Nov 19;1:15071.

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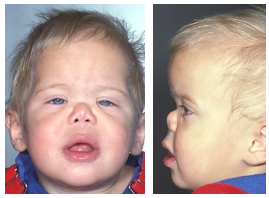
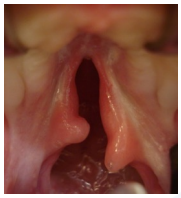
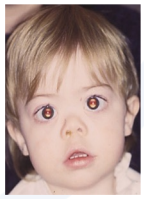
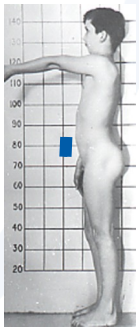
some diagnoses to consider : monogenic diseases

Stickler syndrome
autosomal dominant : ***COL2A1***, *COL11A1/2*
autosomal recessive : *COL9A1/A2/A3*
prevalence 1/7500-9000
cleft palate or bifid uvula or Pierre Robin
high myopia
retinal detachment
congenital vitreous anomaly
cataract
sensorineural or conductive hearing loss
mild spondyloepiphyseal dysplasia
early-onset osteoarthritis
some genotype-phenotype correlation
(https://www.ncbi.nlm.nih.gov/books/NBK1302/)









Gorlin collection

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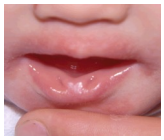
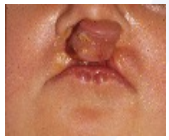
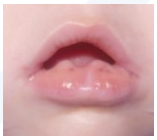
some diagnoses to consider : monogenic diseases

van der Woude syndrome, autosomal dominant
incomplete penetrance, variable expressivity
type 1 : *IRF6* (70%) (Interferon regulatory factor 6, 1q32), transcription factor
prevalence: 1/ 35 000 (2% of patients with cleft)
incomplete penetrance and variable expressivity
pits on the lower lip (80%)
cleft lip , cleft lip and palate, cleft palate (50%)
hypodontia (25%)



lip pits

type 2 : *GRHL3* (5%) (Grainyhead-like TF; 1p36)
transcription factor
CP>>CLP
pits on the lower lip (50%)


conical elevations

37

some diagnoses to consider : monogenic diseases

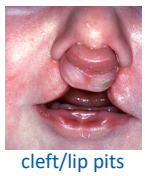
popliteal pterygium syndrome

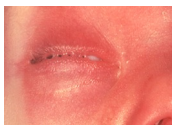
autosomal dominant

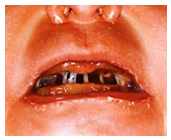
mutation in *IRF6 :* DNA binding domain

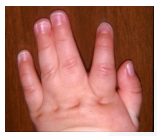
prevalence: 1/ 300 000

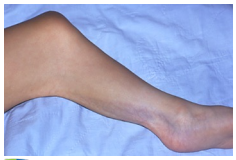
co-occurrence with VWS in the same family

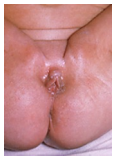
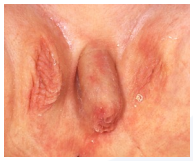

cleft/lip pits

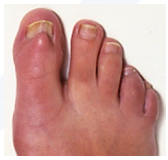

ankyloblepharon


buccal synechiae


skin syndactyly


popliteal webs

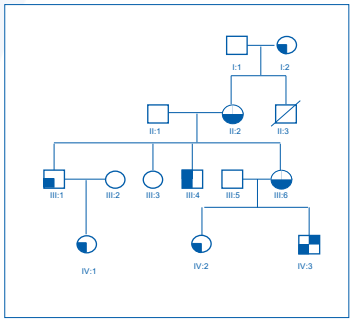


genital anomalies

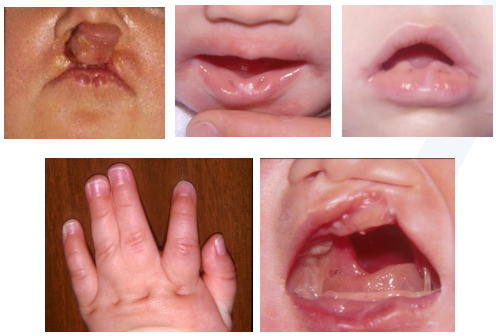

pyramidal skinfold of halluces

Gorlin collection

38

some diagnoses to consider : monogenic diseases





CP
bifid uvula
CL/P
lip pits

ONLINE MUTATION REPORT

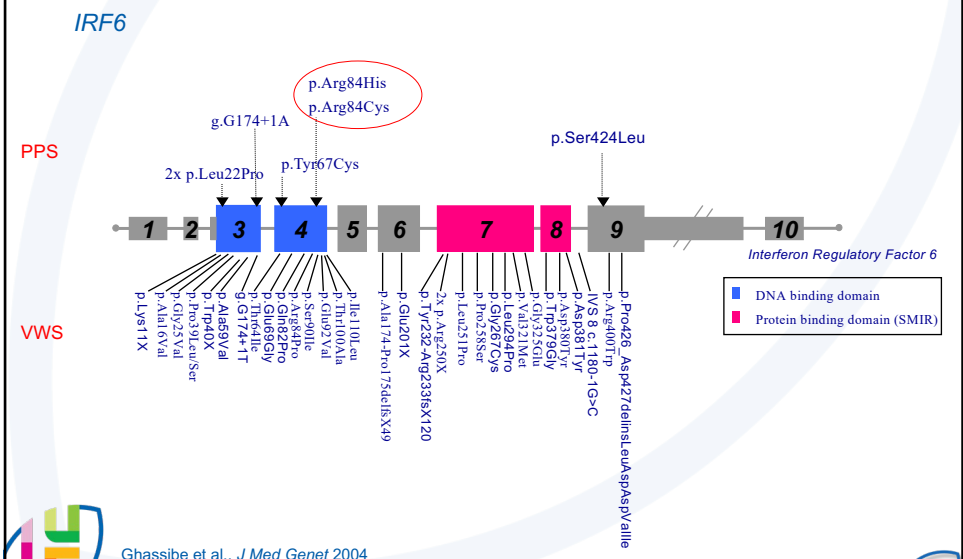
Six families with van der Woude and/or popliteal pterygium syndrome: all with a mutation in the *IRF6* gene

M Ghassibé, N Revencu, B Bayet, Y Gillerot, R Vanwijck, C Verellen-Dumoulin, and M Vikkula

J Med Genet 2004;41:e15 (http://www.jmedgenet.com/cgi/content/full/41/2/e15). doi: 10.1136/jmg.2003.009274

39

some diagnoses to consider : monogenic diseases



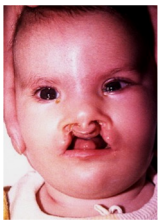
Ghassibe et al., *J Med Genet* 2004
Desmyter, Ghassibe et al., *Molecular Syndromology 2010*

40

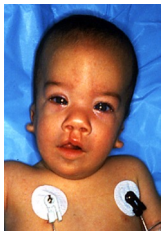
some diagnoses to consider : monogenic diseases

Branchio-oculo-facial syndrome (BOF)

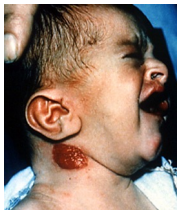
autosomal dominant
mutations in *TFAP2A (6q24.3)*, transcription factor
prevalence is not known
microphtalmia, myopia, cataract
conductive hearing loss
ID possible and variable



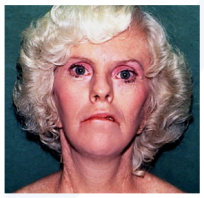
lacrimal duct obstruction
hypertelorism
cleft lip w/o CP



"pseudocleft" (appearance of a repaired cleft lip)



low-set/posteriorly rotated ears
branchial skin defect
(thin skin/hair patch to erythematous lesions)



early loss of hair pigmentation

Gorlin collection

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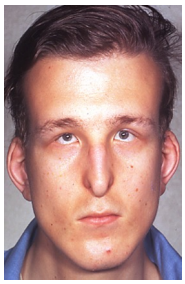
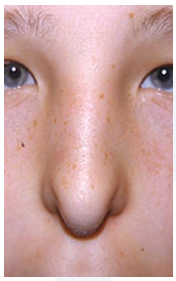
some diagnoses to consider : monogenic diseases

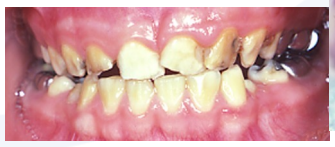
Oculo-dento)- digital dysplasia (ODD)

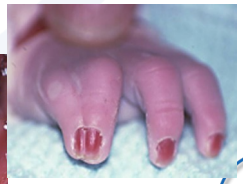
autosomal dominant
rare, but characteristic
mutation in *GJA1*, connexin protein
characteristic face :
- prominent epicanthic folds
- narrow, pinched nose, hypoplastic nasal alae
- prominent columella
- narrow nasal bridge
- cleft palate

microphthalmia and microcornea
teeth are usually small and carious
complete syndactyly of the fourth and fifth fingers









Gorlin collection

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some diagnoses to consider

TP63- related disorders – EEC, AEC

Kabuki syndrome

Smith-Lemli-Opitz syndrome

Treacher-Collins syndrome

CHARGE syndrome

Loeys-Dietz syndrome

Saethre-Chotzen syndrome

…. and many others

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etiology : isolated cleft

the causes of most of the isolated clefts are unknown

multifactorial based on concordance rate in
monozygotic twins : 25 to 60%
dizygotic twins : 3 to 6%

suggests a genetic basis +
involvement of environmental factors

in some patients, **rare variants** in single major genes are present,
such as *IRF6*, *GRHL3*, *TP63*, *FGF8/FGFR1, TBX22, PVRL1, ….*

currently a **mixed model** is favoured :
multifactorial origin in most
monogenic causes in some

Grosen, D., et al., *Risk of oral clefts in twins.* Epidemiology, 2011. **22**(3): p. 313-9.

44

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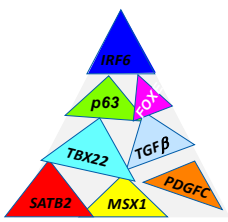
45

isolated cleft : multifactorial origin

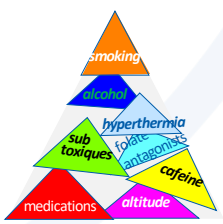
multifactorial origin

combined effects of many independent genes + environmental factors

genetic predisposition



environmental factors



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etiology : environemental factors

little is known about the environnemental factors

many environmental risk factors have been investigated, but relatively few associations have been clearly established and the contribution to cleft is modest

maternal smoking

it has **consistently** been associated with increased risk of CLP

the risk seems to be stronger for CL/P (OR: 1.34) than for CP (OR: 1.22), and increases with the number of cigarettes per day in CL/P [126]

4% of all orofacial clefts and 12% of bilateral CL/P could be attributed to periconceptional maternal smoking

genetic susceptibility in the context of maternal smoke exposure :

polymorphisms in *TGFA, TGFB3, BMP4, MSX1*,… genes have been associated with increased risk of cleft

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etiology : environemental factors

little is known about the environnemental factors

many environmental risk factors have been investigated, but relatively few associations have been clearly established and the contribution to cleft is modest

alcohol

it has **inconsistently** been associated to isolated CLP

the risk could be higher only if high dose of alcohol + if the mother or the fetus carries the *ADH1C* haplotype associated with reduced alcohol metabolism

caffeine

it has **inconsistently** been associated to isolated CLP

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etiology : environemental factors

multivitamin supplements

multivitamin supplements in periconceptional has been linked to **decreased risk**

however, composition of multivitamin complexes are rarely reported, and responsibility (ies) of each component for this reduction is difficult to determine

folate supplement

preventive effect of folic acid on clefts is commonly reported but the evidence is inconsistent

a recent large study on the effects and safety of periconceptional oral folate supplementation for preventing birth defects does not support any protective or negative effect of folic acid supplementation on orofacial cleft

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etiology : environemental factors

maternal illnesses

diabetes mellitus before pregnancy

obesity (body mass index ≥ 30)

infections

hyperthermia

medication

antiepileptic drugs : valproic acid, topiramate

steroid treatment

50

etiology : genetic predisposition

different approaches have been used to identify genetic risk factors :

linkage, GWAS, sequencing of candidate genes, WES

many loci identified

linkage studies : success is limited by the genetic complexity of isolated cleft

meta-analysis combining six studies identified 6 loci : 1q32, 2p13, 3q27–28, 9q21, 14q21–24, and 16q24 (*IRF6, FOXE1*, …)

GWAS : > 40 genes and loci associated with isolated CL/P

51

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monogenic causes in some

Grosen, D., et al., *Risk of oral clefts in twins.* Epidemiology, 2011. **22**(3): p. 313-9.

52

etiology : isolated cleft - some have monogenic origin

WES : genes involved in **syndromes** can also be involved in **isolated** cleft lip/palate

the line between syndromic and non-syndromic clefts is blurred

Whole exome sequencing identifies mutations in 10% of patients with familial non-syndromic cleft lip and/ or palate in genes mutated in well-known syndromes

Mirta Basha,[1] Bénédicte Demeer,[1,2,3] Nicole Revencu,[1,4] Raphael Helaers,[1] Stephanie Theys,[5] Sami Bou Saba,[6] Odile Boute,[7] Bernard Devauchelle,[8] Geneviève Francois,[9] Bénédicte Bayet,[10] Miikka Vikkula[1]

J Med Genet. 2018 Jul;55(7):449-458

Received: 2 May 2018 | Revised: 15 August 2018 | Accepted: 17 August 2018
DOI: 10.1002/ajmg.a.40630

WILEY American Journal of medical genetics A

RESEARCH ARTICLE

Unmasking familial CPX by WES and identification of novel clinical signs

Bénédicte Demeer[1,2,3] | Nicole Revencu[1,4] | Raphael Helaers[1] | Bernard Devauchelle[3,5] | Geneviève Francois[6] | Bénédicte Bayet[7] | Miikka Vikkula[1]

- 106 individuals from 63 families
- mutations identified in 7 families
  - *TBX1*
  - *TBX22* (2 families)
  - *LRP6*
  - *GRHL3* (2 families)
  - *TP63*

(*IRF6* was tested before)

53

etiology : isolated cleft - some have monogenic origin

Genetics in Medicine (2023) 25, 100918
ELSEVIER
Genetics in Medicine
An Official Journal of the ACMG
www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Rare variants found in clinical gene panels illuminate the genetic and allelic architecture of orofacial clefting

Kimberly K. Diaz Perez[1], Sarah W. Curtis[1], Alba Sanchis-Juan[2], Xuefang Zhao[2], Taylor Head[3], Samantha Ho[1], Bridget Carter[1,4], Toby McHenry[5], Madison R. Bishop[1], Luz C. Valencia-Ramirez[6], Claudia Restrepo[6], Jacqueline T. Hecht[7], Lina M. Uribe[8], George Wehby[9], Seth M. Weinberg[5], Terri H. Beaty[10], Jeffrey C. Murray[11], Eleanor Feingold[12], Mary L. Marazita[5,12], David J. Cutler[1], Michael P. Epstein[1], Harrison Brand[2], Elizabeth J. Leslie[1,*]

Cohort
841 index cases
- 621 "simplex"
- 220 "multiplex" (at least 1 other affected relative, up to the 3rd degree)

most trios (child and parents)
- CLP: 660
- CP : 74
- CL: 107

no other major malformations
no intellectual deficiency

Control sample : 294 child-parent trios

GS : 418 genes analysed

76 likely pathogenic variants identified in 39 genes
9.04% of cases and 1.02% of controls

likely pathogenic variants identified in :
- CLP : 9.09% (60/660)
- CP : 17.6% (13/74)
- CL: 2.8% (3/107) (not significantly different than controls)

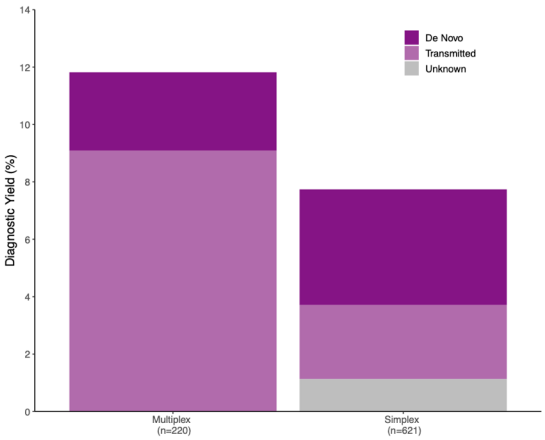
54

etiology : isolated cleft - some have monogenic origin


Genetics Medicine

ARTICLE

Rare variants found in clinical gene panels illuminate the genetic and allelic architecture of orofacial clefting



- there was no statistic difference in diagnostic yield between individuals from **multiplex** and **simplex** families (11.8% multiplex vs 7.73% simplex, P = .089)
- 25% of LP variants were de novo in multiplex families versus 52% in simplex cases

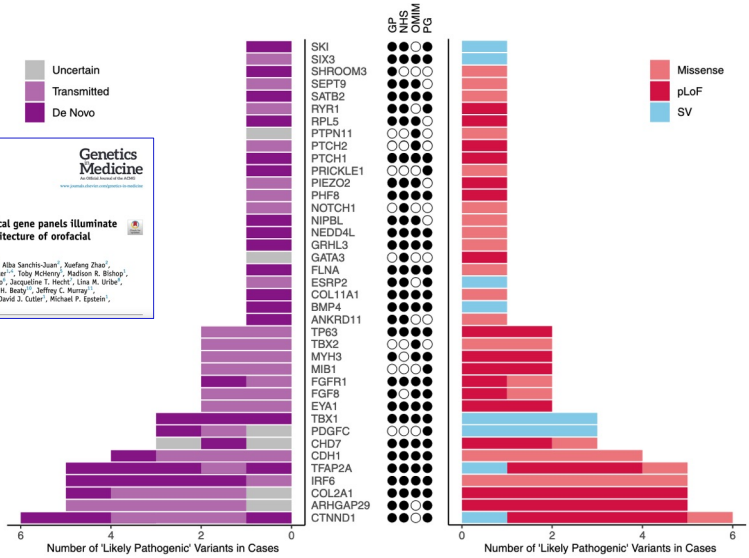
55

etiology : isolated cleft - some have monogenic origin

Genetics Medicine

ARTICLE

Rare variants found in clinical gene panels illuminate the genetic and allelic architecture of orofacial clefting



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genetic testing : when? what?

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what genetic testing should be performed?

points to be taken into consideration :

- type of cleft : CL, CLP, CP, PR
- additional symptoms
- family history

- European guidelines for PR (2024)

- for CL, CLP, CP no definitive guidelines concerning :
  - when a genetic testing should be proposed
  - the type of genetic testing that should be proposed

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before performing any genetic testing

discuss with the parents the option of genetic testing

if a test is performed, explain the type of test and the possible results, the TAT

special attention should be paid to :

- the possible risk of identifying a syndrome that could have consequences later in life (developmental delay, additional symptoms)
- the possible risk of unclear results
- the possible risk of incidental findings

obtain the informed consent

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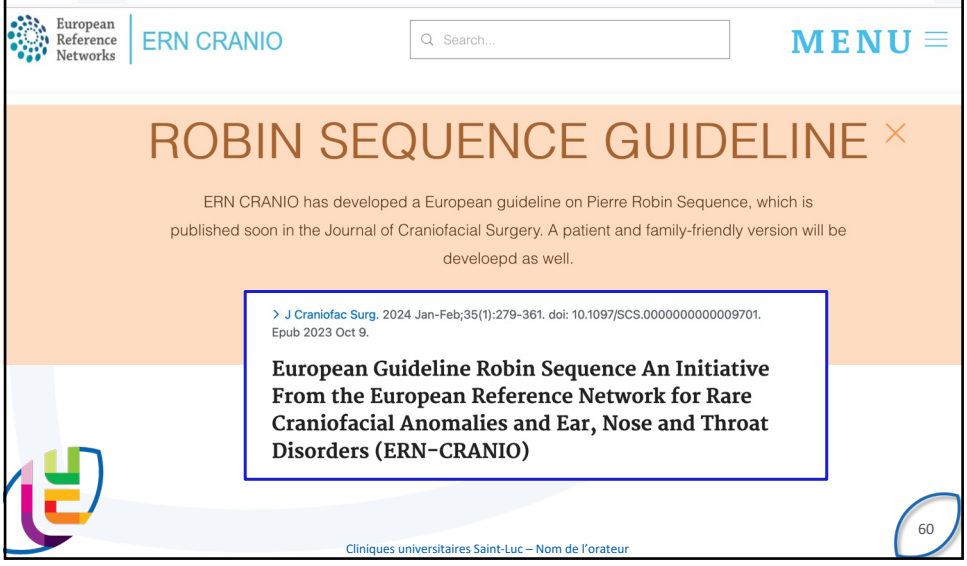
what genetic testing should be performed?

European guideline on Pierre Robin Sequence



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ERN cranio - recommendations for patients with Pierre-Robin

- offer genetic counselling antenatally to all parents when ultrasound shows signs of retrognathia.
- refer all neonates/ infants with PR as soon as possible to a clinical geneticist within a center of expertise. If early referral is not feasible referral at the age of 6 months is recommended.
- refer all children with PR after 2 to 3 years to a clinical geneticist for clinical and genetic re-evaluation, if initial screening yielded no underlying diagnosis
- perform genetic testing minimally comprising **CNV**-analysis and **(trio)-WES based gene panel** analysis targeting PR-associated genes. If this not feasible perform **at least CNV-**analysis and a limited targeted gene panel for **Stickler syndrome**

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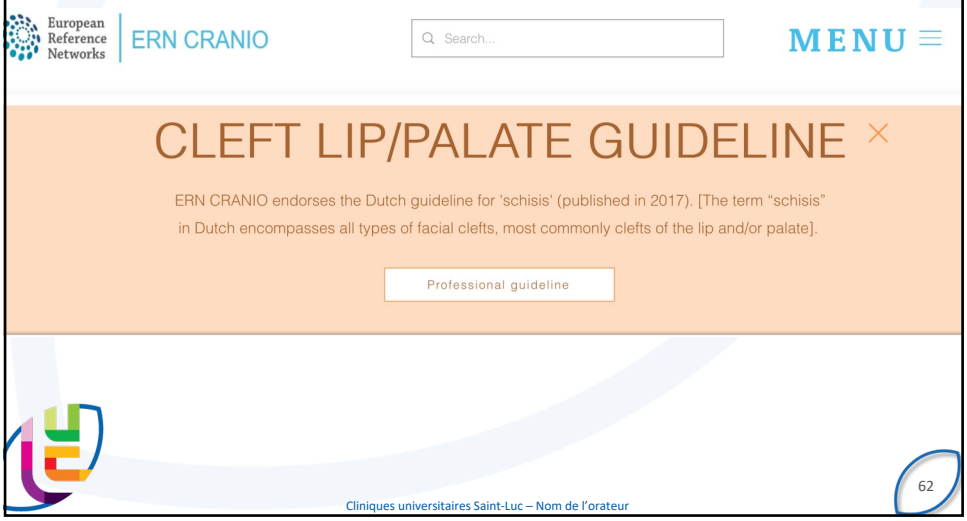
ERN cranio - recommendations for patients with CL/P and CP

No definitive guidelines
ERN CRANIO endorses the Dutch guideline



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ERN cranio - recommendations for patients with CL/P and CP

Isolated CL:

- Consider CLA/P **gene panel** analysis (incl. CNV analysis) in trio

Isolated CLP and CP:

- CLA/P **gene panel** analysis (incl. CNV analysis) in trio
- Consider supplementing with **SNP array** and/or other gene panels

Isolated cleft + family history

- CLA/P **gene panel** analysis (incl. CNV Analysis) in trio
- Consider expanding with **SNP array** /other gene panels, possibly followed by open **exome**

Cleft with associated aberrations and/or suspected chromosomal aberration

- **SNP array**
- CLA/P **gene panel** analysis in trio, if necessary, in addition to other gene panels, with subsequent **open exome** analysis, if strong suspicion/VOUS supplemented with RNA analysis/whole genome sequencing/testing other tissue etc

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when a genetic test is prescribed

provide **detailed phenotype** and working diagnosis (if any) :

- type of cleft (CL, CLP, CP, PR)
- unilateral/bilateral
- isolated or syndromic
- sporadic or familial

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what genetic testing can be considered

Dutch (ERN) approach versus Belgian centres

	iCL		iCLP		iCP		discontinous		Fam		Syndr.	
	CMA	P/ES	CMA	P/ES	CMA	P/ES	CMA	P/ES	CMA	P/ES	CMA	P/ES
Ghent	X		X		X	P	X	P	X	P	X	P
Antwerp			X		X	Stickler				P		P
UCL*	(X)		X		X	P/ES *	X	P/+ES*	X	P/+ES*	X	P/ES
IPG	X		X		X						X	ES
Liège			X	+/- other	X	+/- other			X	+/- other	X	+/- other
VUB			X		X	IRF6+ US/O			X	IRF6+ US/O	X	+/- other
Leuven											X	P/ES
ERN		+/-P	+/- X	P	+/-X	P			X	P/ES	X	P/ES

* research project offered to patients with cleft (trio)

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ERN cranio - recommendations for patients with CL/P and CP

"unfortunately, the current literature does not provide information about the exact yield of different diagnostic genetic tests in an unbiased well subphenotyped cleft population.

more specific, the type of clefting in different studies are not uniformly subclassified

furthermore, the genetic techniques differ between the various available studies. "

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ERN cranio - recommendations for patients with CL/P and CP

« further studies, including broad genotype-phenotype evaluation in well subphenotyped population and treatment outcome studies, are necessary to define those children in which genetic testing will have most benefit and determine the optimal strategy of genetic testing in cleft cases ! »

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recurrence risk

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recurrence risk for isolated cleft lip w/o cleft palate

Relationship to index case	Recurrence risk (%)
sibling unilateral CL	2-3%
sibling unilateral CL/P	4%
sibling bilateral CL/P	5-6%
two affected siblings	10%
affected sibling and parent	10%*
affected parent	4%

*could represent dominant risk

some of the patients with isolated cleft have mutation in a single gene

69

recurrence risk for isolated cleft palate

Relationship to index case	Recurrence risk (%)
sibling	2-3%
parent	4%

keep in mind that some of the patients with isolated cleft have mutation in a single gene

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recurrence risk for syndromic cleft

precise estimation possible if the diagnosis is known

majority – autosomal dominant inheritance

- incomplete penetrance
- variable expressivity
- « de novo » mutation, germline mosaicism

some – X-linked (*TBX22*, *MID1*, etc.) or autosomal recessive (*NECTIN1, EPG5, etc.)*

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Thank you for your attention !

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