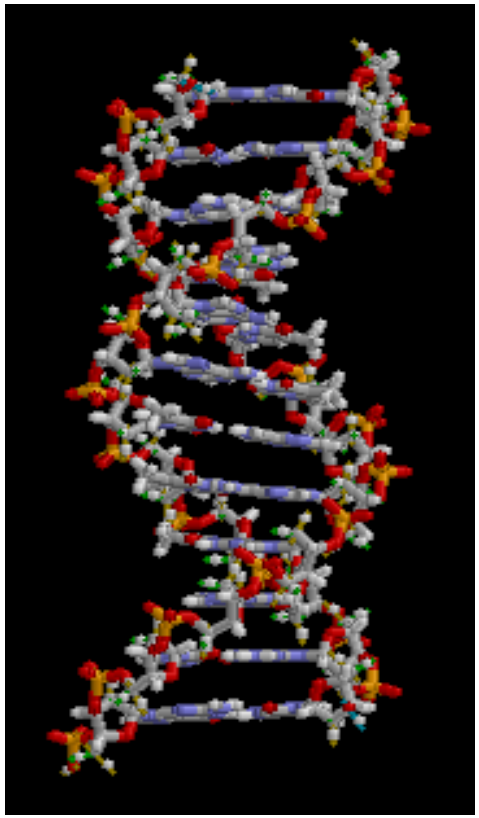

The embryological/fetal origin of anomalies

MANAMA

13/02/2024

Pr I.Maystadt

UNIVERSITÉ DE NAMUR

IPG

1. Definitions

2. Molecular mechanisms in embryology and physiopathology of malformations
   - Developmental genes and signaling pathways
   - Illustration: limbs development and defects

3. Molecular families of developmental syndromes: a few examples
   - Ciliopathies
   - RASopathies
   - TGF-β signaling related diseases
   - Chromatinopathies (BAF complex, COMPASS complex, cohesinopathies)
   - Neurocristopathies

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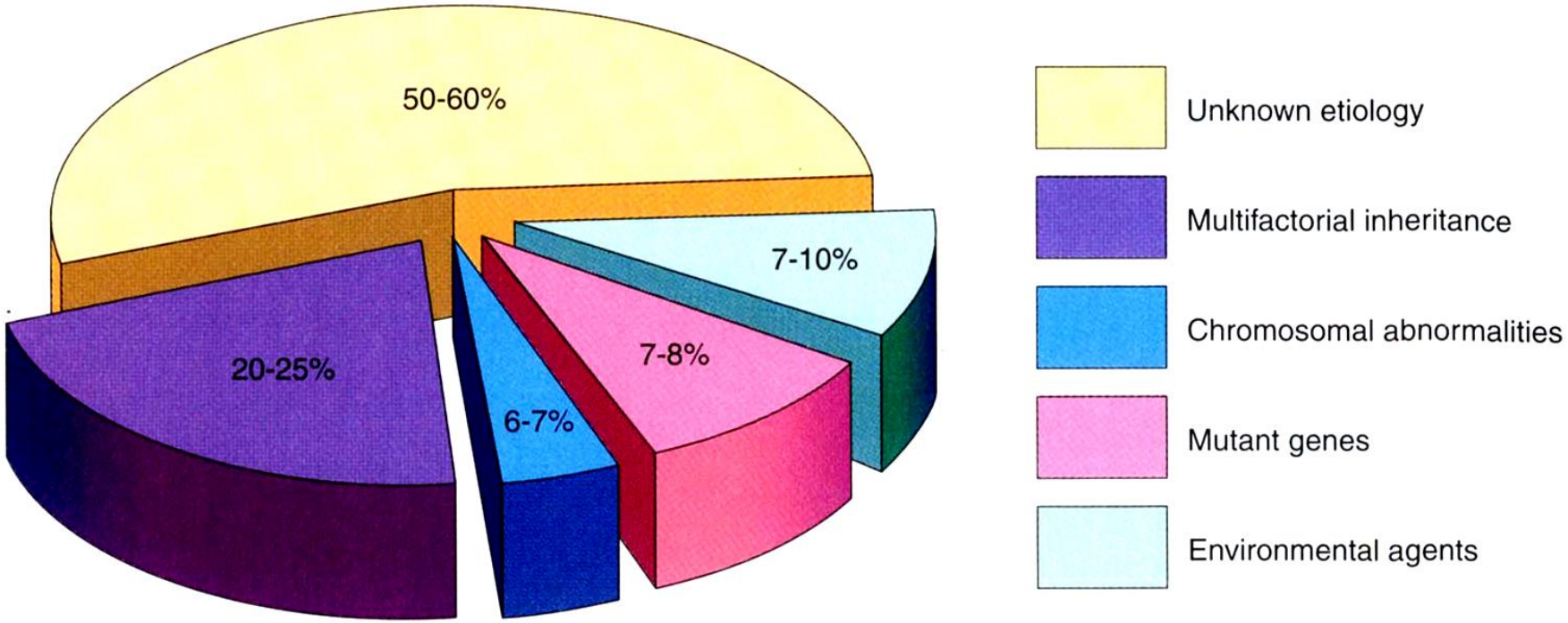
DEFINITIONS

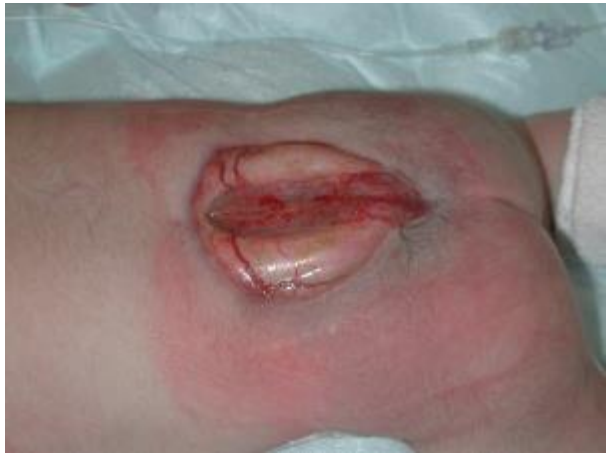
Congenital malformations/birth defects

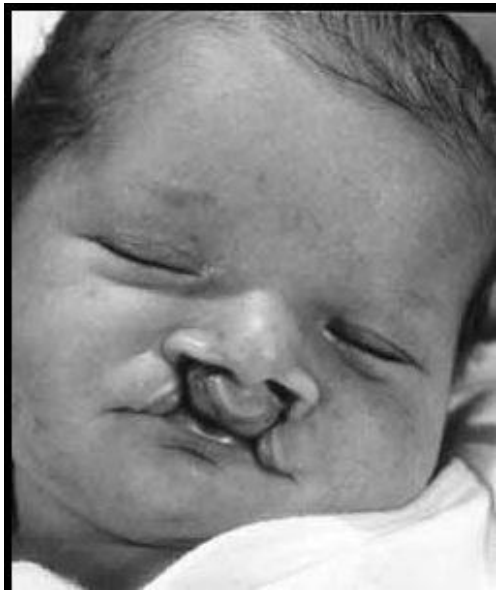
- 2-3% of births
- *WHO definition: Irreversible structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy (e.g. hearing defects).*
- CNS > heart > kidneys > limbs

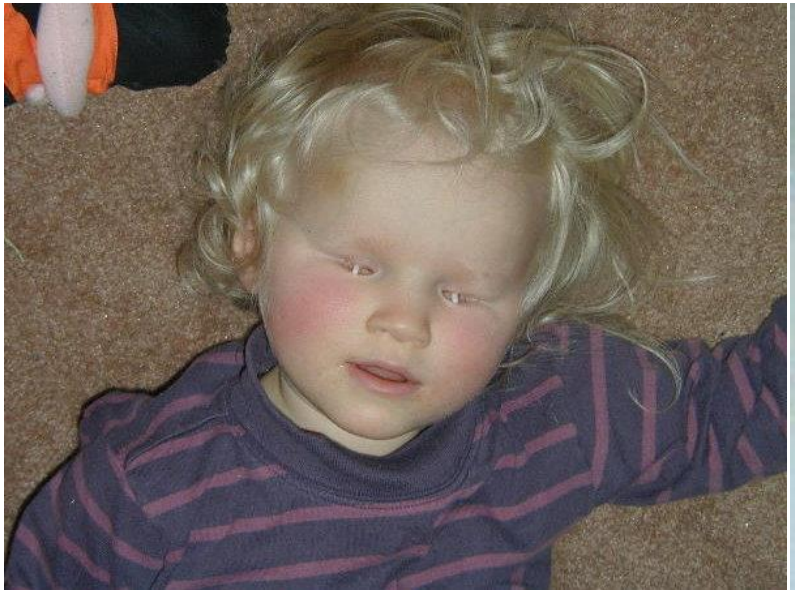


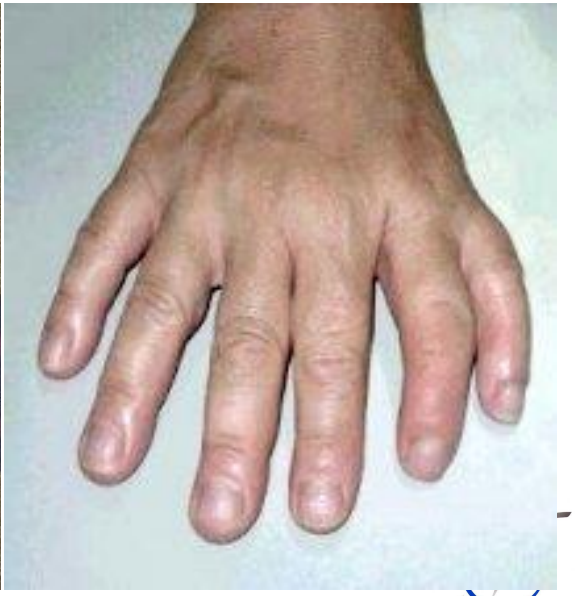
Primary abnormality

Defect in the structure of an organ or a part of an organ due to an intrinsic anomaly in its development (genetic origin).



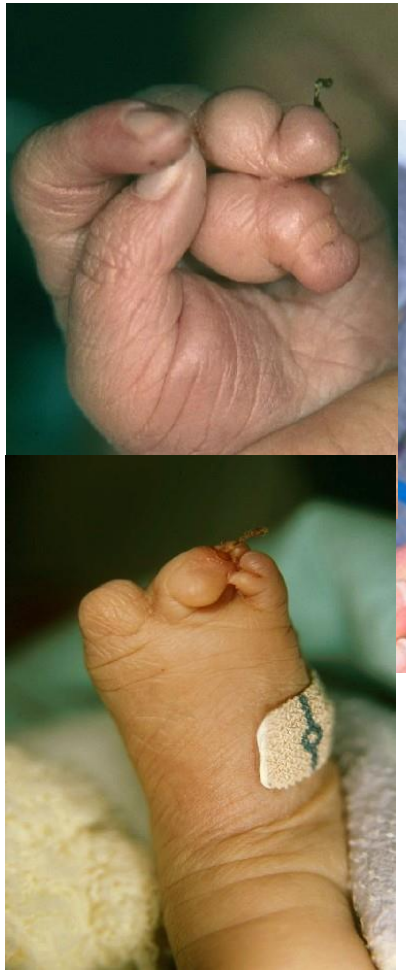


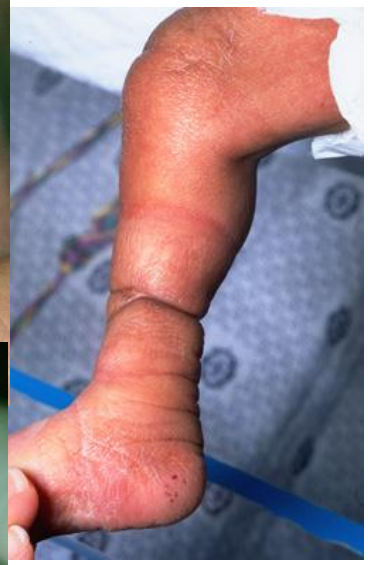




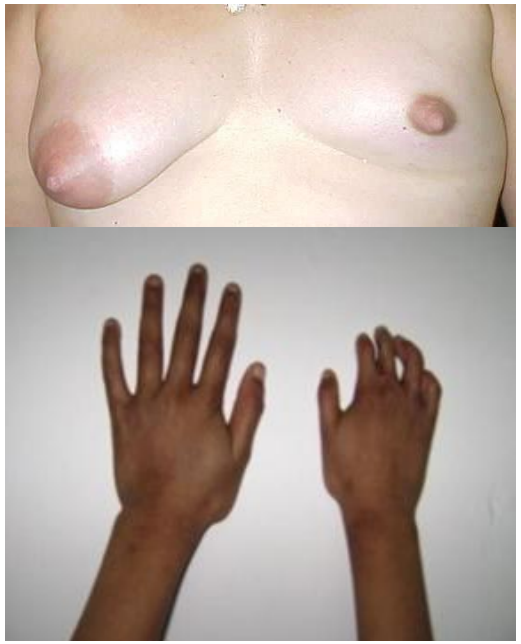
Secondary abnormality (disruption)

Interruption of the normal development of an organ that can be traced back to outer influences: teratogenic agents (infections, chemical substances, ionizing radiations) or a trauma (amniotic bands, vascular defect).

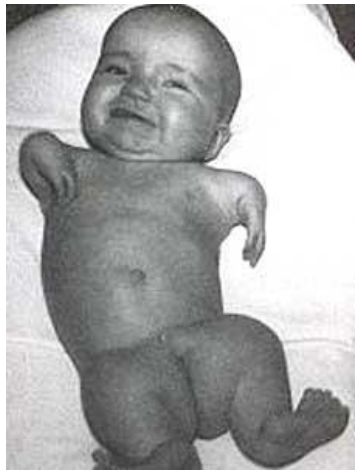




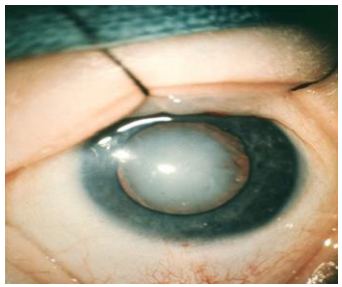
amniotic bands



Poland syndrome

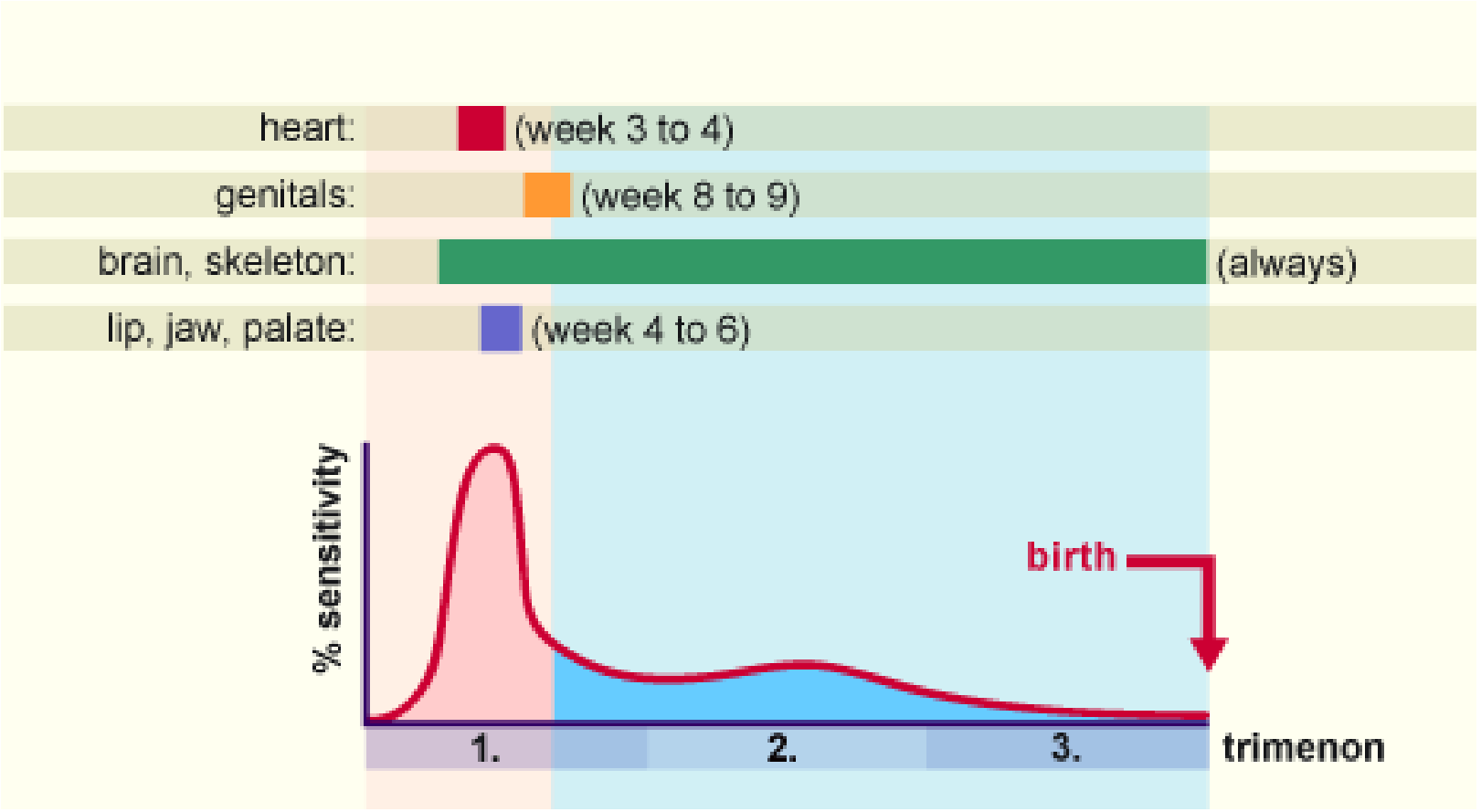


Thalidomide (Softenon®)



Congenital Rubella

Secondary abnormality (disruption)



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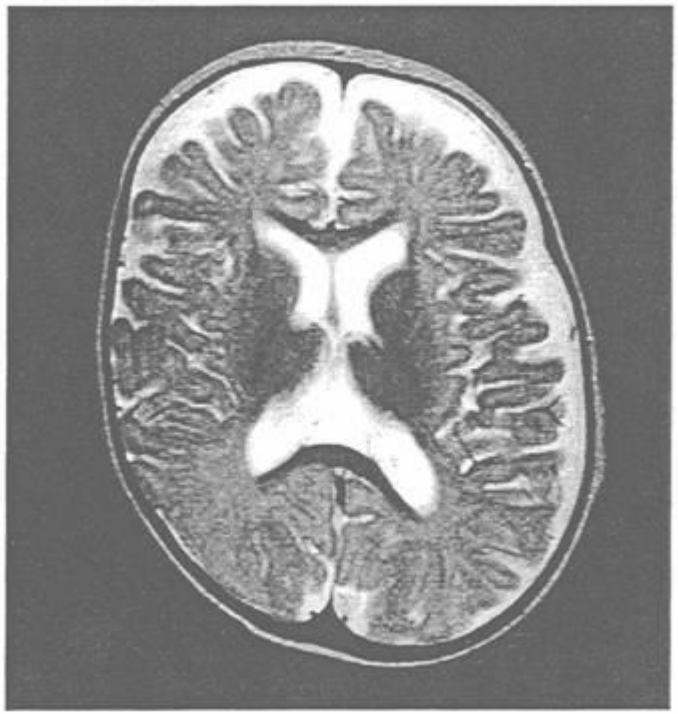
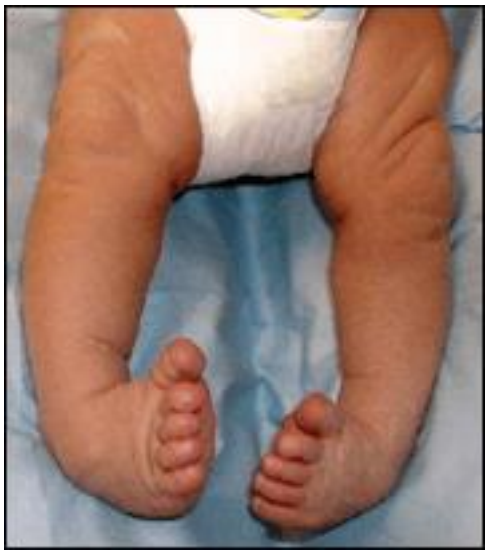
(Deformation)

Anomalies that occur due to outer mechanical effects on existing normal organs or structures (reversible, so no "birth defect")



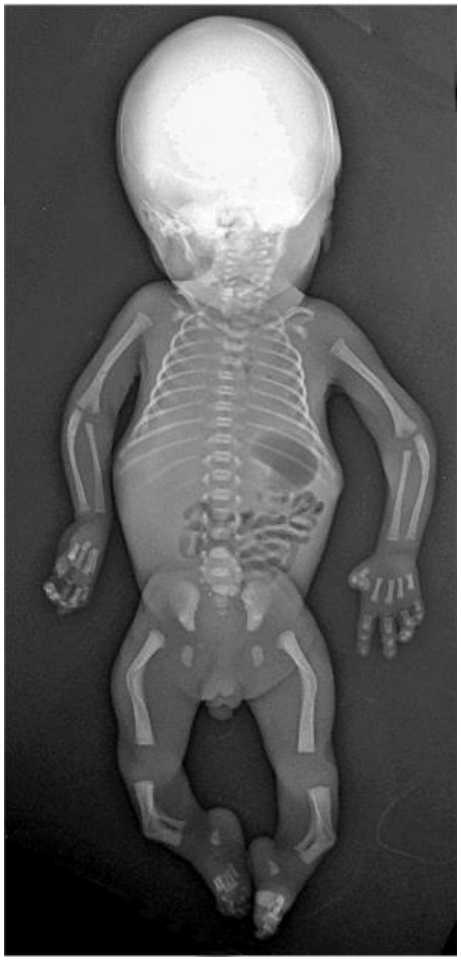
Positional plagiocephaly



Positional « club-feet »

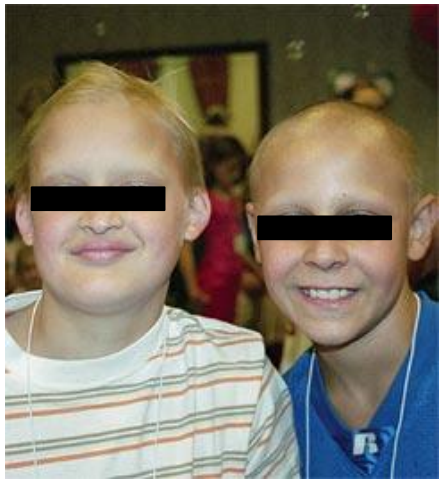
Dysplasia

Abnormal organization of the cells in a tissue

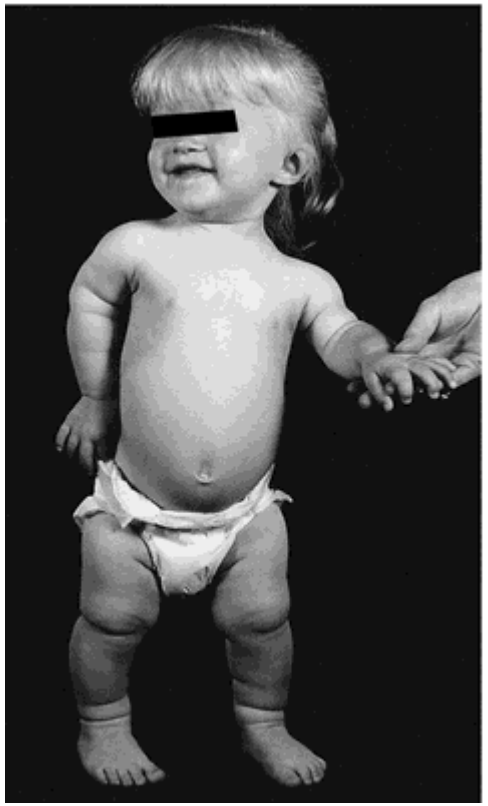


campomelic dysplasia

Osteogenesis imperfecta



Ectodermal dysplasia



Achondroplasia

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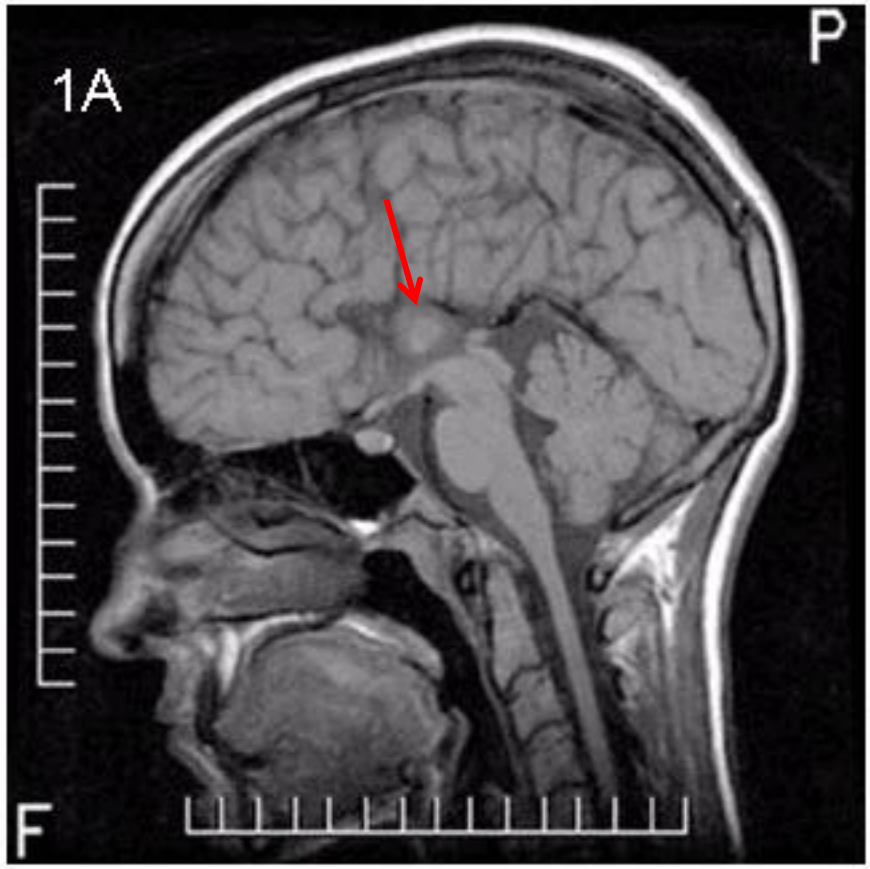
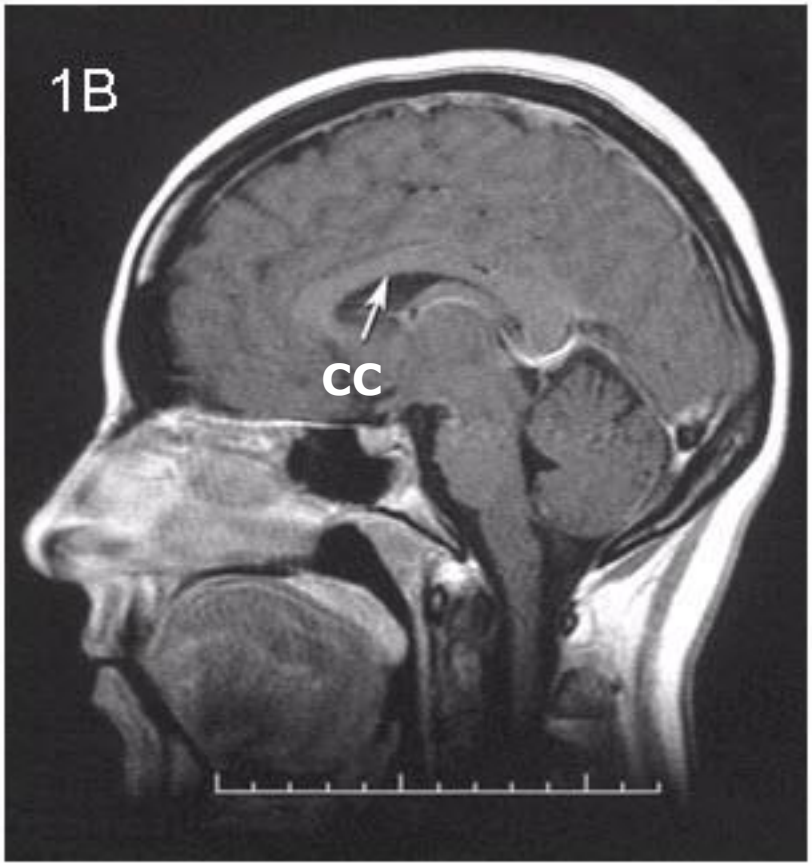
Agenesia

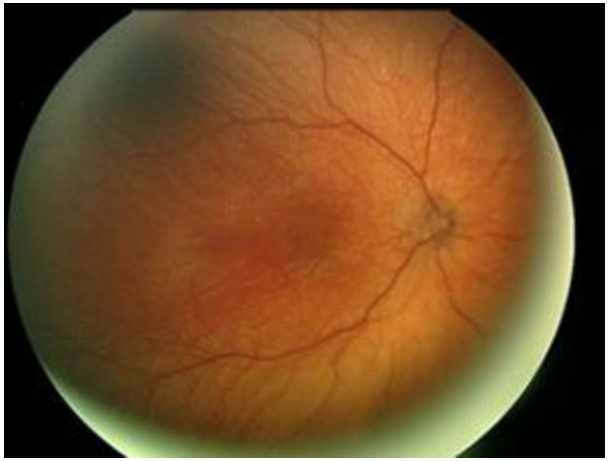
The absence of an organ due to a development that failed to happen during the embryonic period



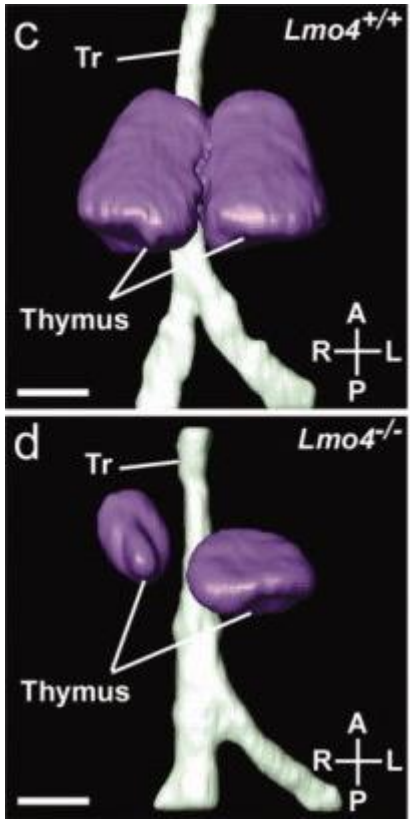


Hypoplasia

Underdevelopment or incomplete development of a tissue or organ during the embryonic period



Optic nerve hypoplasia

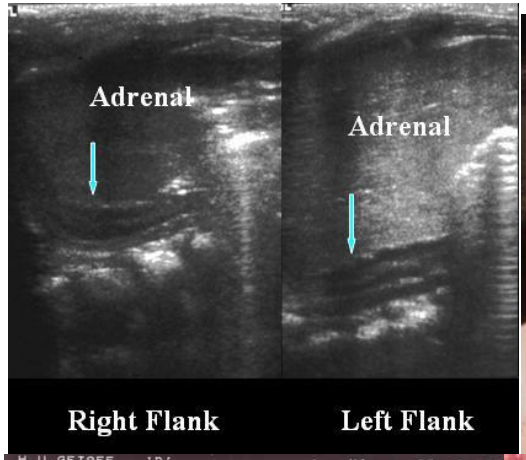


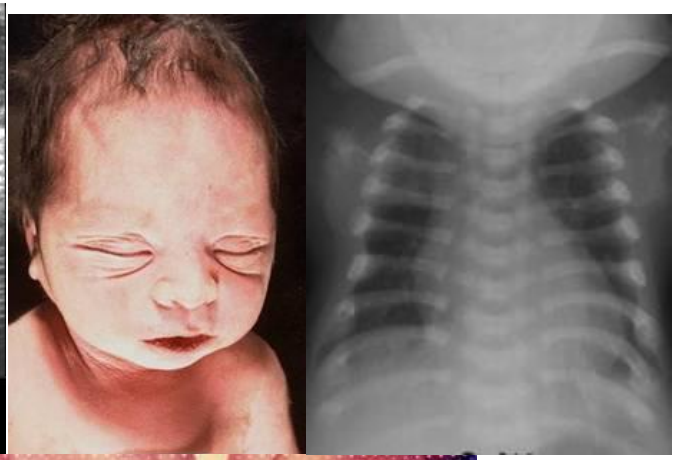
Thymic hypoplasia

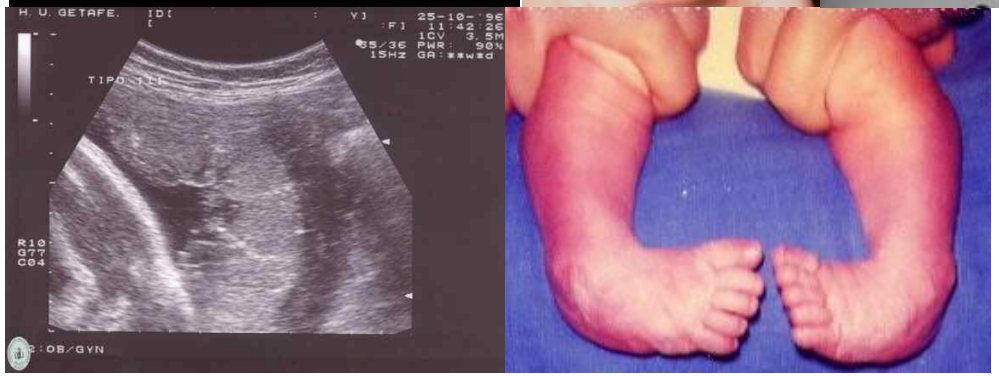
Enamel hypoplasia

Sequence

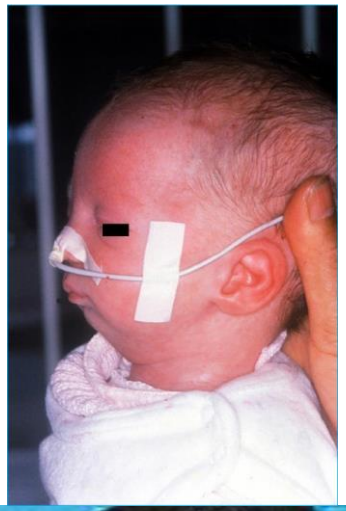
When one, single factor results in numerous secondary effects, leading to several anomalies (domino effects)

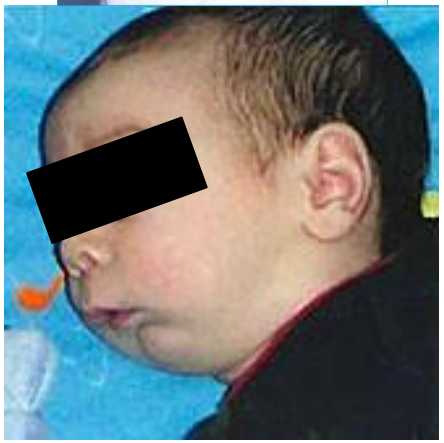






Potter's sequence

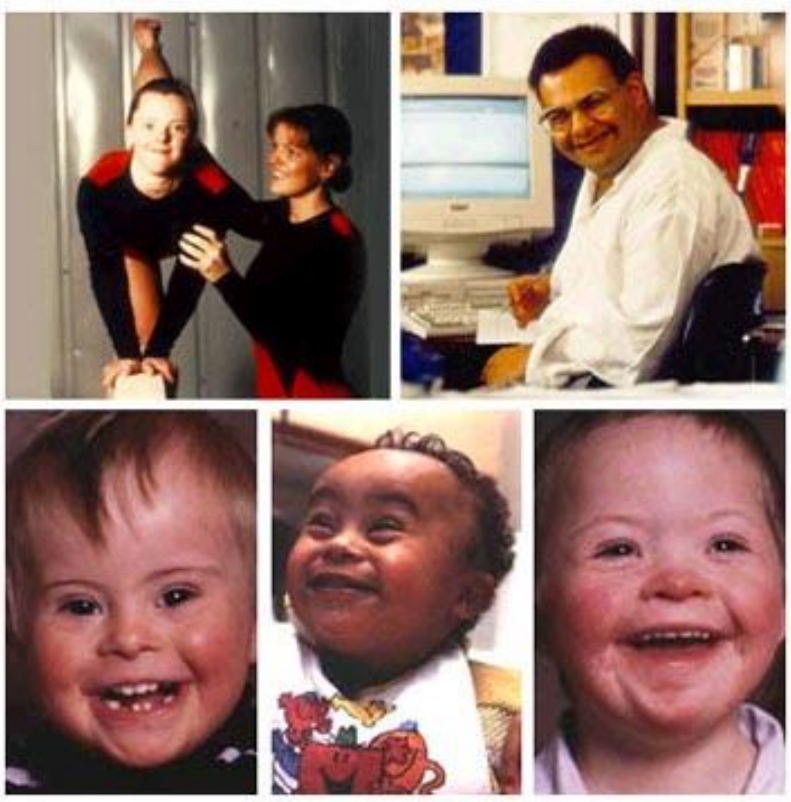




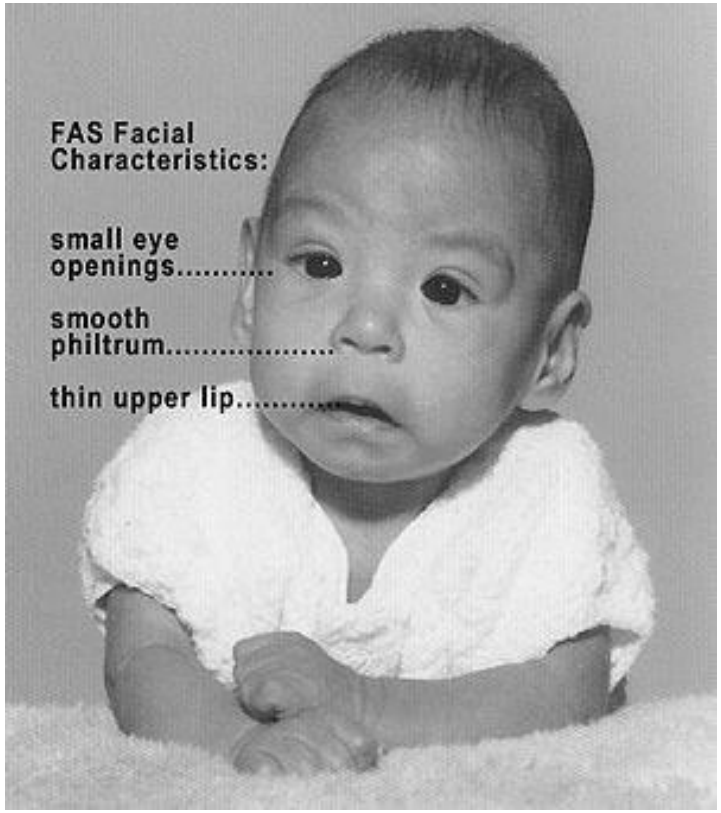
Pierre Robin sequence

Syndrome

A recognizable pattern of multiple defects is described as a "malformation syndrome" when a common cause has resulted in a number of anatomically unrelated errors in morphogenesis (genetic or teratogenic origin)



Down syndrome



Fetal alcohol syndrome

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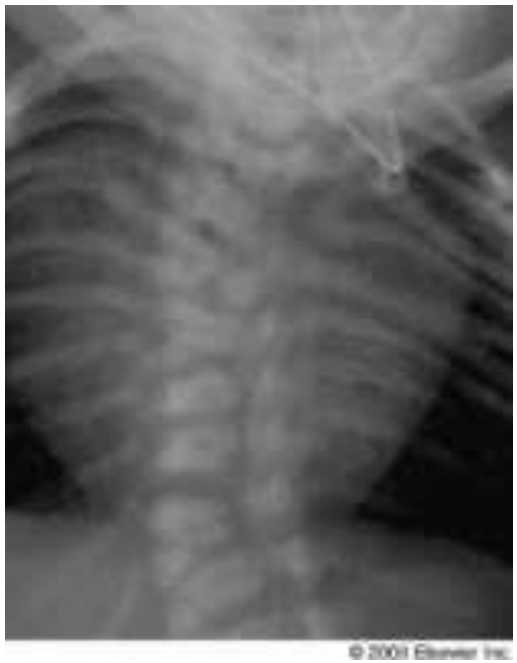
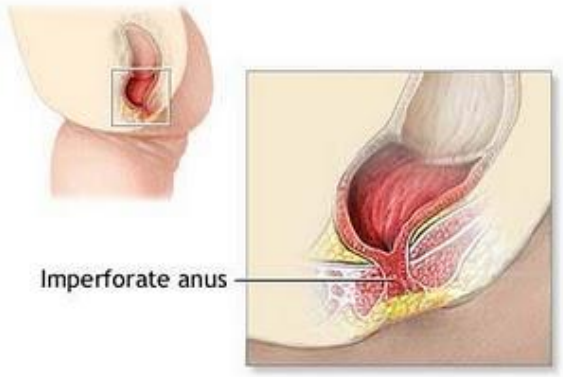
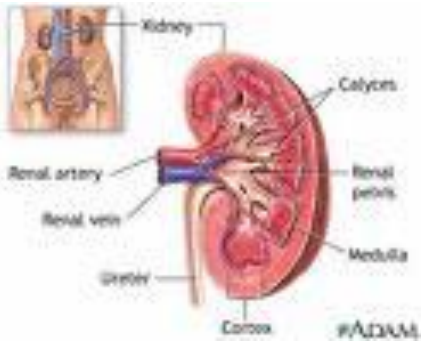
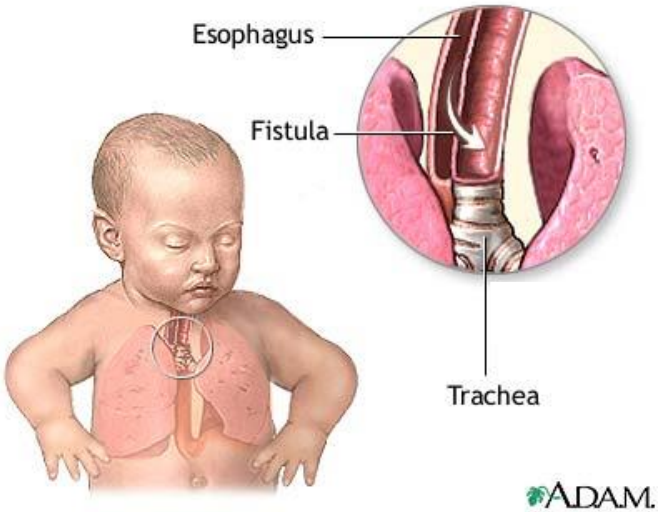
Association

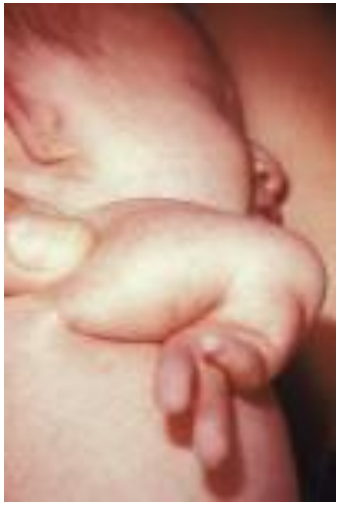
An association is defined as a combination of anomalies which occur together more frequently than by chance alone, but the origin is (still) unknown

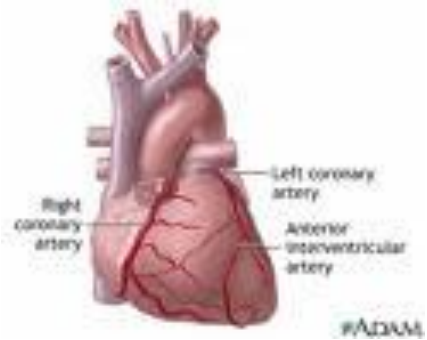








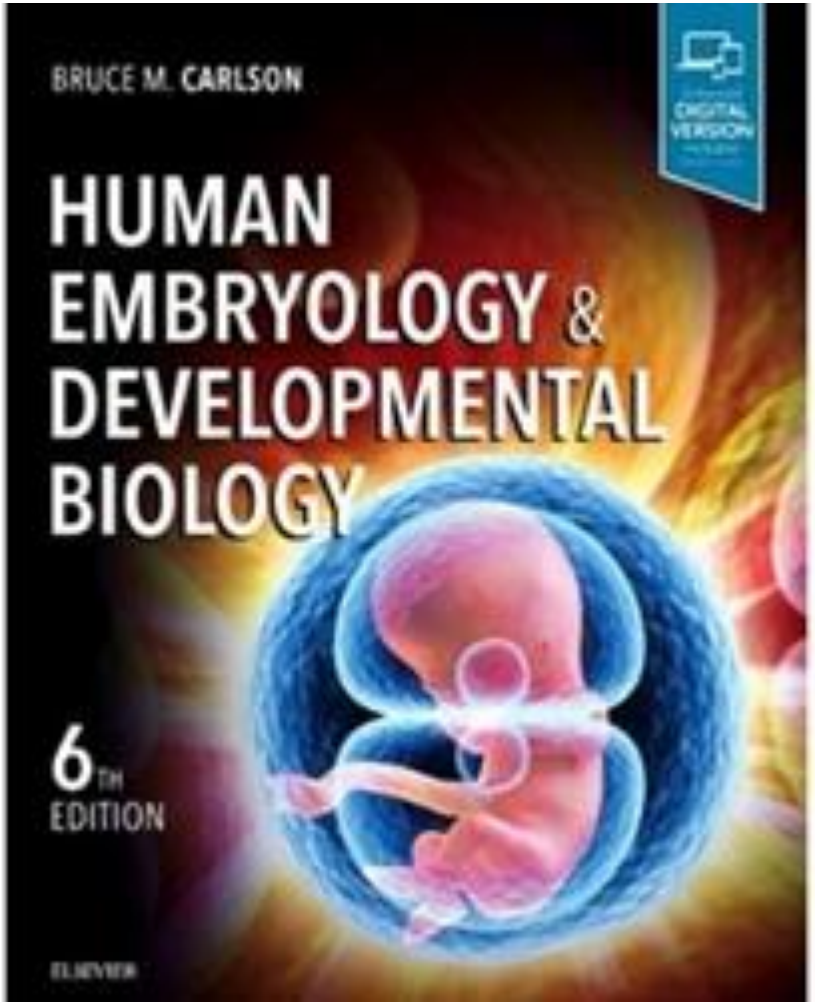




VACTERL association

MOLECULAR MECHANISMS IN EMBRYOLOGY

PHYSIOPATHOLOGY OF BIRTH DEFECTS



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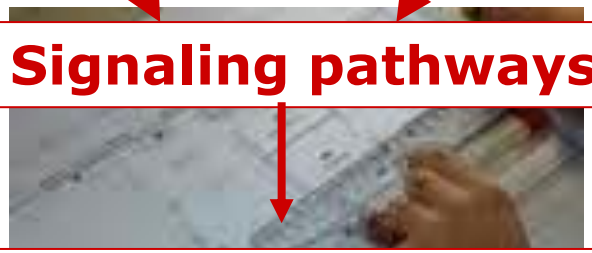
Induction

Signaling molecules

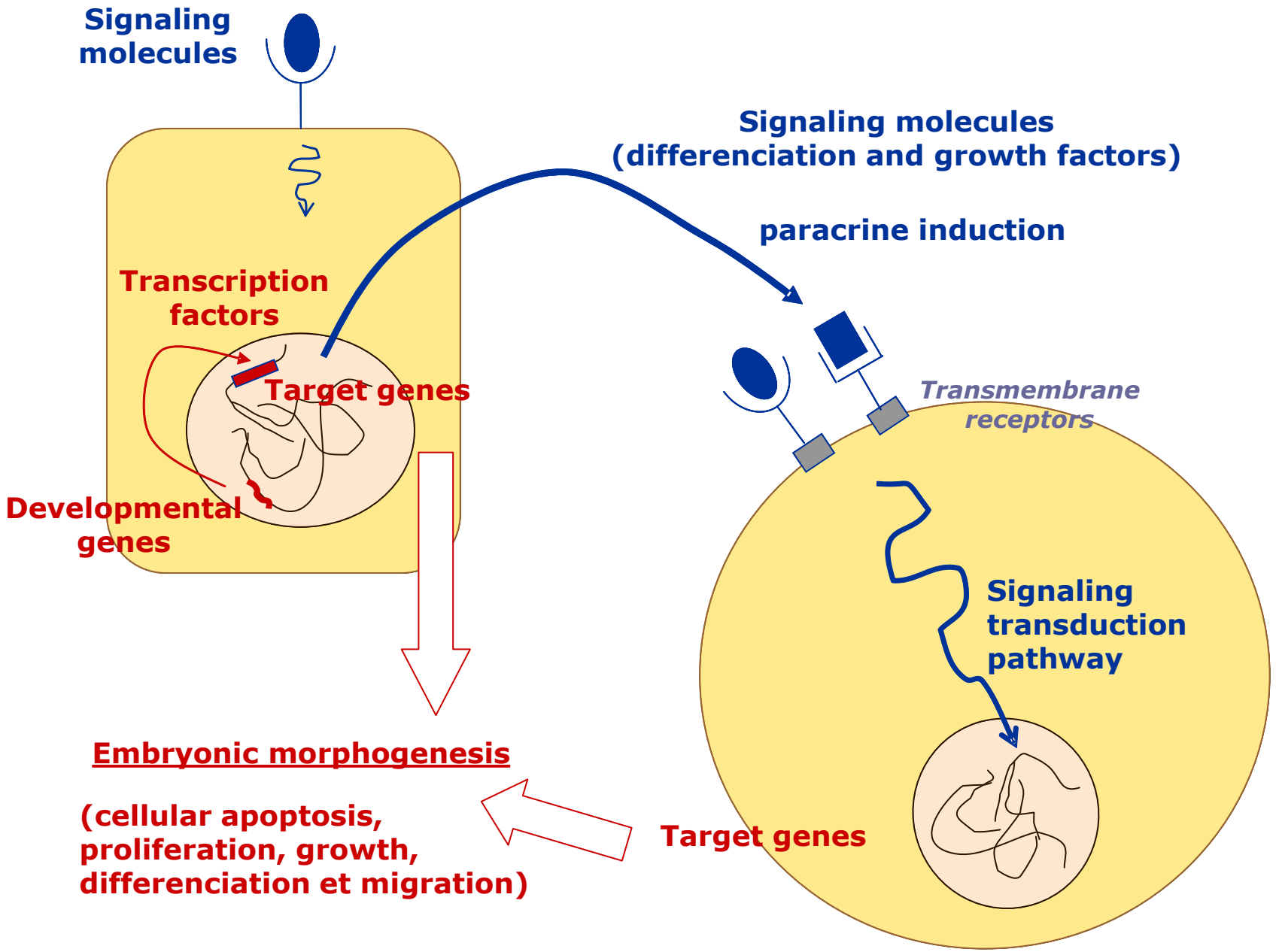
Signaling pathways



Developmental genes *(transcription factors)*

Target genes

Cellular proliferation, differenciation, migration, apoptosis processes


Signaling molecules
Signaling molecules (differenciation and growth factors)
paracrine induction
Transcription factors
Target genes
Developmental genes
Transmembrane receptors
Signaling transduction pathway
Embryonic morphogenesis
(cellular apoptosis, proliferation, growth, differenciation et migration)
Target genes

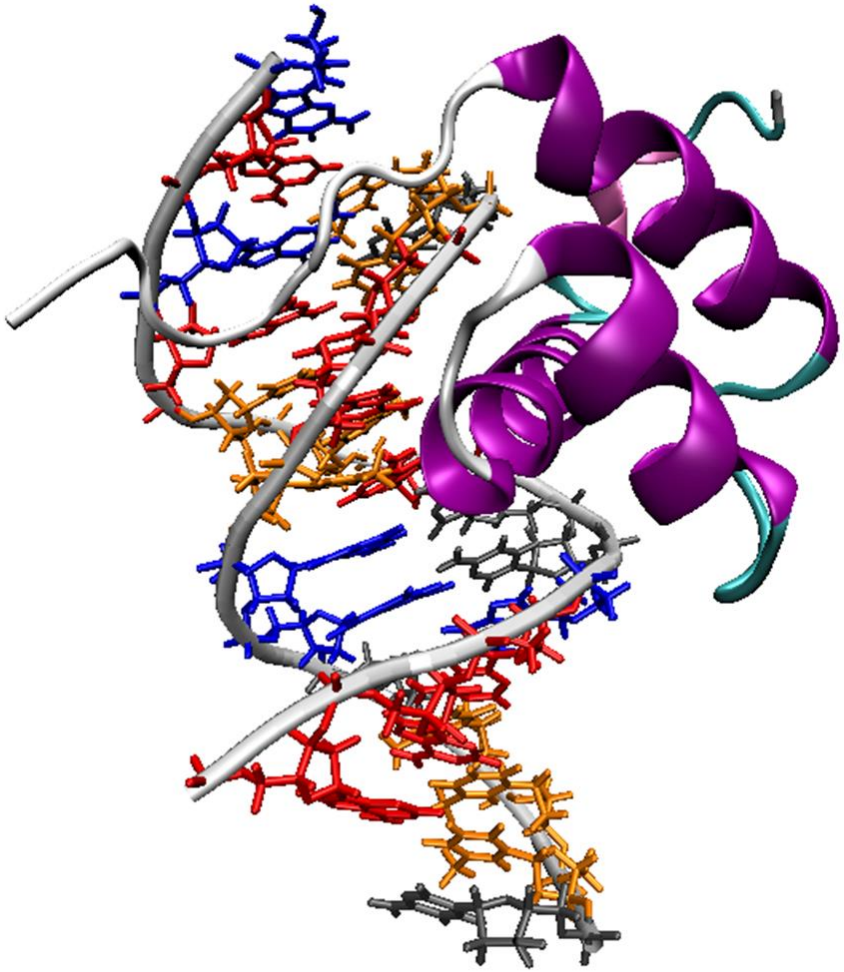
Developmental genes

Transcription factors

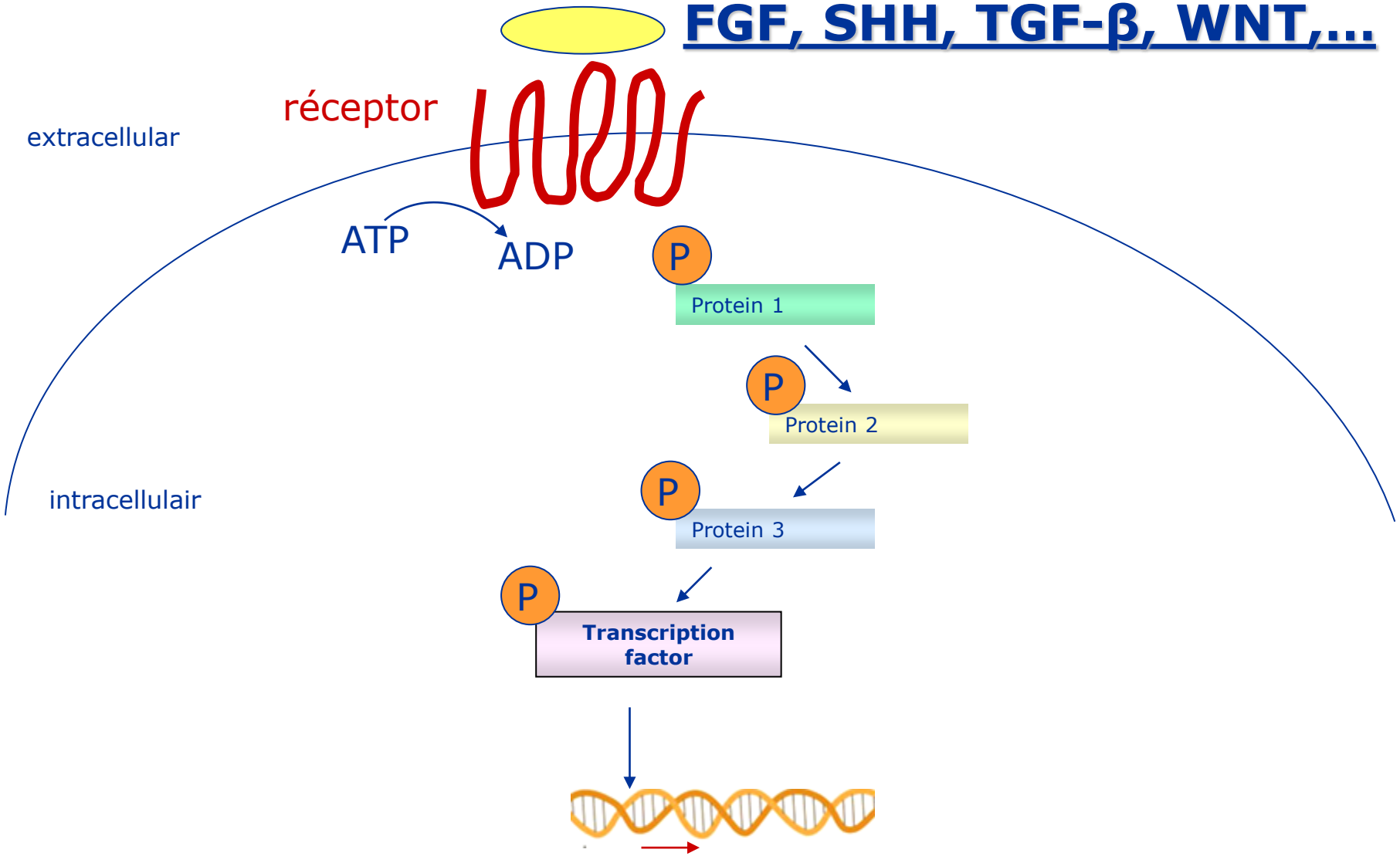
- DNA binding domain

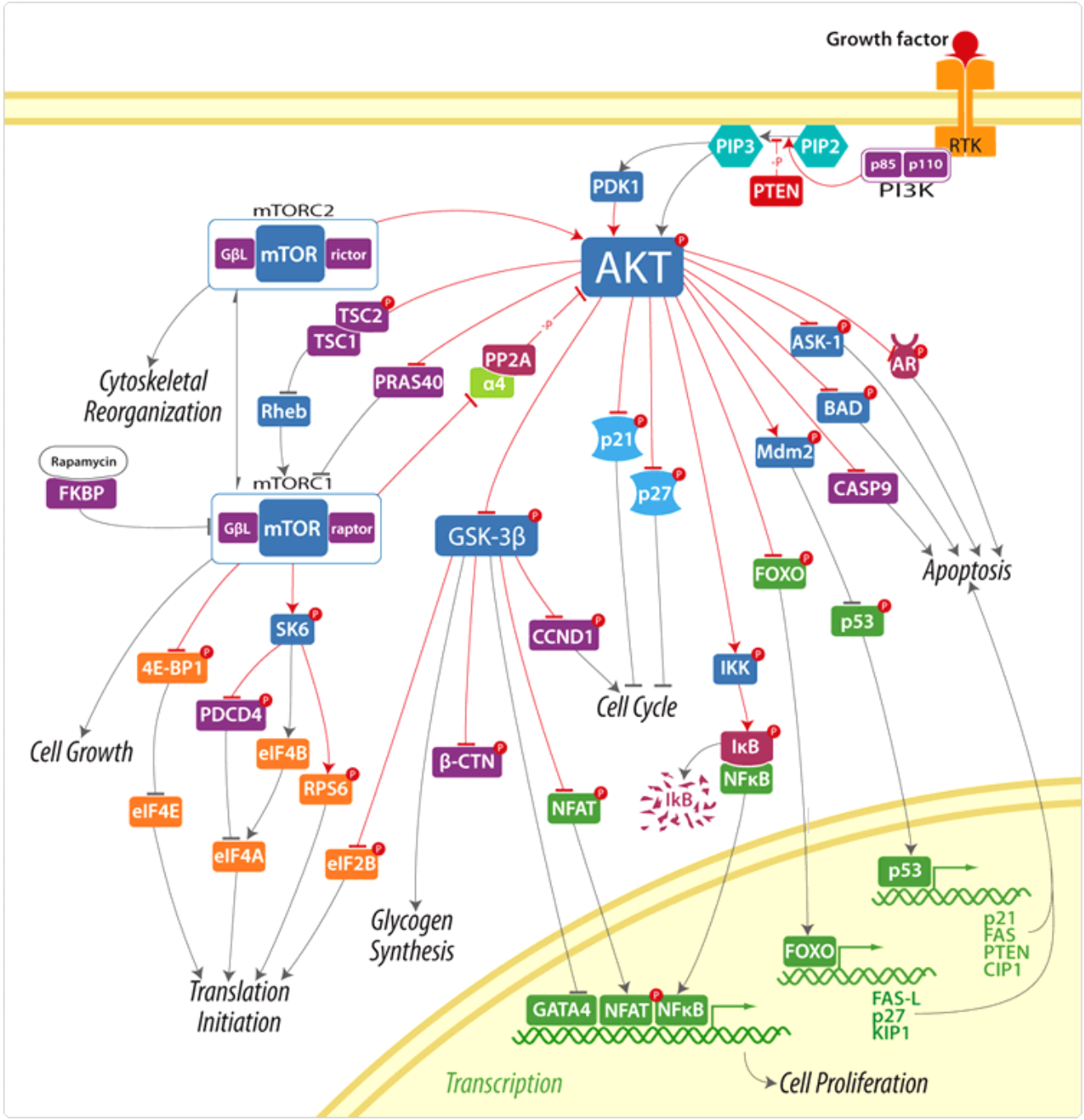
Several families

- homéodomaine proteins (Hox)
- zinc-finger proteins (ZFP)
- Paired Box proteins(Pax)
- basic Helix Loop Helix (bHLH)
- POU proteins
- Winged helix proteins
- T-Box proteins(TBX)
- Etc…

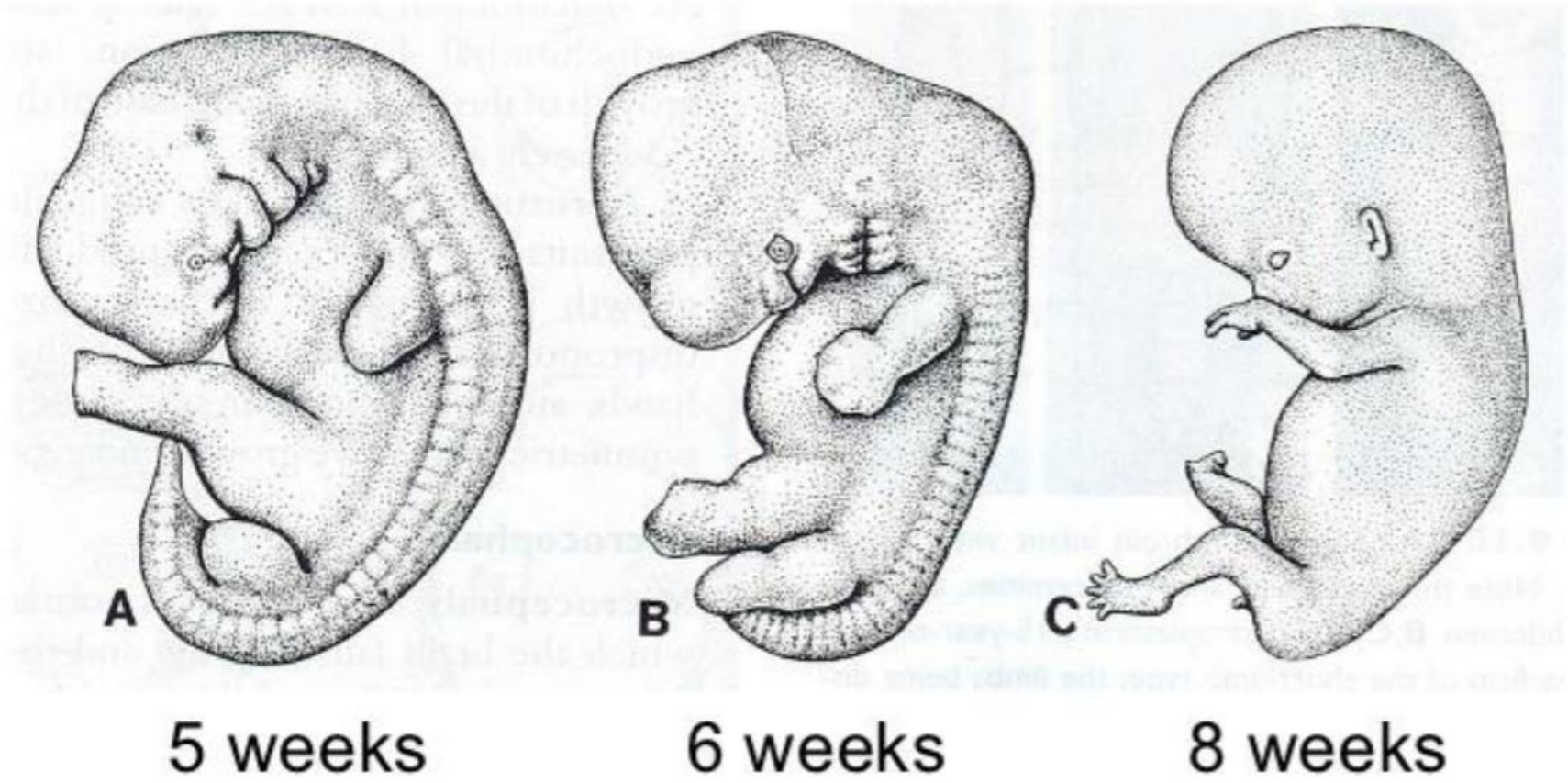


Signaling molecules



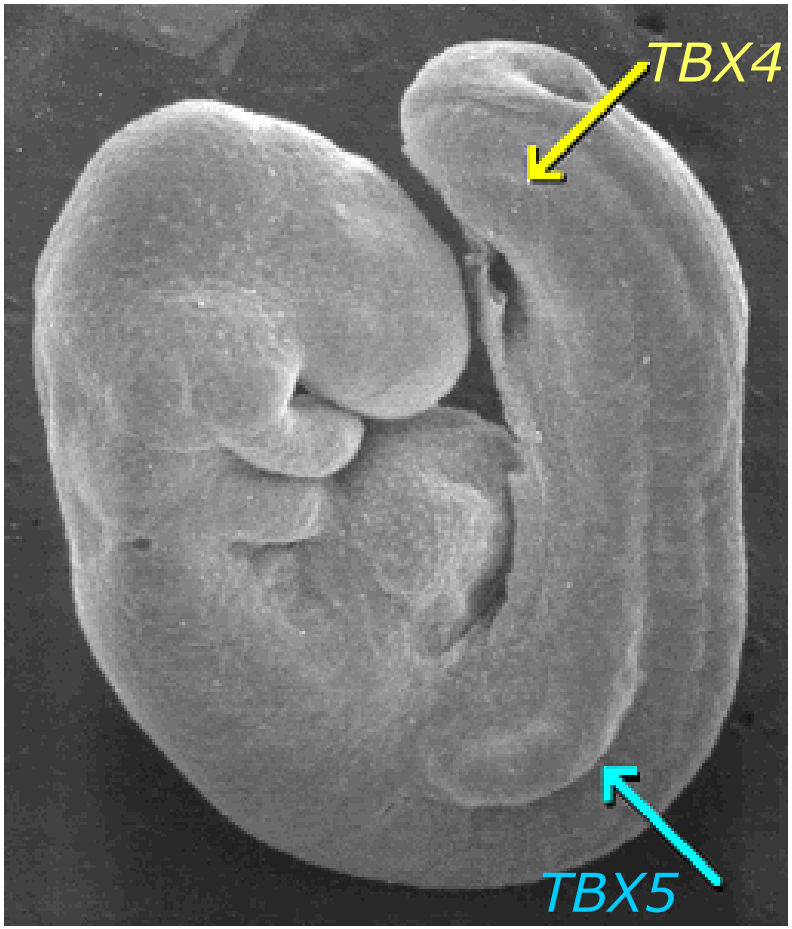

Growth factor
RTK
PIP3
PIP2
-P
PTEN
p85
p110
PI3K
PDK1
AKT
mTORC2
GβL
mTOR
rictor
TSC2
TSC1
PRAS40
Rheb
PP2A
α4
Cytoskeletal Reorganization
Rapamycin
FKBP
mTORC1
GβL
mTOR
raptor
ASK-1
AR
BAD
Mdm2
CASP9
p21
p27
Apoptosis
GSK-3β
FOXO
p53
SK6
CCND1
IKK
4E-BP1
Cell Cycle
PDCD4
eIF4B
Cell Growth
β-CTN
IκB
NFκB
RPS6
eIF4E
NFAT
IκB
eIF4A
eIF2B
p53
p21
FAS
PTEN
CIP1
Glycogen Synthesis
FOXO
FAS-L
p27
KIP1
GATA4
NFAT
NFκB
Translation Initiation
Transcription
Cell Proliferation

ILLUSTRATIVE EXAMPLE
LIMBS DEVELOPMENT



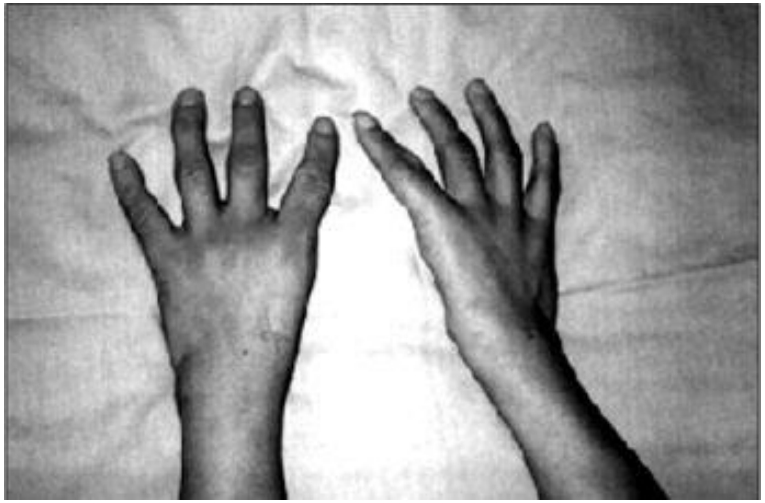
Limb buds at the end of the 4th week of embryonic development

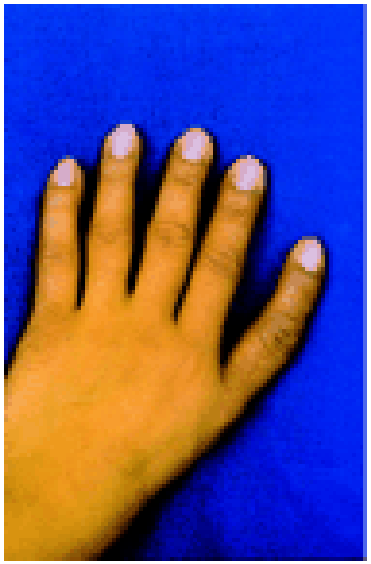
TBX5 gene for the upper buds
TBX4 gene for the lower buds

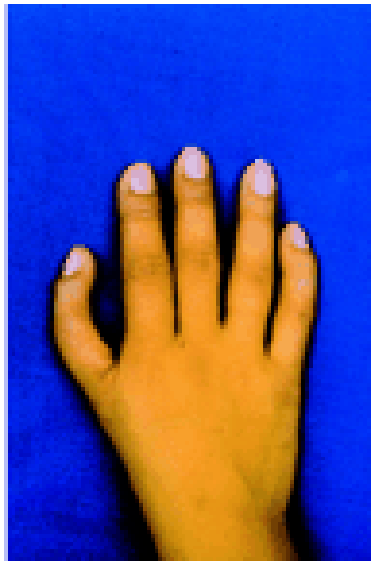


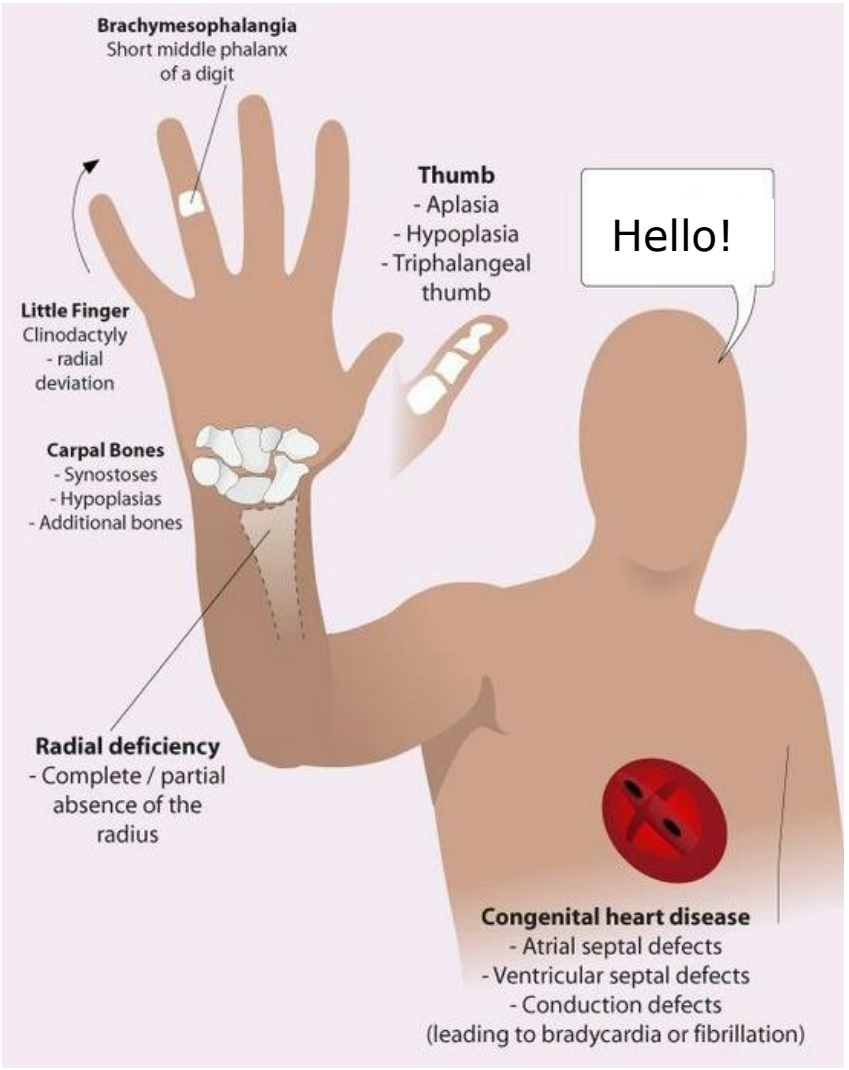
HOLT-ORAM SYNDROME (heart-limbs)

TBX5 mutation

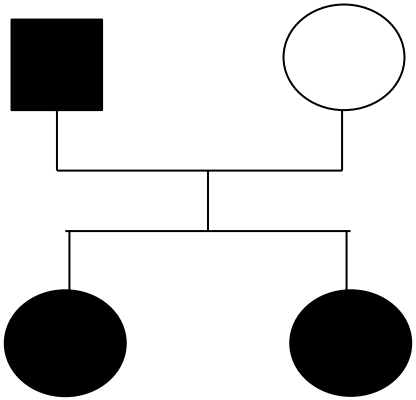


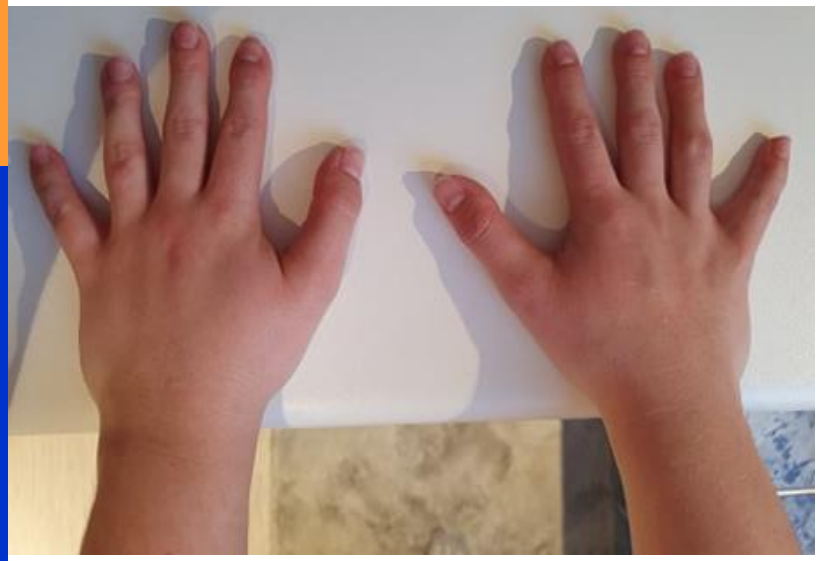


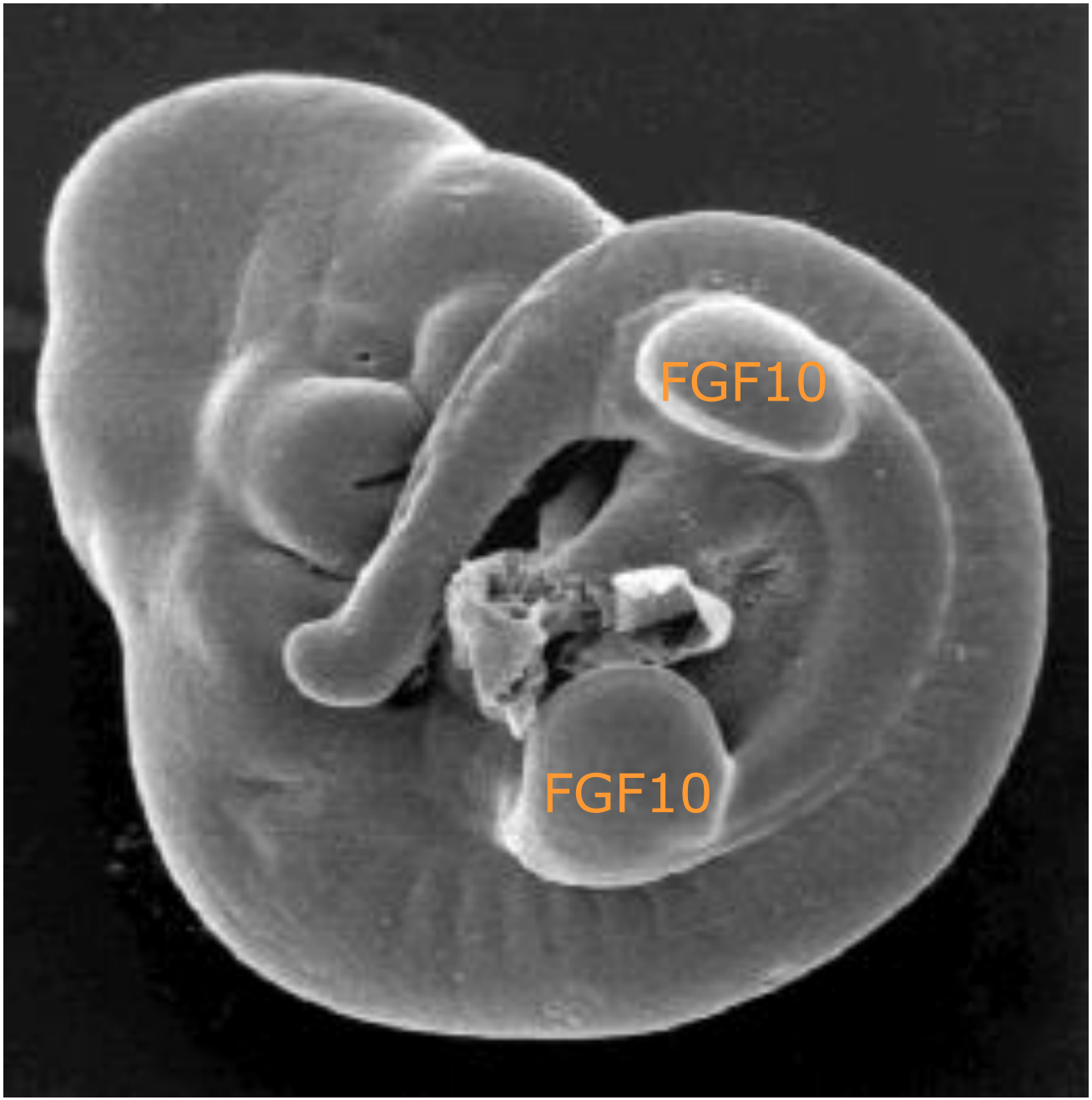


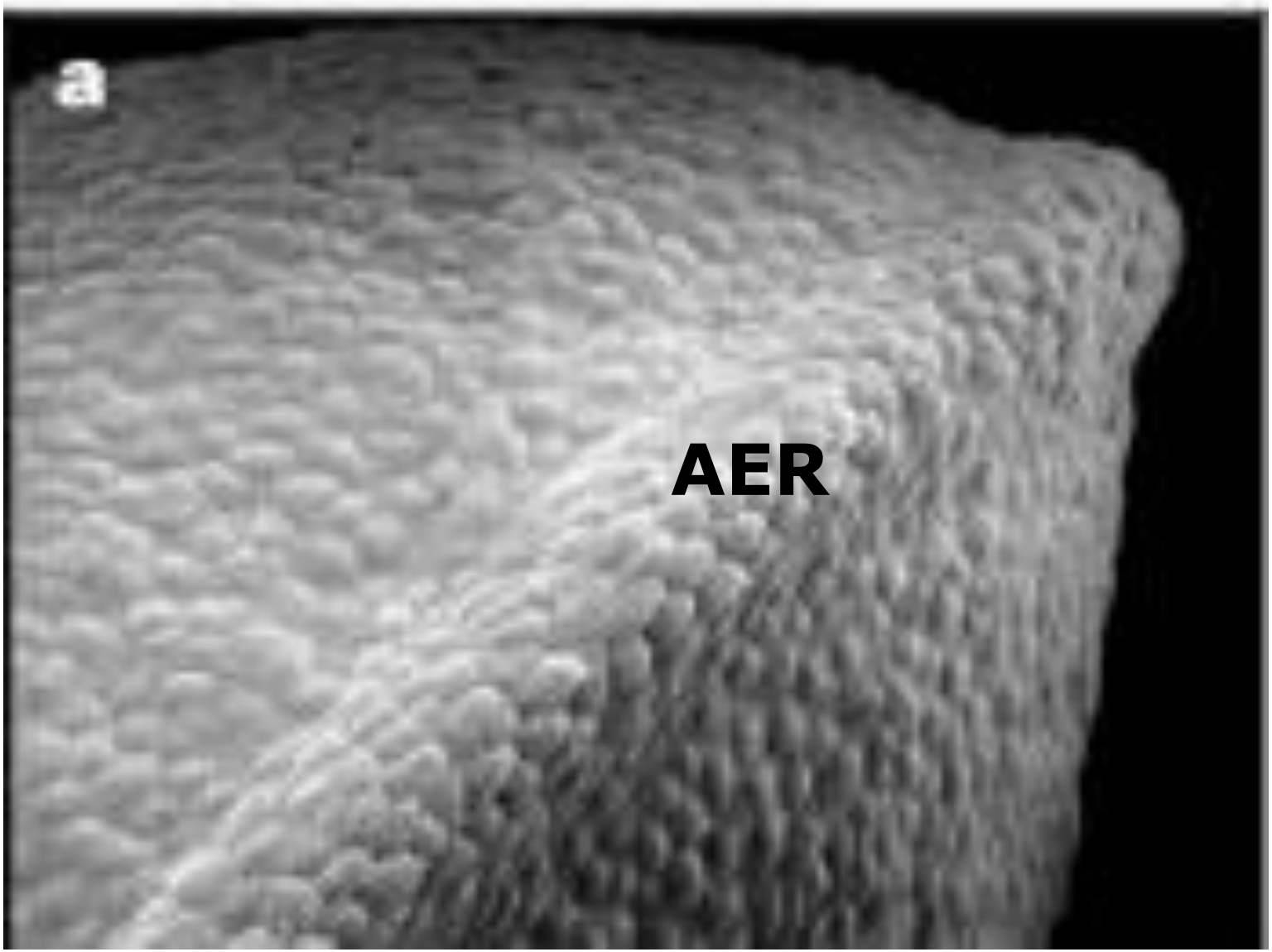


HOLT-ORAM SYNDROME (heart-limbs)



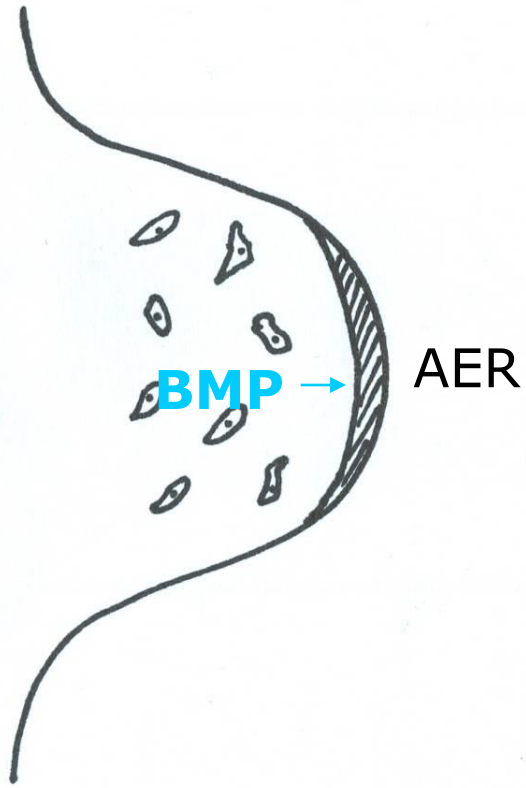


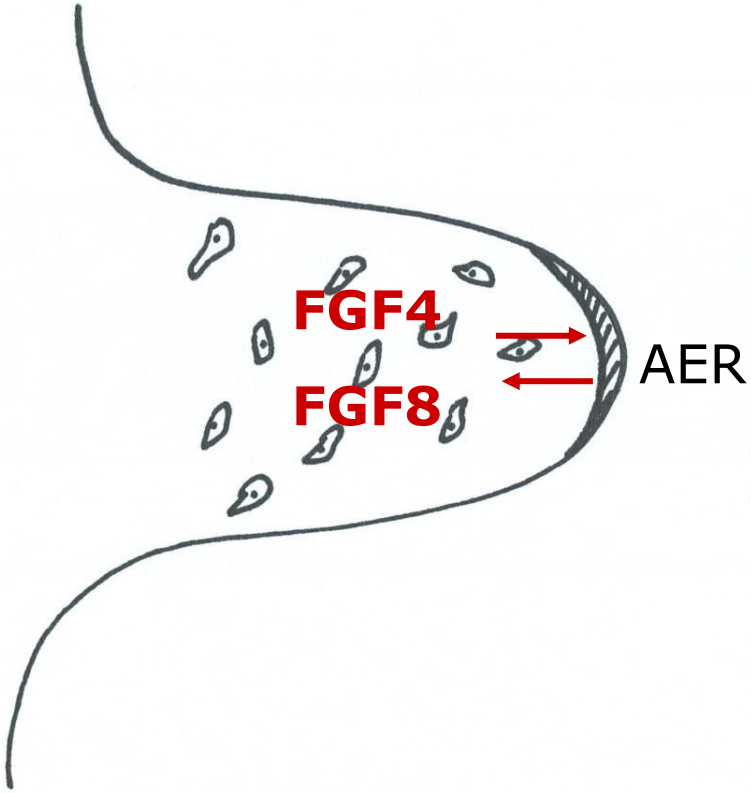

FGF10
FGF10



F.V.Mariani, *Nature 2003,* 423: 319-325

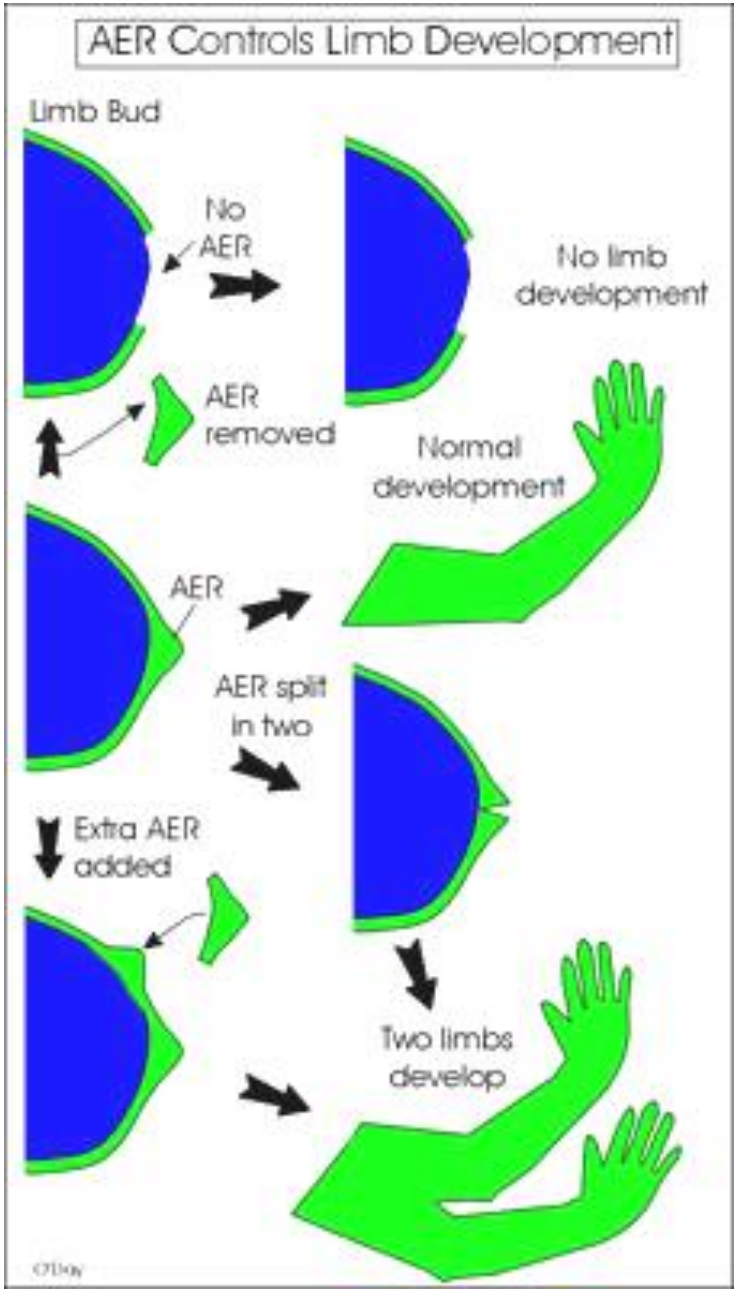
Limb growth





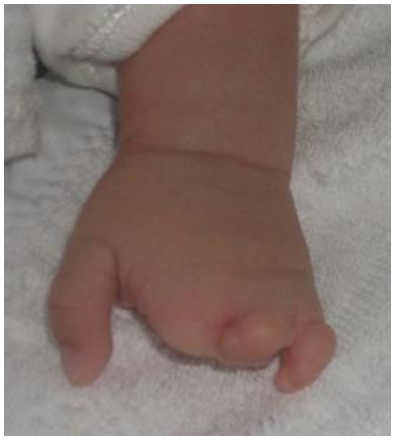
AER: Apical Ectodermal Ridge
BMP: Bone Morphogenic Proteins
FGF: Fibroblast Growth Factor

Apical Ectodermal Ridge Disruption

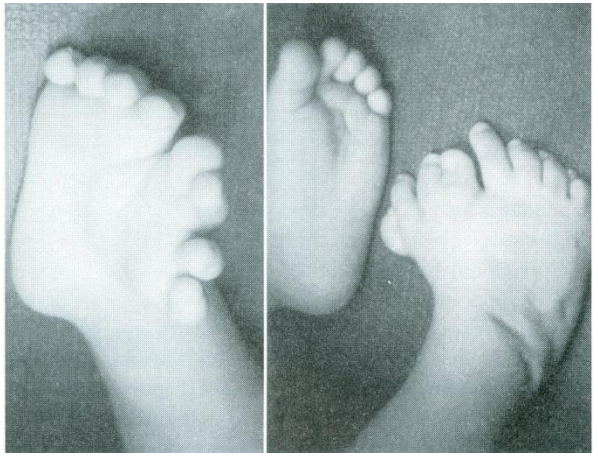


Extrait de www.utm.utoronto.ca

amelia

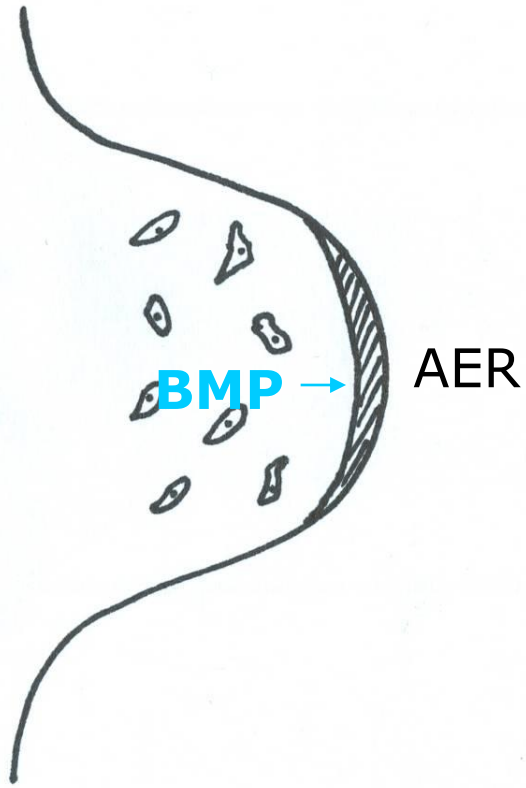


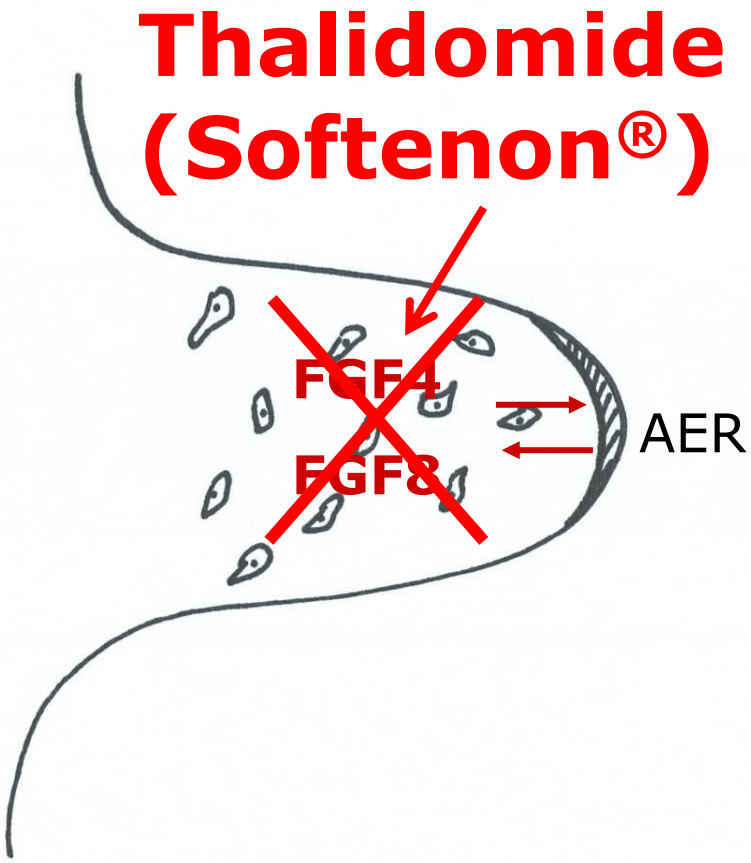
Terminal transverse limb defect (amniotic bands)



Diplopodia

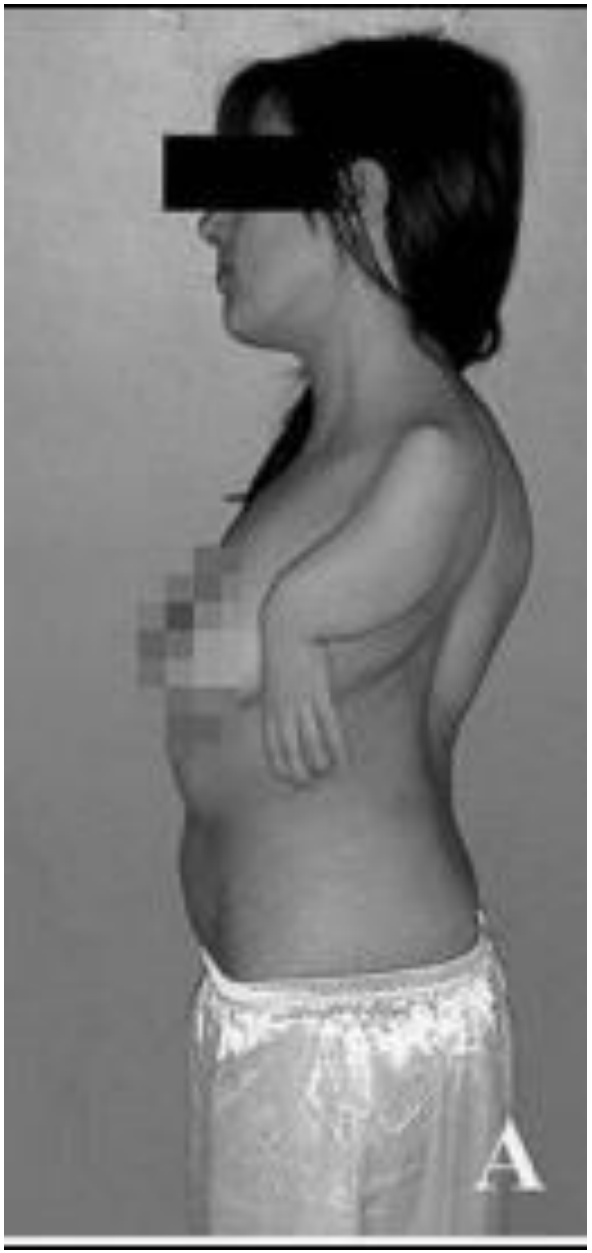
Limb growth



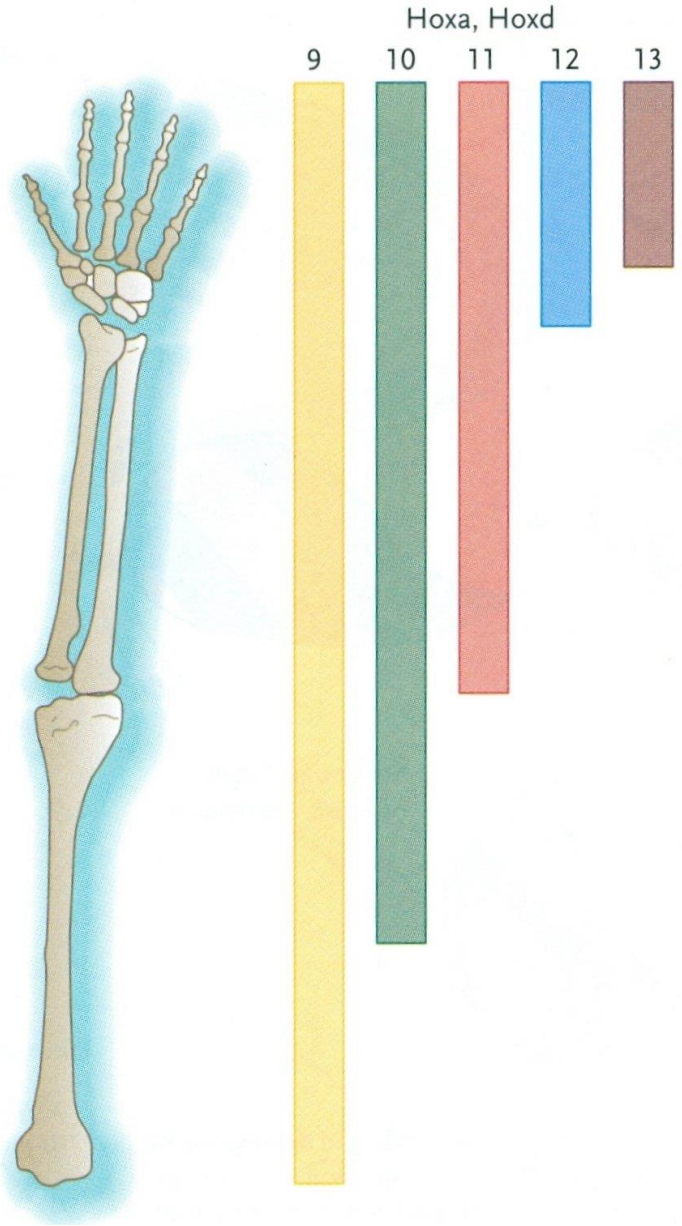


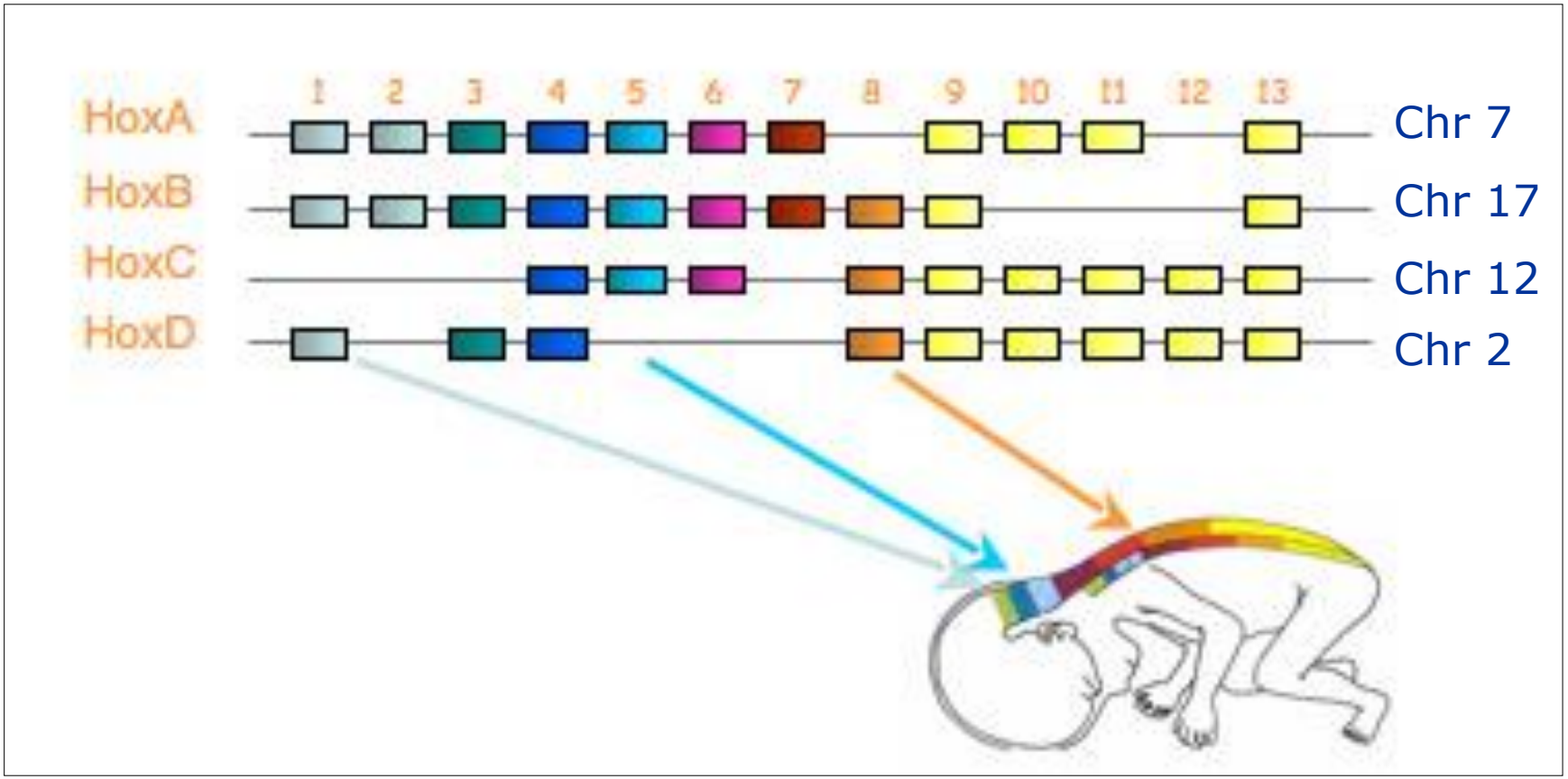
AER: Apical Ectodermal Ridge
BMP: Bone Morphogenic Proteins
FGF: Fibroblast Growth Factor

Phocomelia

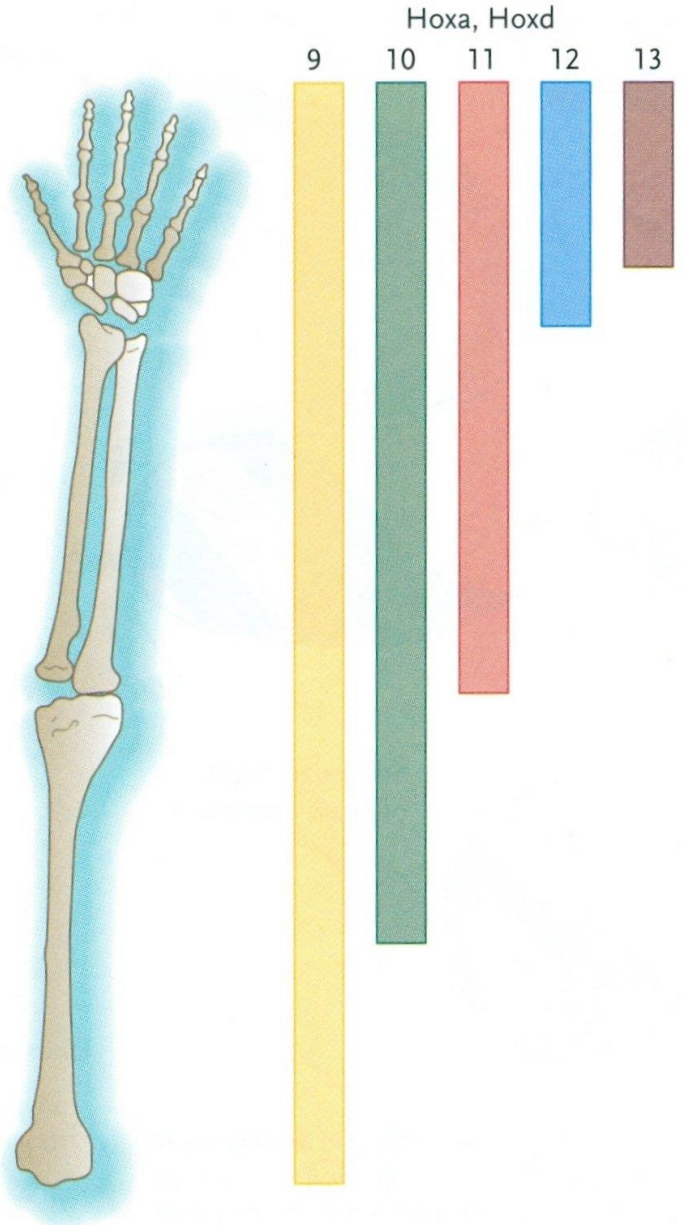


Skeletal differenciation



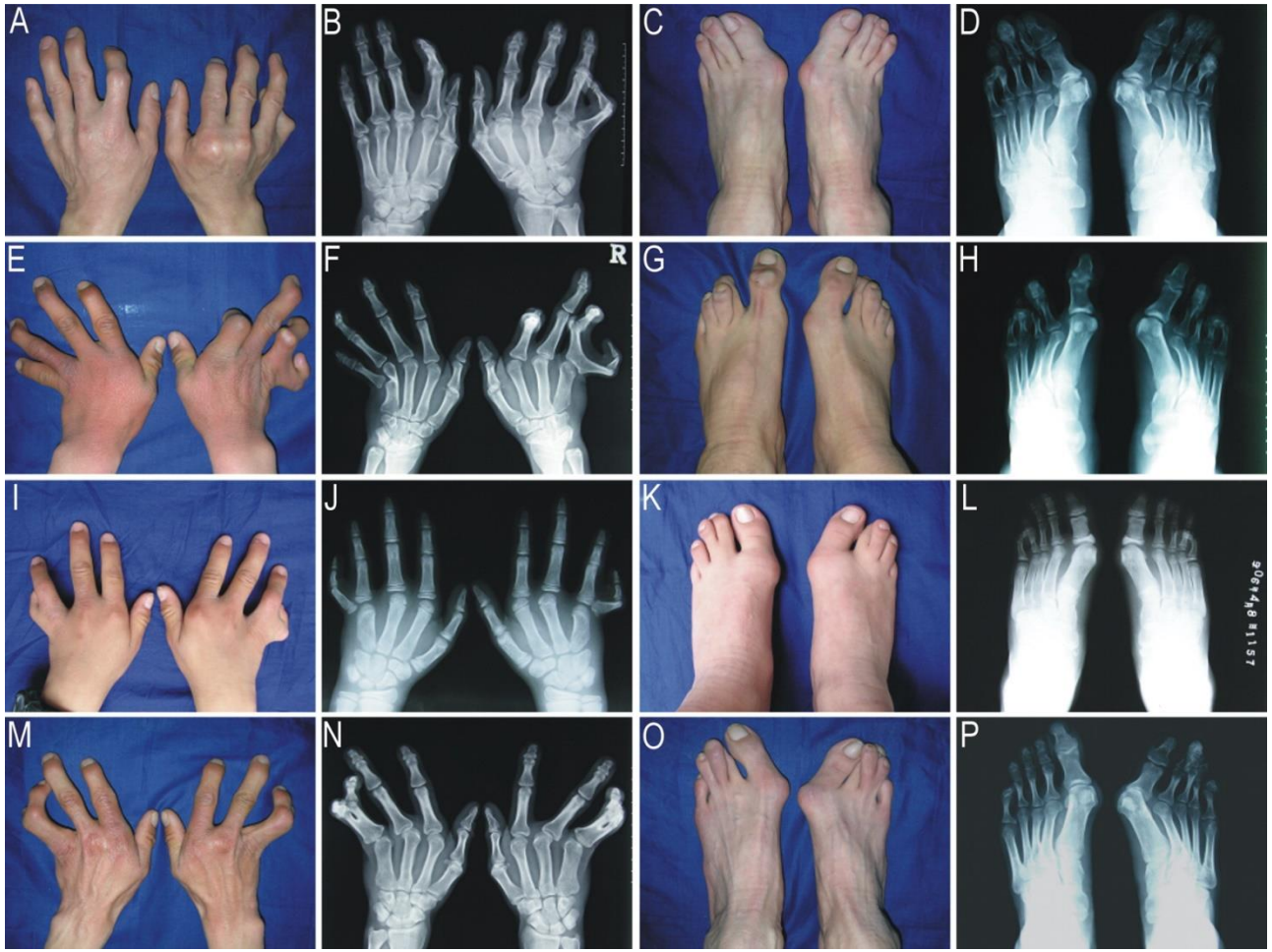

1 2 3 4 5 6 7 8 9 10 11 12 13
HoxA
HoxB
HoxC
HoxD
Chr 7
Chr 17
Chr 12
Chr 2

Skeletal differenciation

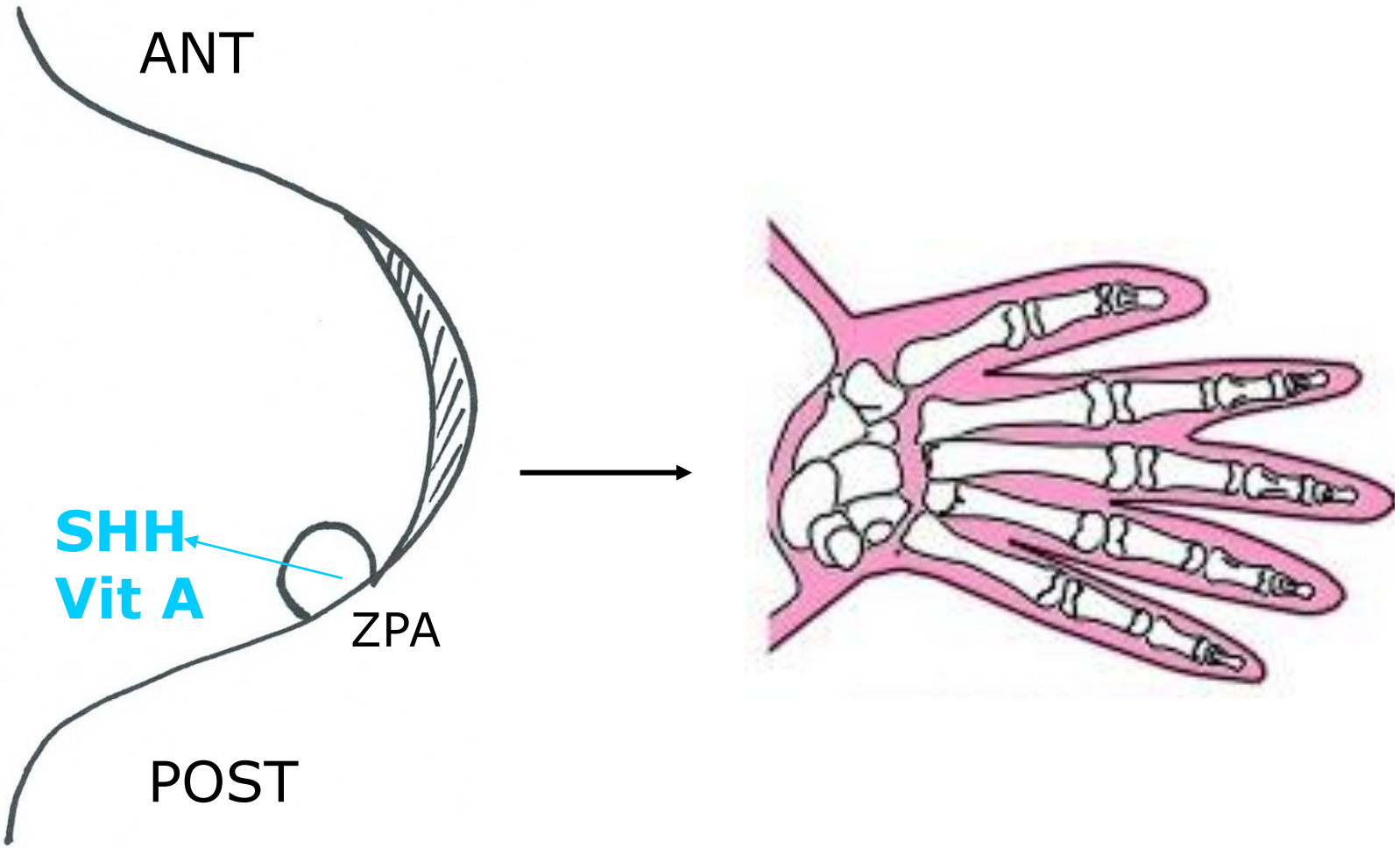


HOXD13 mutation

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
2q31.1	?Brachydactyly-syndactyly syndrome	610713		3
	Brachydactyly, type D	113200	AD	3
	Brachydactyly, type E	113300	AD	3
	Syndactyly, type V	186300	AD	3
	Synpolydactyly 1	186000	AD	3

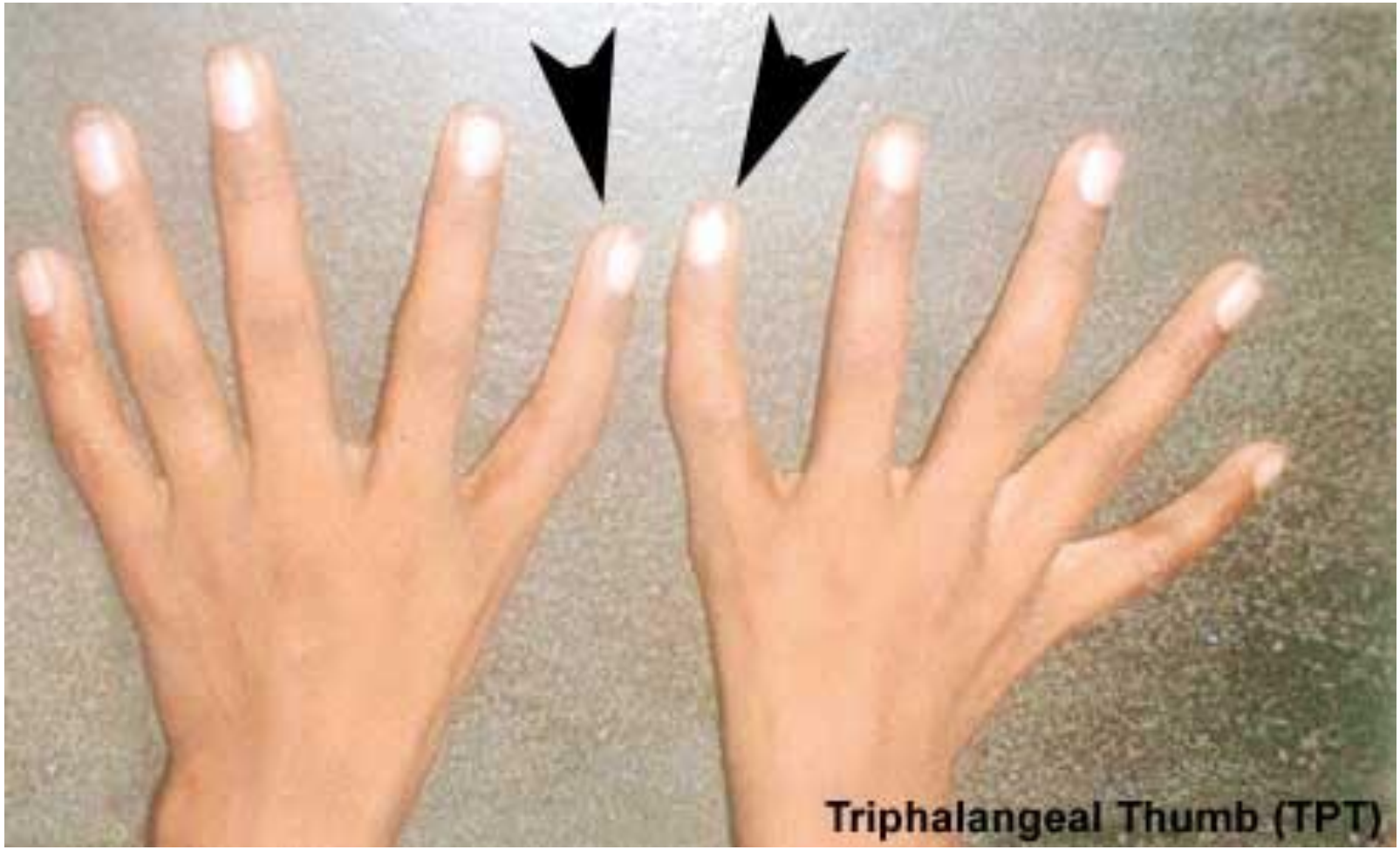


Antero-posterior differentiation



ZPA: Zone of Polarizing activity
SHH: Sonic Hedgehog
Vit A: vitamine A (retinoic acid)

Triphalangeal thumbs
ZRS gain-of-function mutation
(ZRS = ZPA Regulatory Sequence)



Triphalangeal thumbs
ZRS gain-of-function mutation
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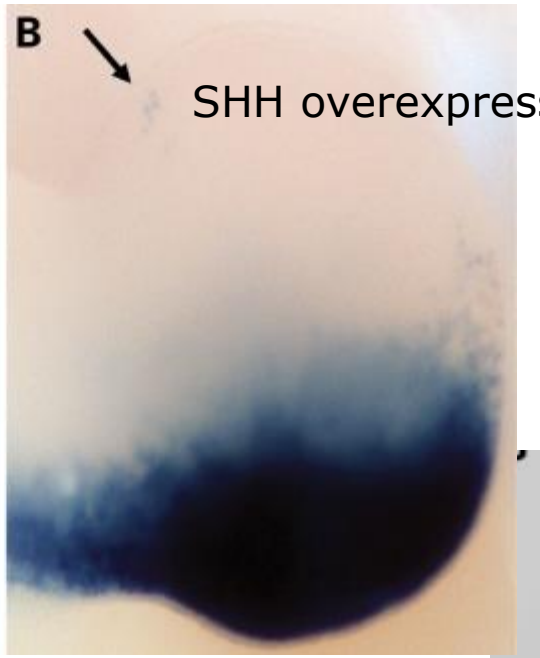
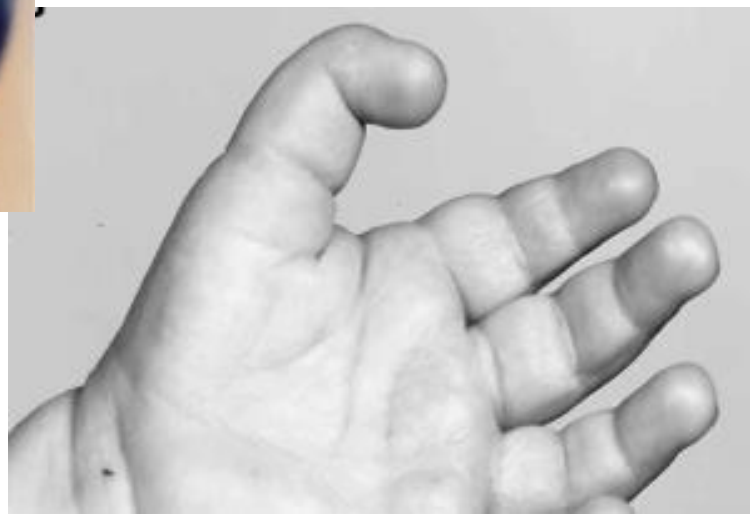
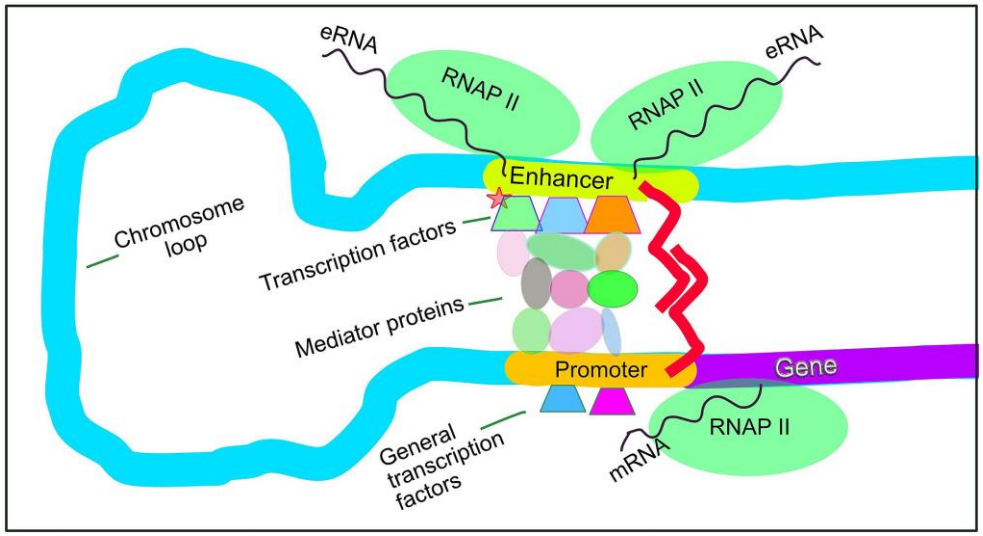
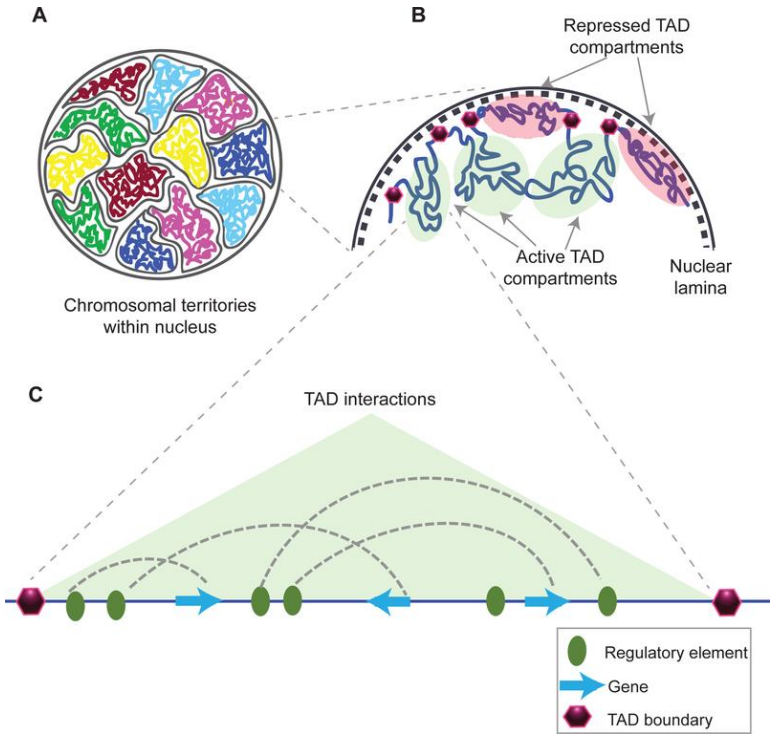


SHH overexpression

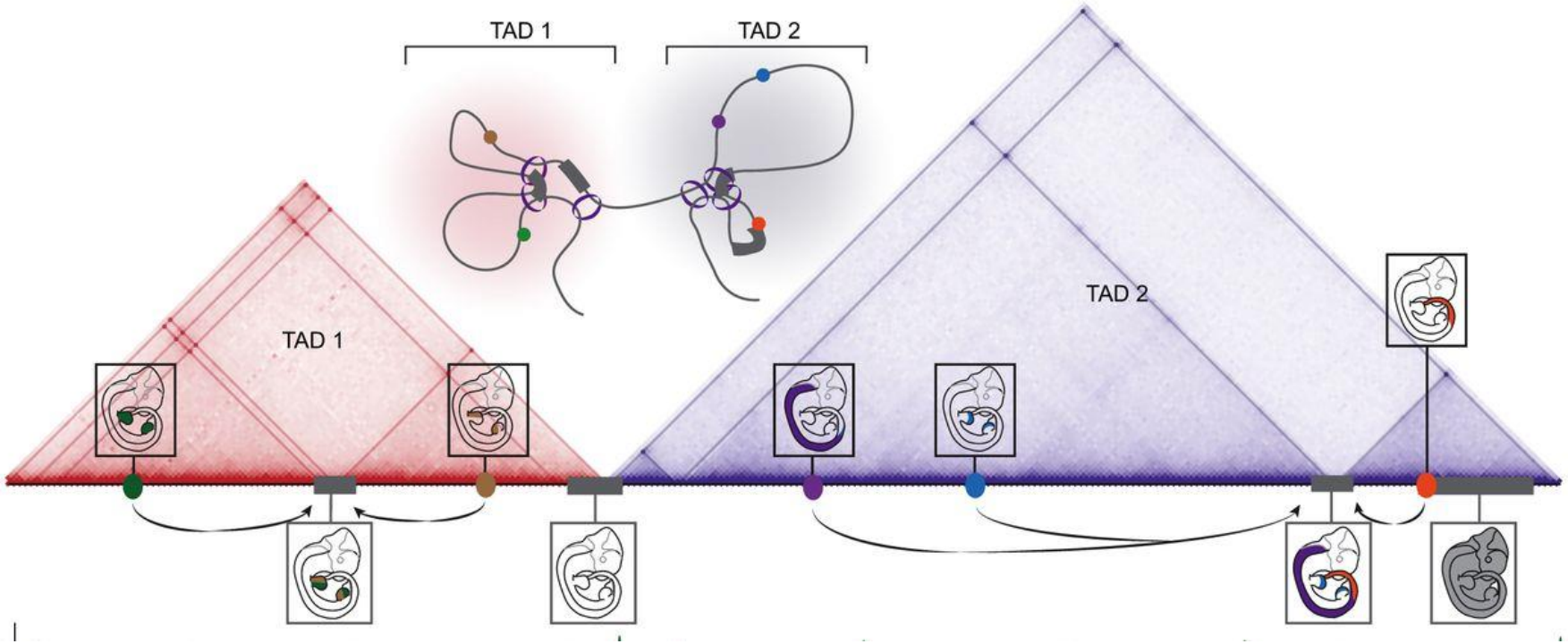


Hum Mol Genet. 2008; 17(16): 2417–2423.

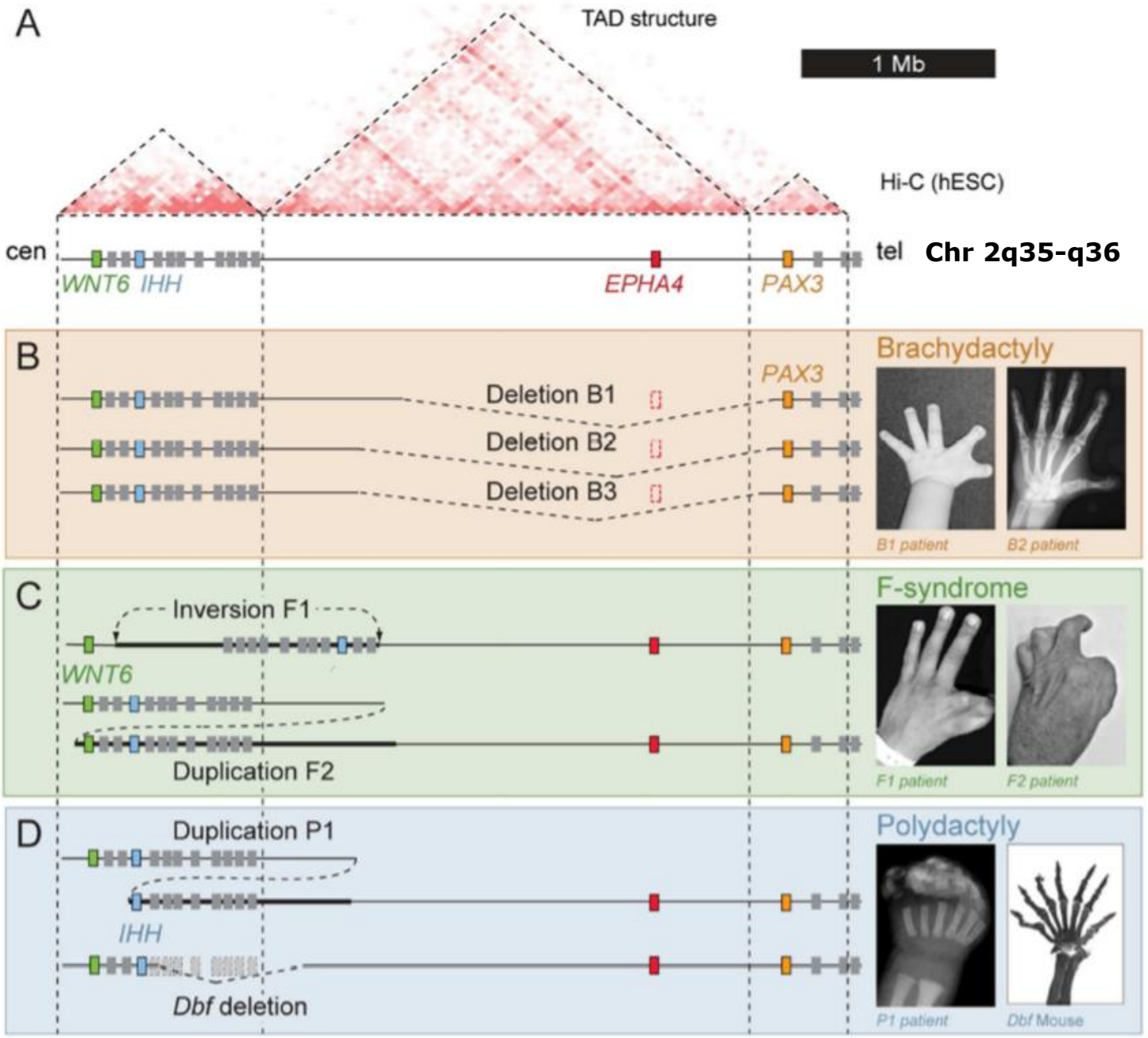




TADs
topologically associating domains

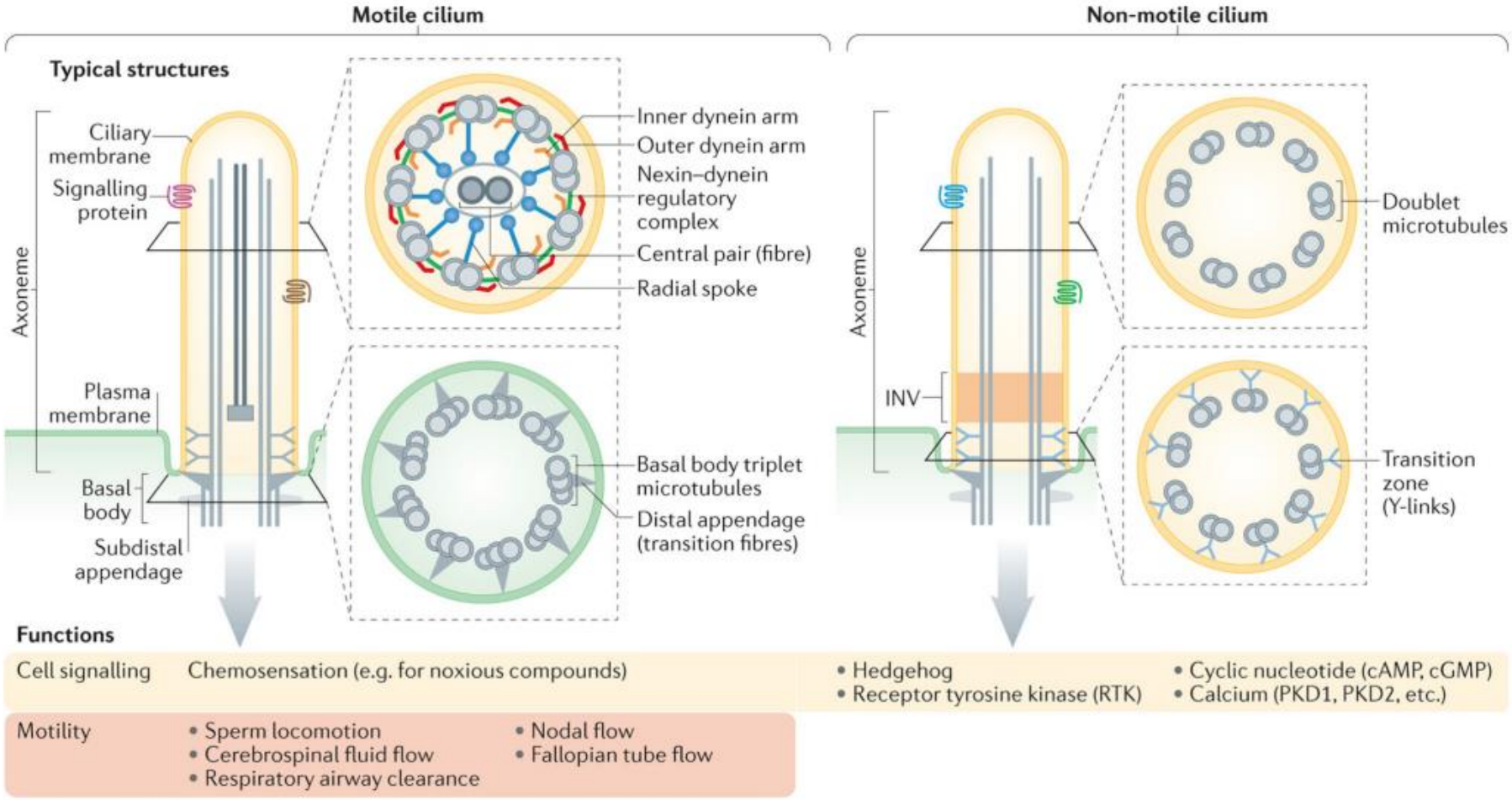


Guillaume Andrey, Stefan Mundlos
Development 2017 144: 3646-3658;
doi: 10.1242/dev.148304


A
TAD structure
1 Mb
Hi-C (hESC)
cen
tel
Chr 2q35-q36
WNT6 IHH
EPHA4
PAX3
B
Brachydactyly
PAX3
Deletion B1
Deletion B2
Deletion B3
B1 patient
B2 patient
C
F-syndrome
Inversion F1
WNT6
Duplication F2
F1 patient
F2 patient
D
Polydactyly
Duplication P1
IHH
Dbf deletion
P1 patient
Dbf Mouse

FAMILIES OF DEVELOPMENTAL SYNDROMES: A FEW EXAMPLES

CILIOPATHIES



Reiter et al, Nat Rev Mol Cell Biol, 2017

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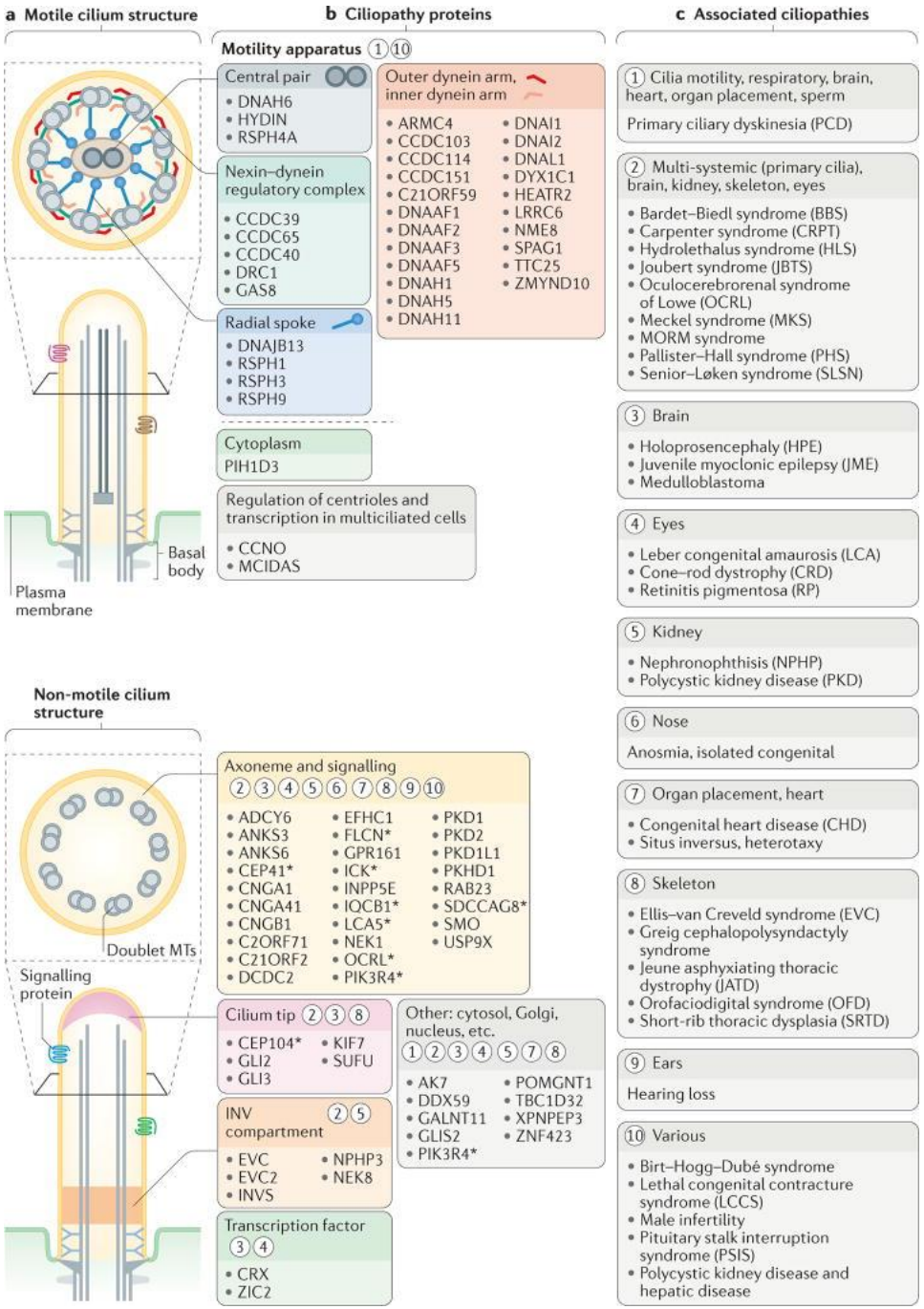
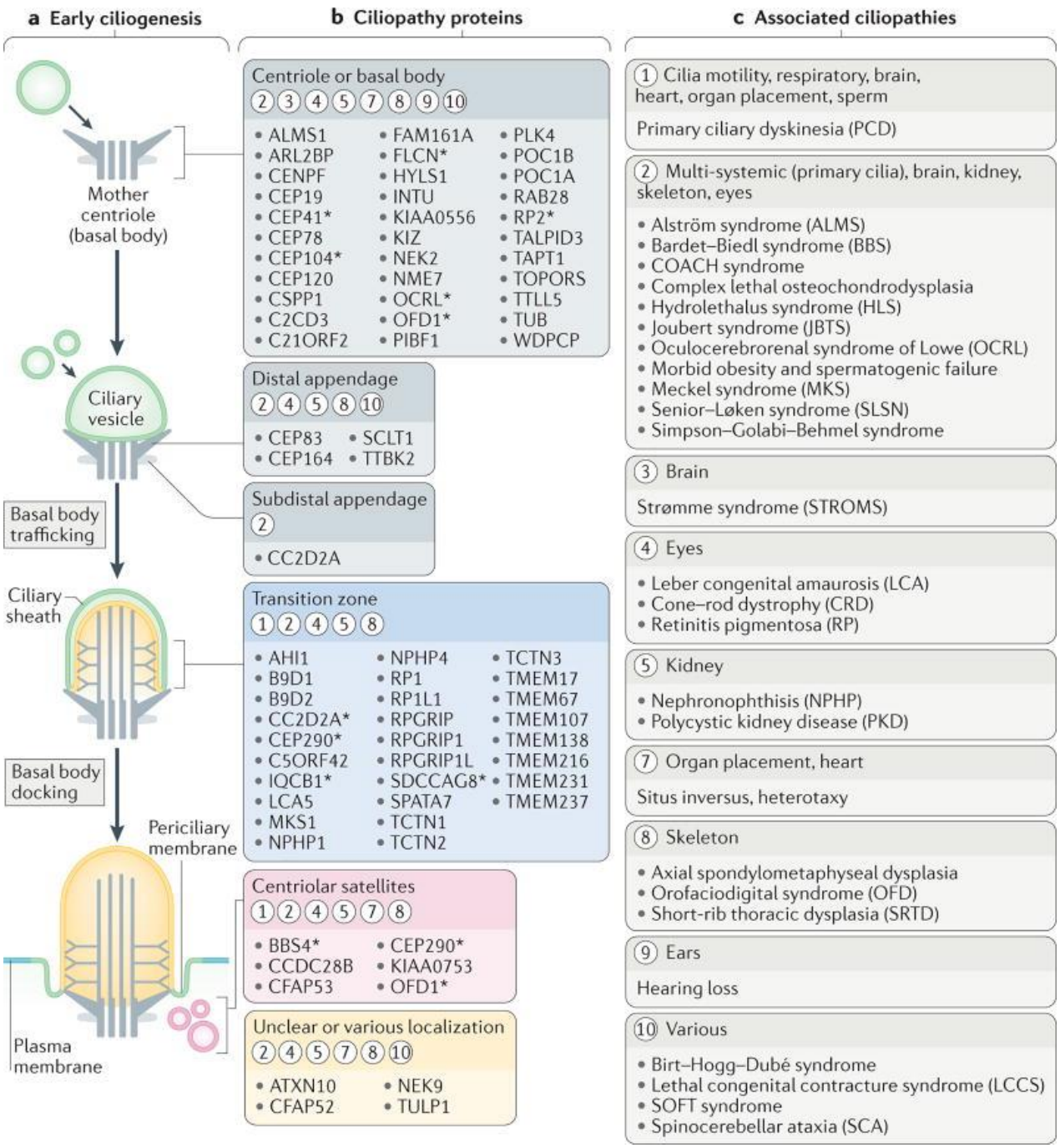
Structural defect



Reiter et al, Nat Rev Mol Cell Biol, 2017

IPG

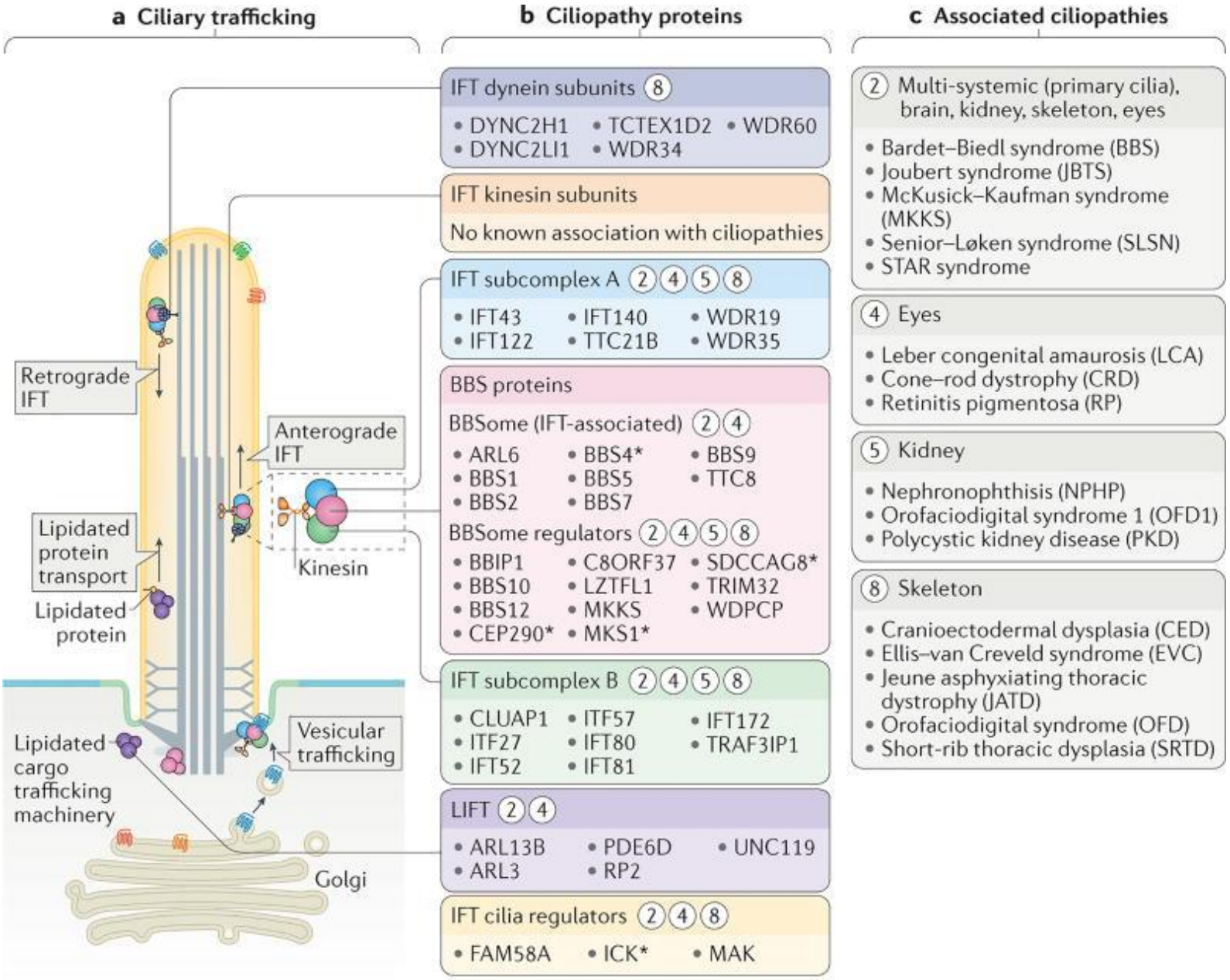
Early ciliogenesis



Reiter et al, Nat Rev Mol Cell Biol, 2017

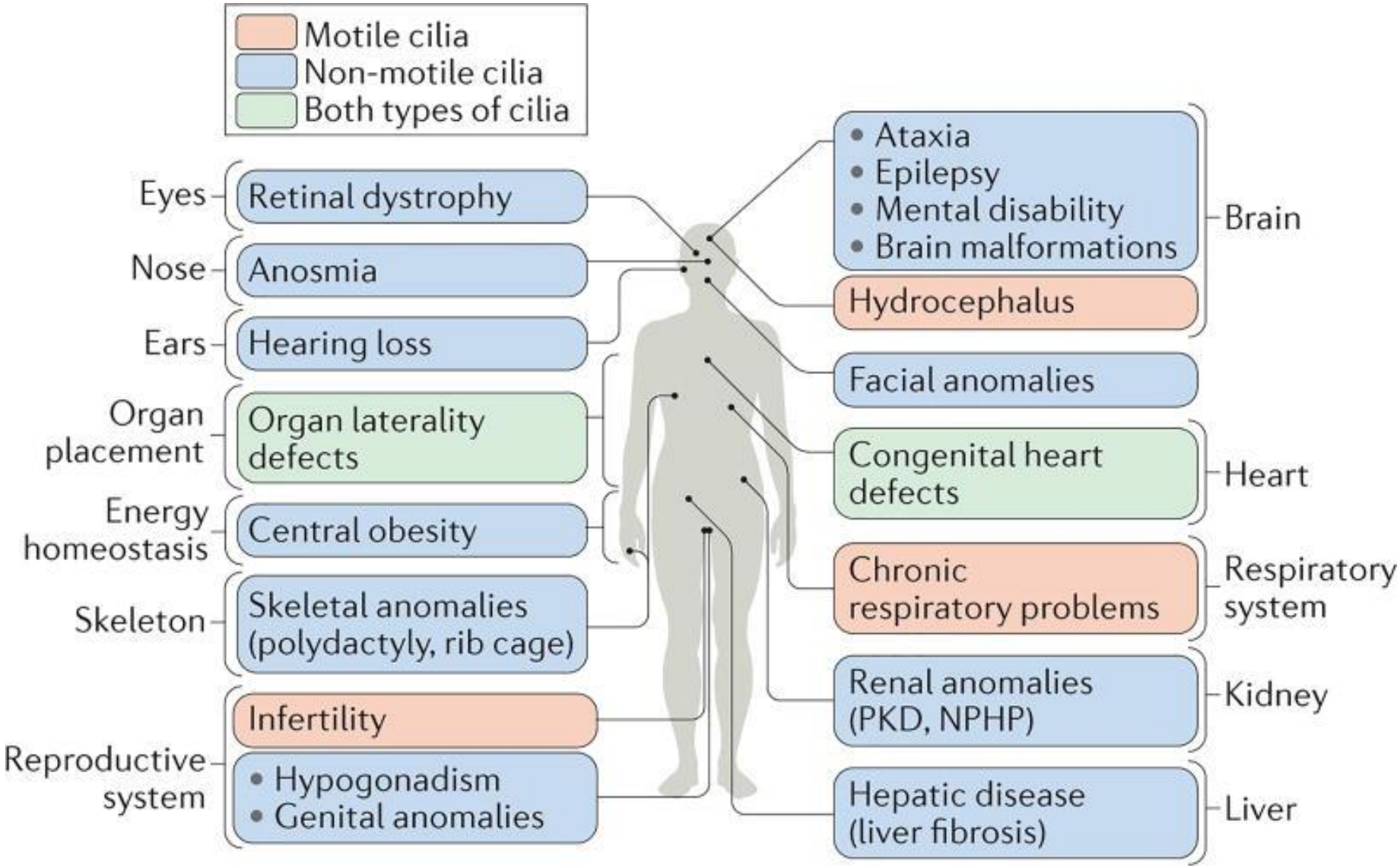
IPG

Ciliary trafficking



Reiter et al, Nat Rev Mol Cell Biol, 2017

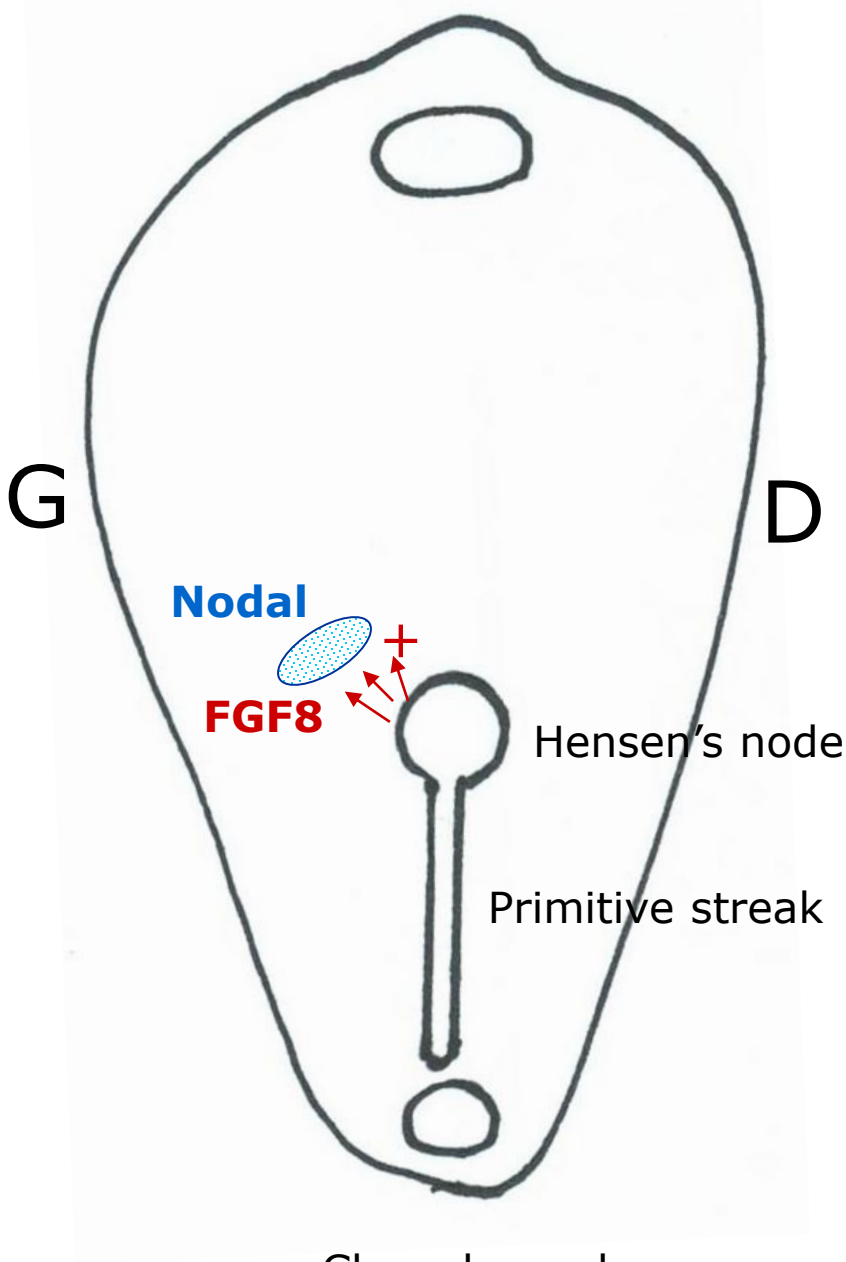
IPG

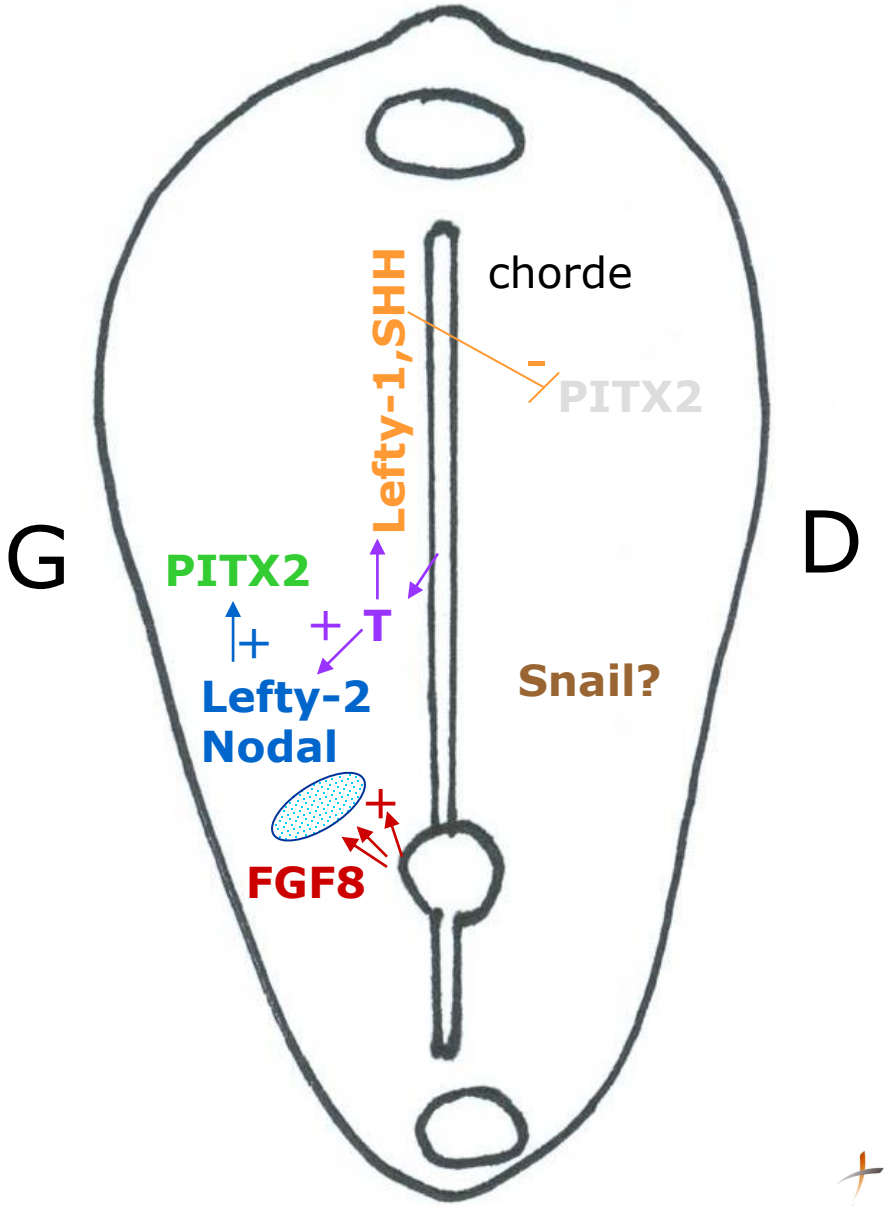


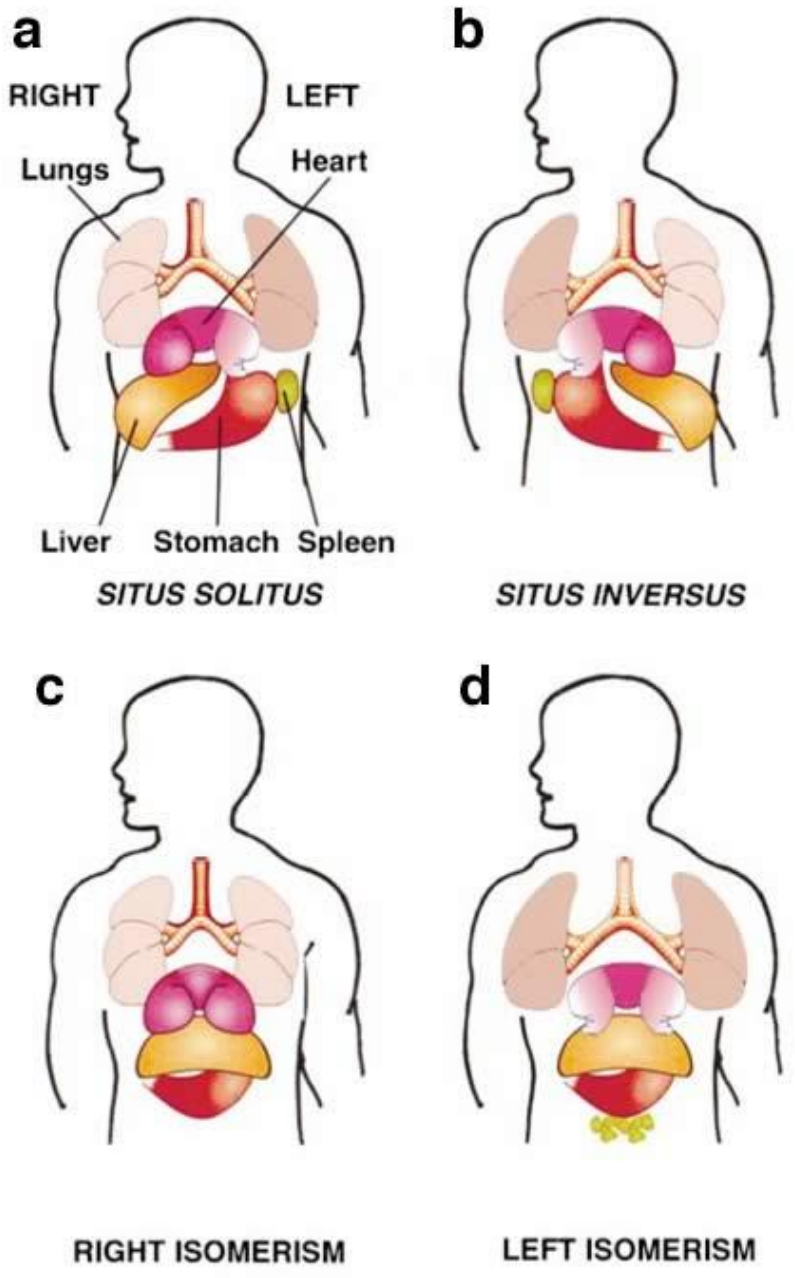
Reiter et al, Nat Rev Mol Cell Biol, 2017

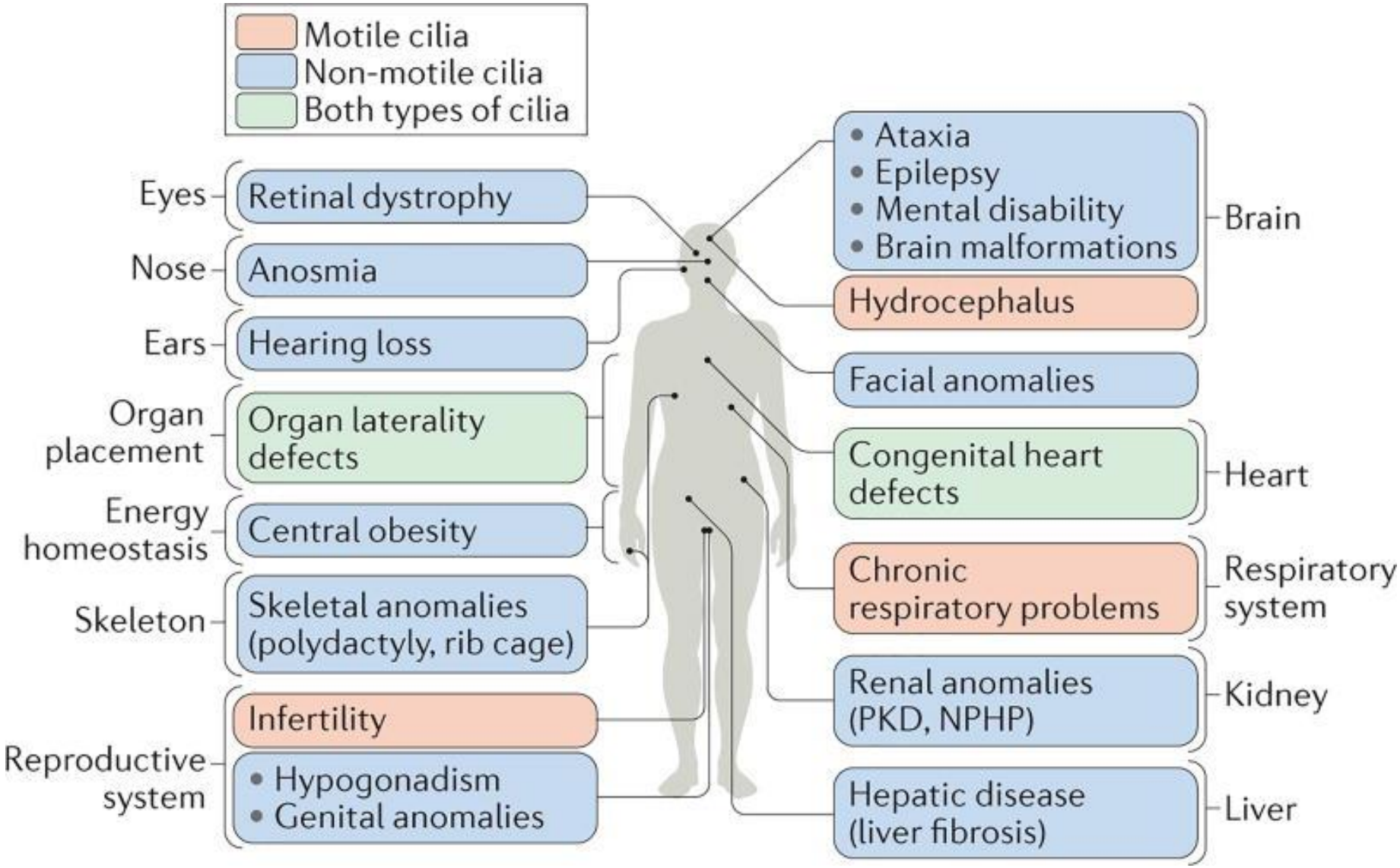
IPG

3rd week of development: gastrulation



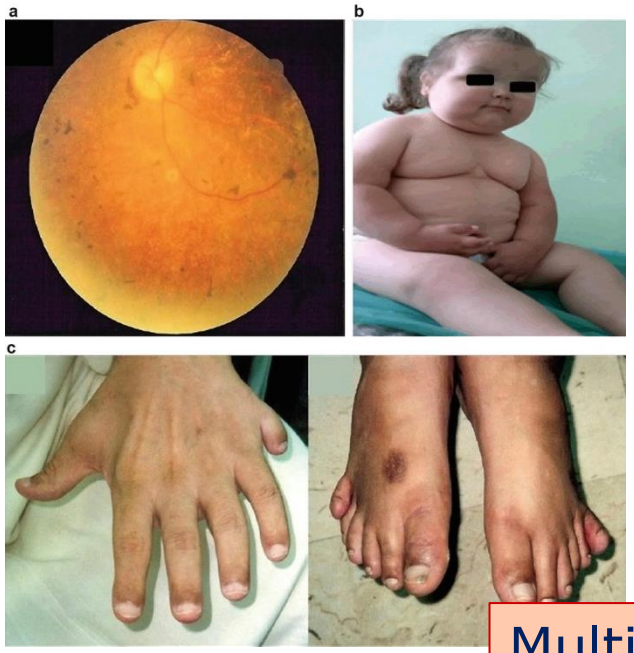



a
RIGHT
LEFT
Lungs
Heart
Liver
Stomach
Spleen
SITUS SOLITUS
b
SITUS INVERSUS
c
RIGHT ISOMERISM
d
LEFT ISOMERISM

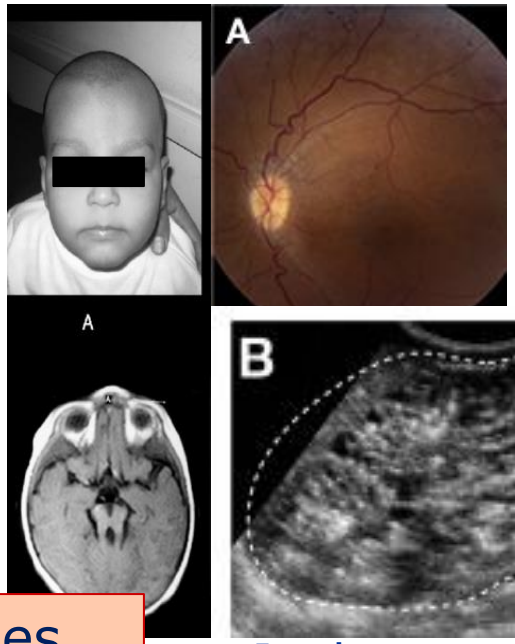


Reiter et al, Nat Rev Mol Cell Biol, 2017

IPG

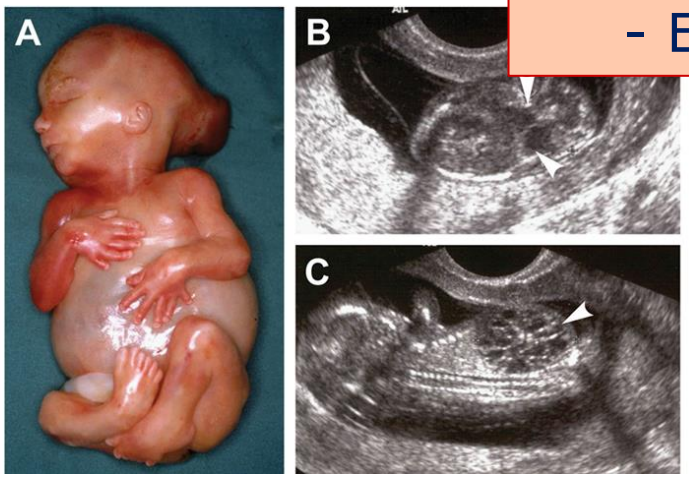


Bardet Biedl

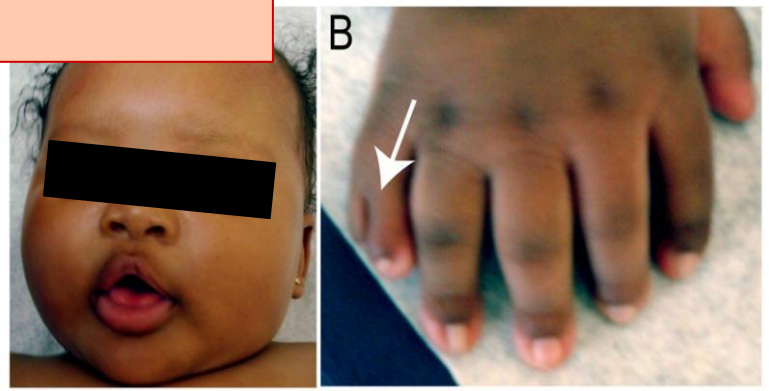


Joubert

Multisystemic diseases
- Brain
- Kidney
- Skeleton
- Eyes



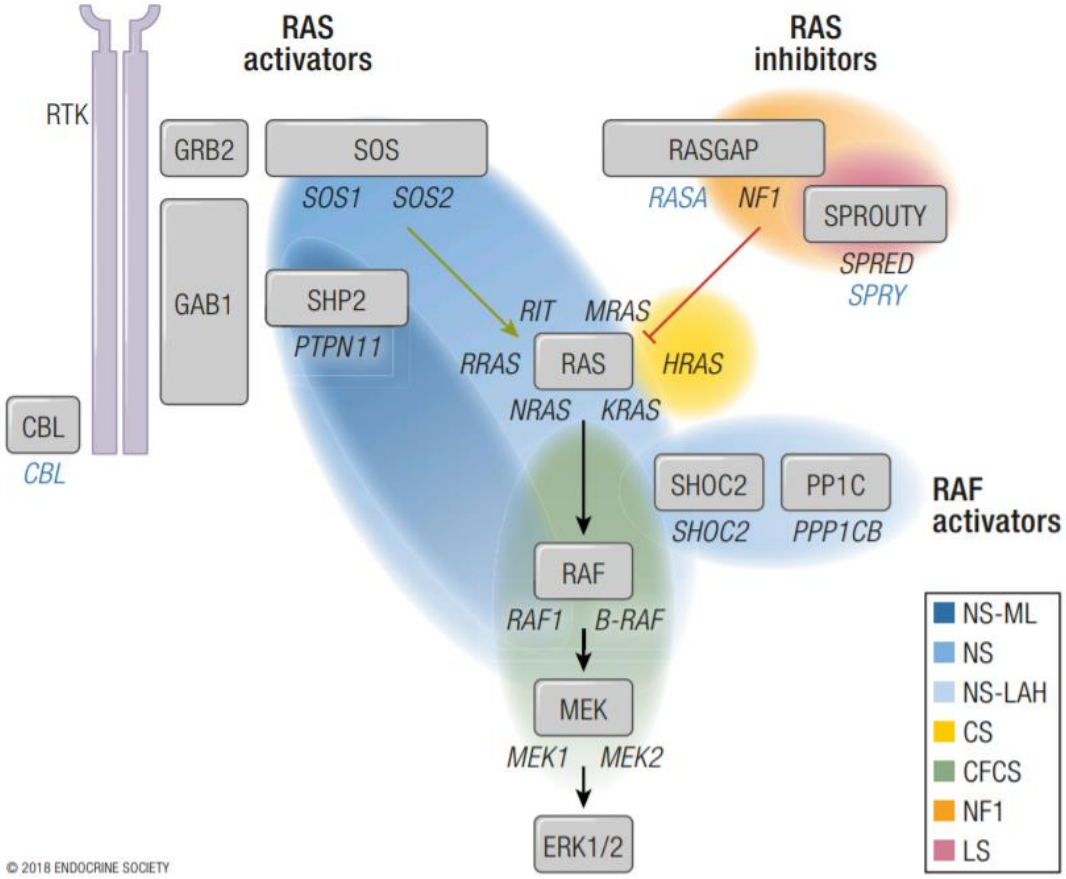
Meckel Gruber



Orofaciodigital type 1

RASopathies

RAS/MAPK pathway *(Tajan et al, Endocrine Reviews 2018)*



<u>*regulation of the cell cycle, differentiation, growth, and cell senescence*</u>
*(*in neural crests, peripheral nervous system, nascent blood vessels and the early forming structures of the ear, eye and heart)

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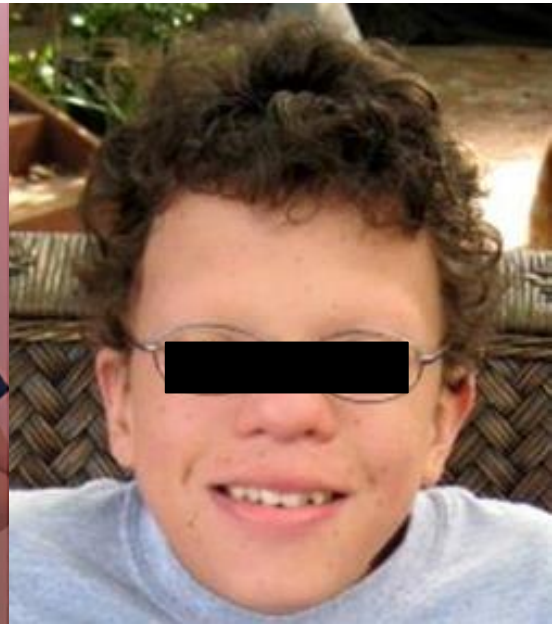
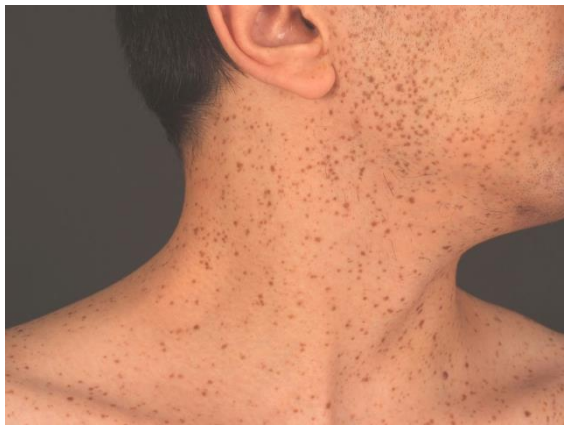
Noonan

Noonan with loose anagen hair

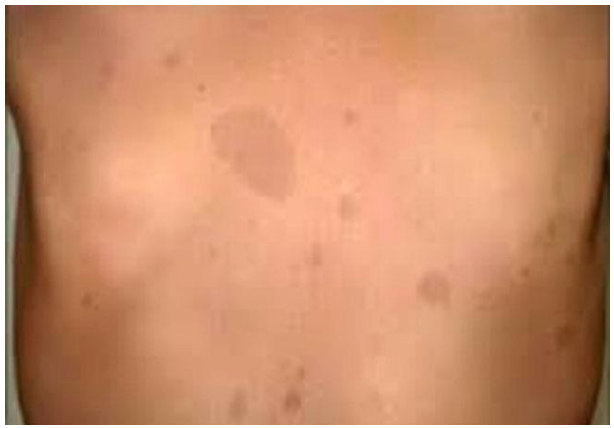
Costello



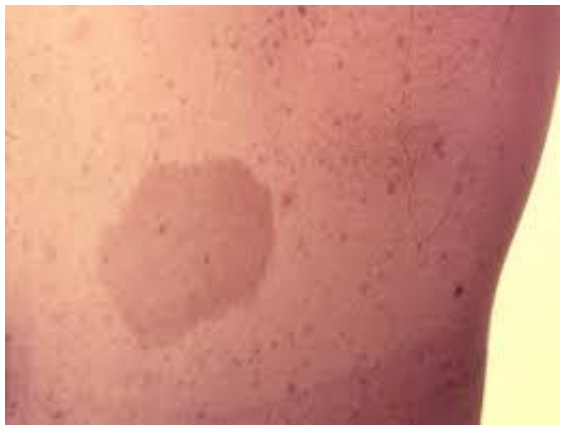
Cardio-facio-cutaneous



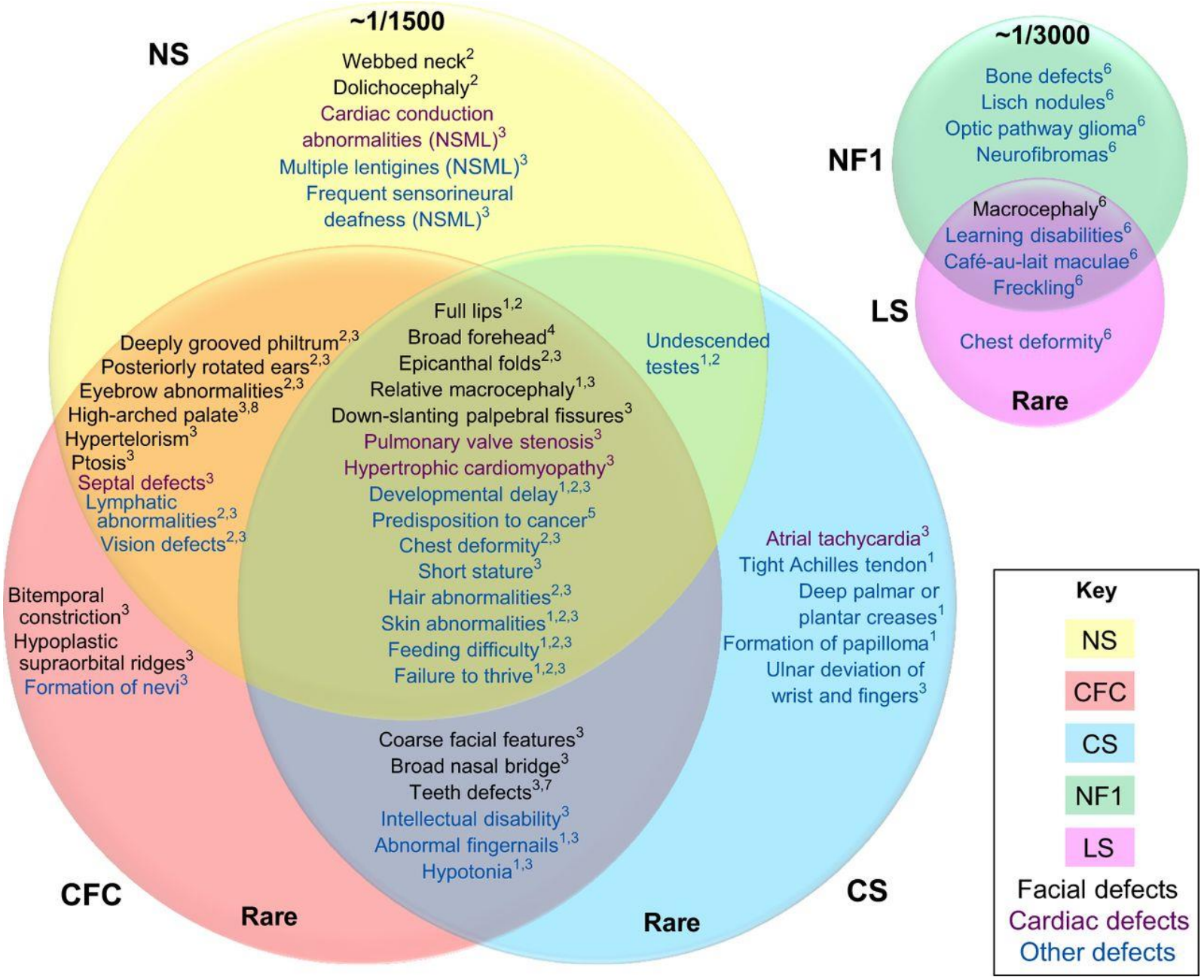
Noonan with multiple lentigines



Neurofibromatosis type 1



Legius syndrome



Jingal et al, Disease models and mechanisms, 2015

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The RASopathies

Syndrome	Gene	Chromosome location	Protein function	Clinical phenotype
Autosomal dominant intellectual disability,type 5	*SYNGAP1*	6p21.3	RasGAP	Typically nondysmorphic to mild dysmorphic craniofacial features, moderate to severe intellectual disability, global developmental delay with behavioral issues, autism spectrum disorder, ophthalmologic findings, hypotonia, seizures.
Capillary malformation-AV malformation	*RASA1*	5q14.3	RasGAP	Nondysmorphic craniofacial features, multifocal capillary malformations which may be associated with arteriovenous malformations and fistulae.
Cardio-facio-cutaneous	*BRAF*	7q34	Kinase	Dysmorphic craniofacial features, congenital heart defects, failure to thrive with short stature, ophthalmologic abnormalities, multiple skin manifestations including progressive formation of nevi; variable neurocognitive delay; hypotonia, may be predisposed to cancer
	MAP2K1	15q22.31	Kinase	
	MAP2K2	19p13.3	Kinase	
	KRAS	12p12.1	GTPase	
Costello	*HRAS*	11p15.5	GTPase	Dysmorphic craniofacial features, congenital heart defects, failure to thrive with short stature, ophthalmologic abnormalities, multiple skin manifestations including papilloma; variable neurocognitive delay; hypotonia; predisposition to cancer.
Legius	*SPRED1*	15q14	Negative Regulator	Café-au-lait maculae, intertriginous freckling, normal to mild neurocognitive impairment, macrocephaly; unclear predisposition to cancer.
Noonan	*PTPN11*	12q24.1	Phosphatase	Craniofacial dysmorphic features, congenital heart defects, short stature, undescended testicles, ophthalmologic abnormalities, bleeding disorders, normal to mild neurocognitive delay; predisposition to cancer.
	SOS1	2p22.1	RasGEF	
	RAF1	3p25.1	Kinase	
	KRAS	12p12.1	GTPase	
	NRAS	1p13.2	GTPase	
	SHOC2	10q25.2	Scaffolding	
	CBL	11q23.3	Ubiquitin ligase	
	RRAS	19q13.33	GTPase	
	RIT1	1q22	GTPase	
	RASA2	3q23	RasGAP	
	SOS2	14q21.3	RasGEF	
	MAP3K8	10p11.23	Kinase	
	SPRY1	4q28.1	Inhibitor	
	MYST4	10q22.2	Acetyltransferase	
	LZTR1	22q11.21	Adaptor	
	A2ML1	12p13.31	Protease inhibitor	
Noonan with multiple lentigines	*PTPN11*	12q24.1	Phosphatase	Same as Noonan syndrome but may develop multiple skin lentigines as individuals gets older; unclear predisposition to cancer.
	RAF1	3p25.1	Kinase	
Neurofibromatosis 1	*NF1*	17q11.2	RasGAP	Café-au-lait maculae, intertriginous freckling, neurofibromas and plexiform neurofibromas, iris Lisch nodules, osseous dysplasia, optic pathway glioma, normal to mild neurocognitive delay; predisposition to cancer

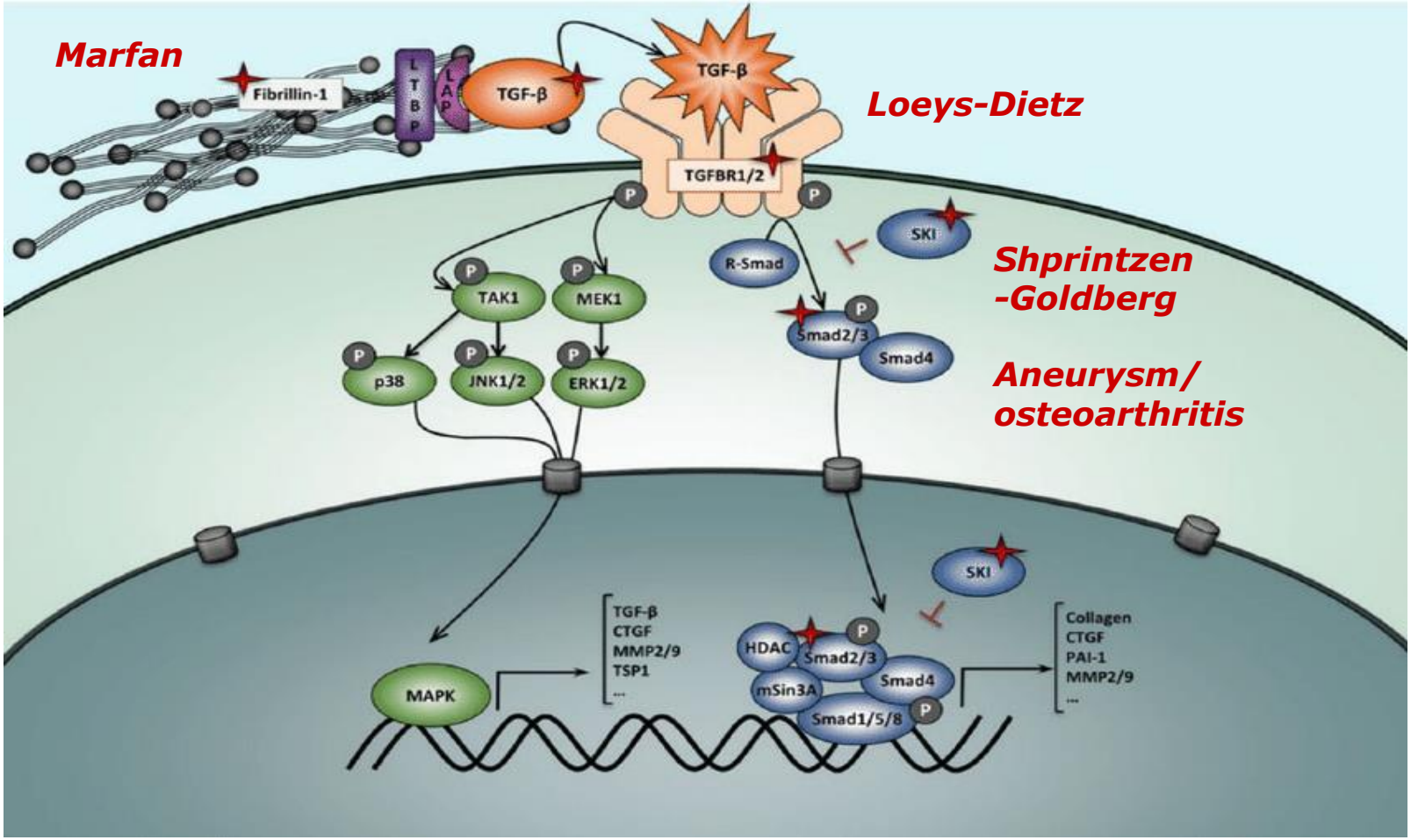
- Dysmorphic features
- Cognitive impairment
- Failure to thrive
- Predisposition to cancer
- Congenital heart defect
- Skin anomalies

Tidyman et al, Hum Mol Genet, 2016

IPG

TGF-β signaling related diseases

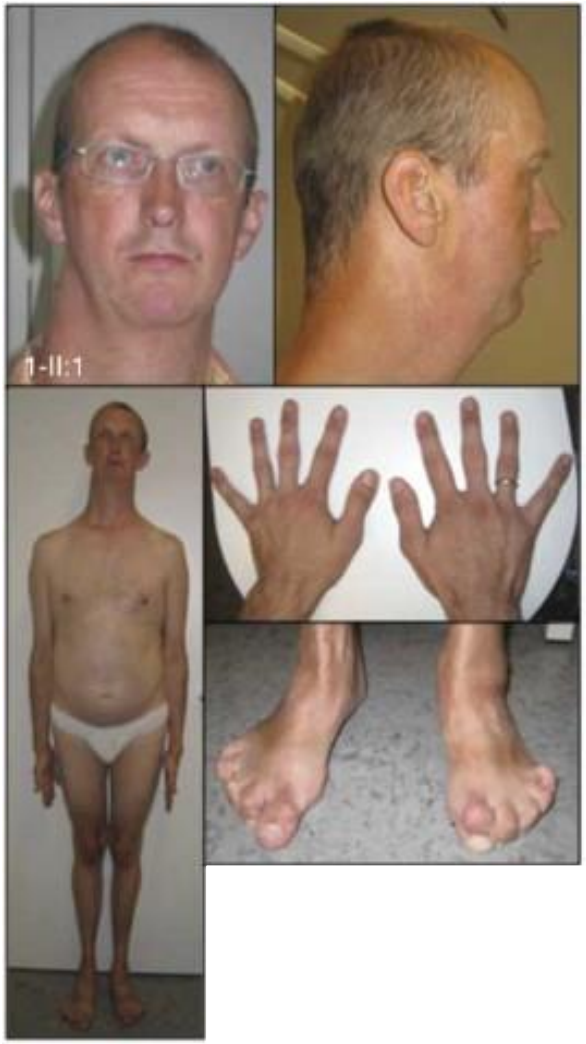
TGF-β signaling pathway



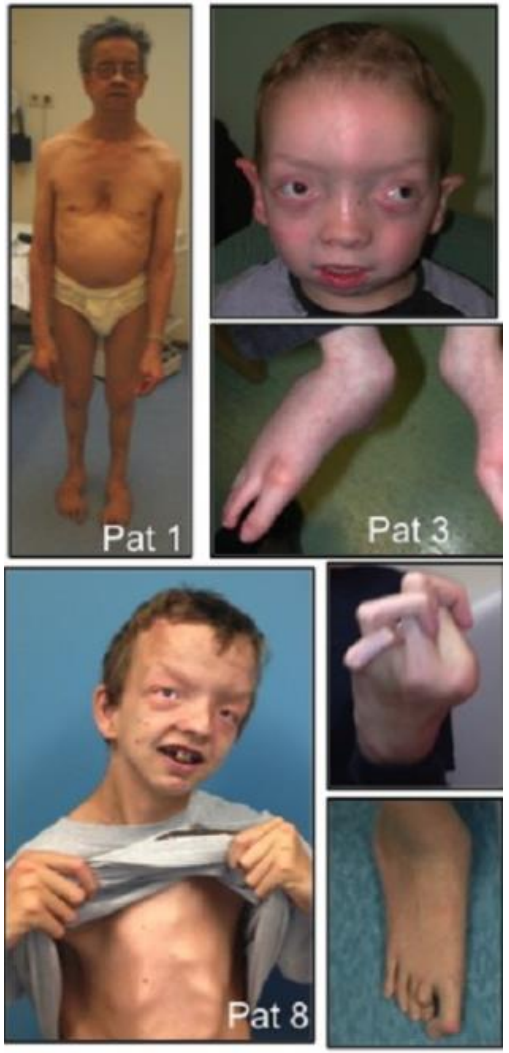
skeletal, ocular, pulmonary, and cardiovascular development

IPG

Marfan



Loeys Dietz

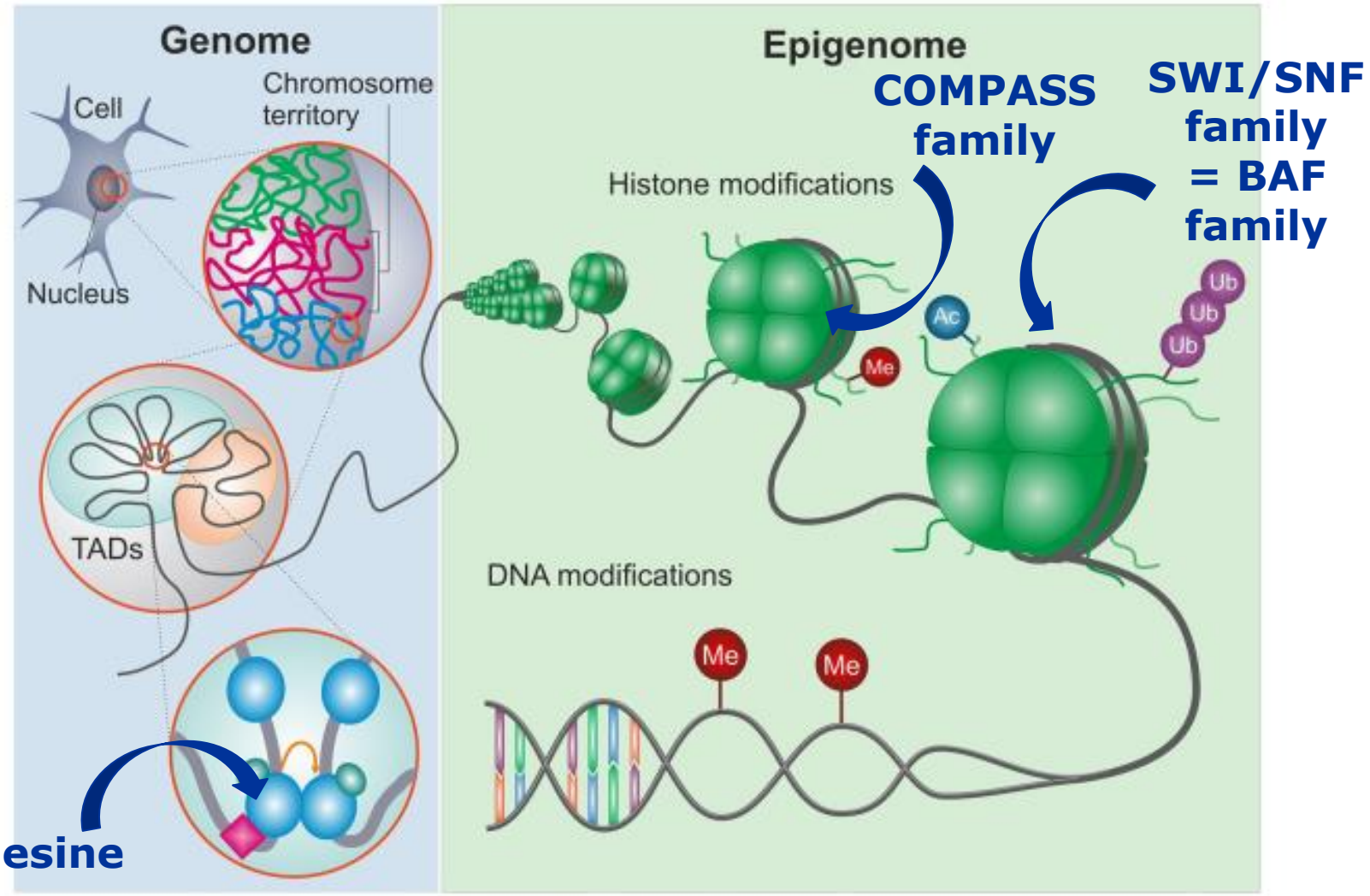


Shprintzen-Goldberg

- Syndromic thoracic aortic aneurysm (TAA)

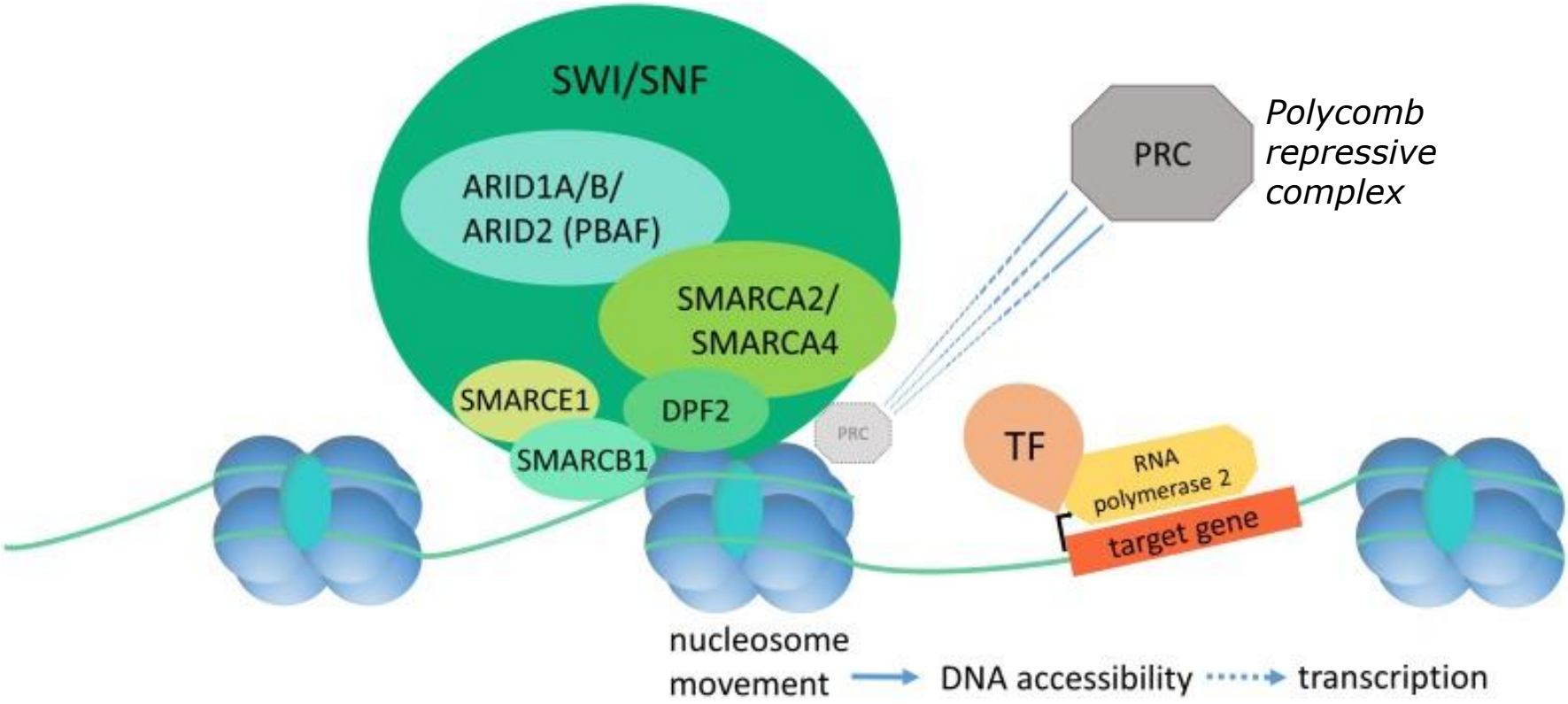
IPG

CHROMATINOPATHIES



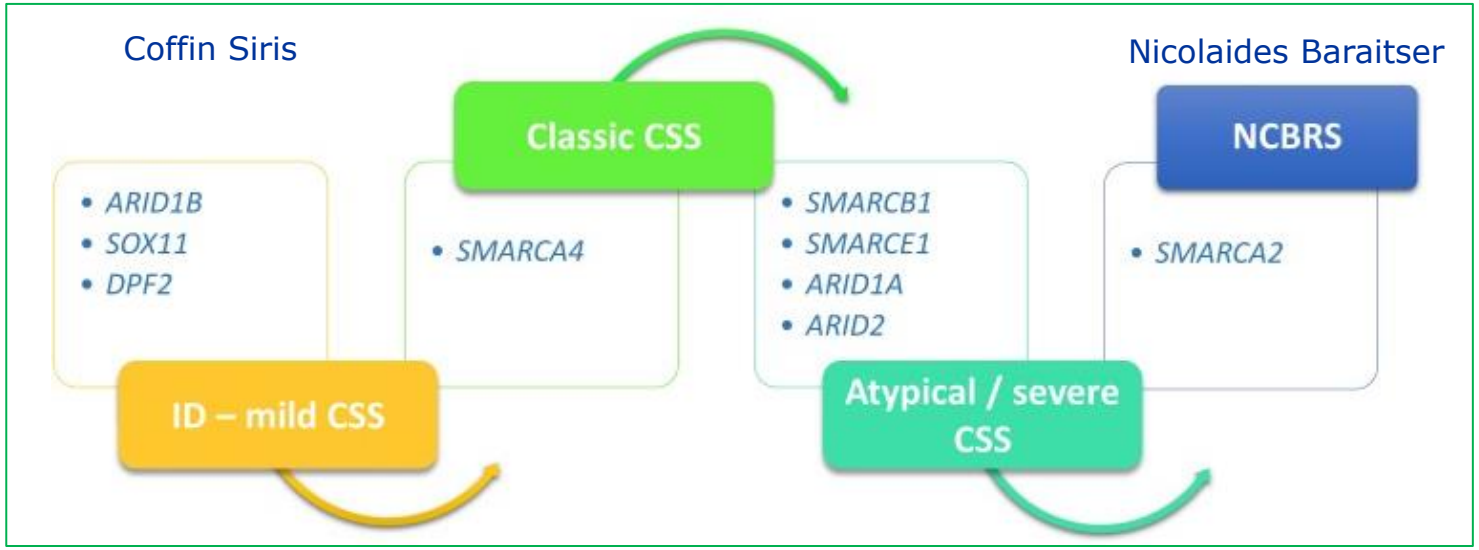
Mossink et al, Cellular and molecular life sciences, 2020

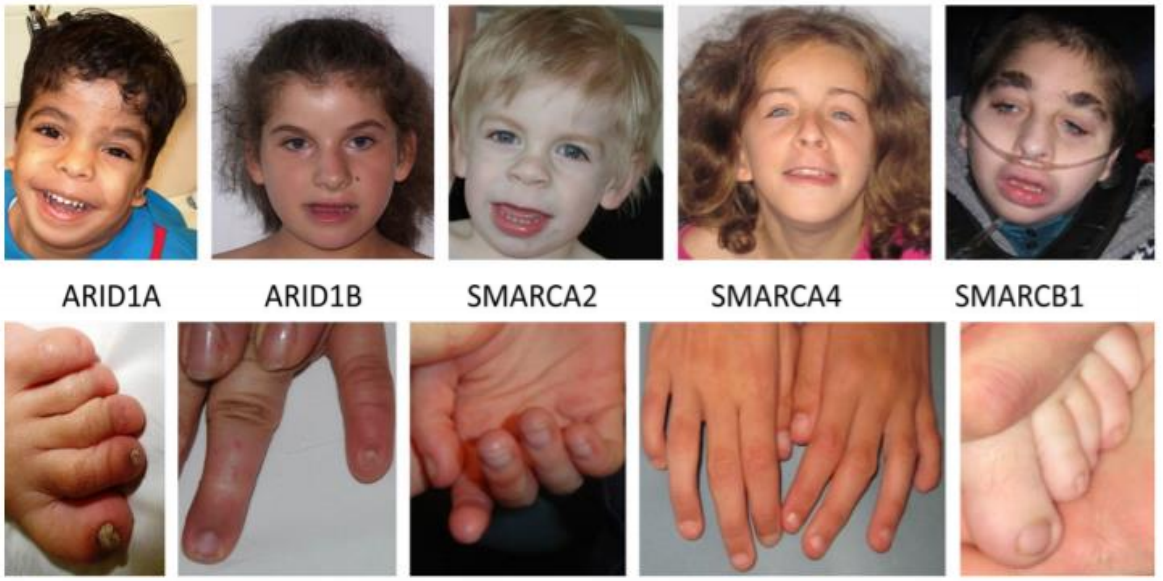
SWI/SNF (switching/sucrose non-fermenting) chromatine remodellers = BAF complex



Bögershausen et al, Frontiers in molecular neurosciences, 2018

"SWI/SNF-related intellectual disability disorders" (SSRIDDs)





Santen et al, Hum Mutation, 2013

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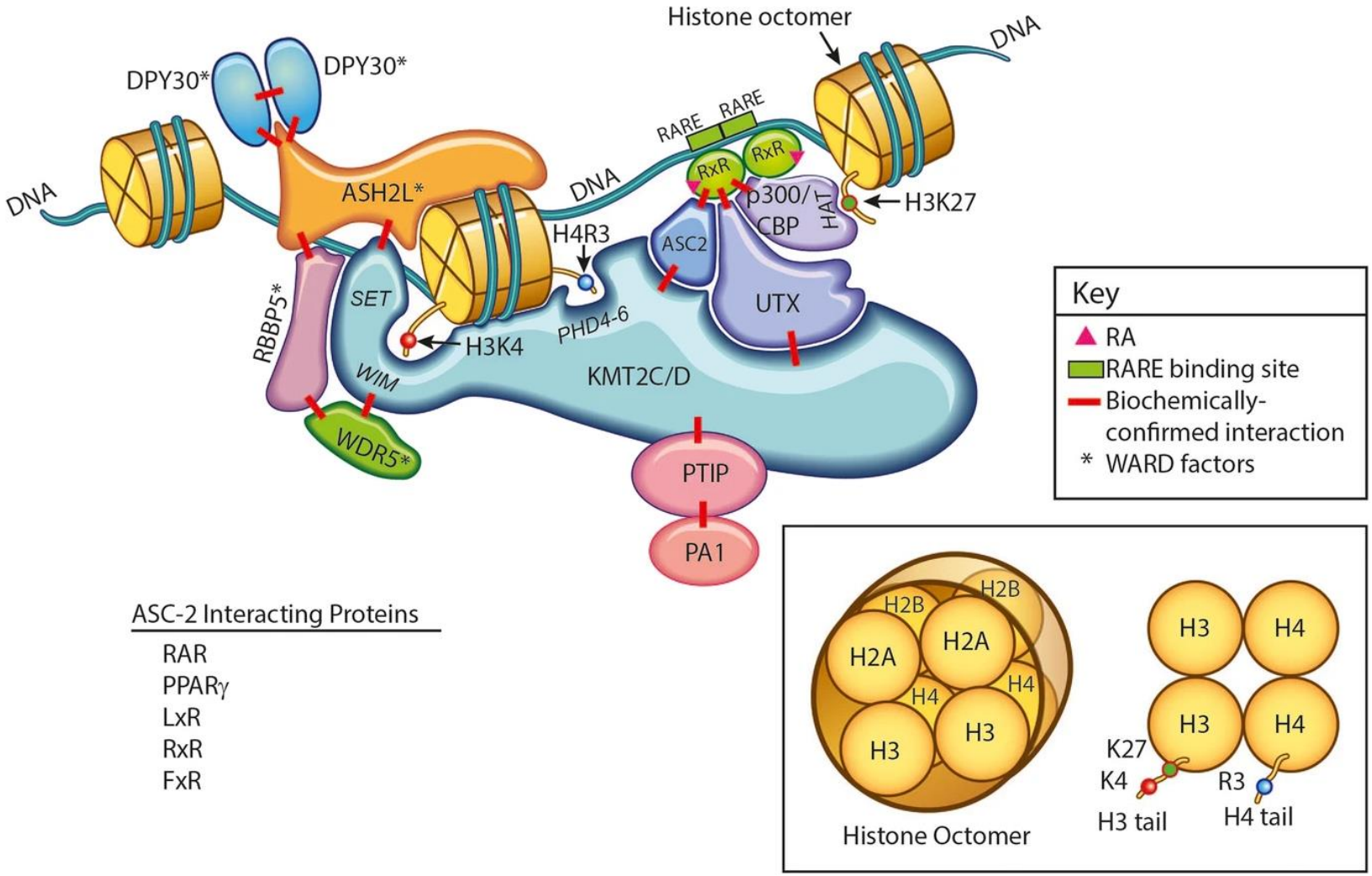
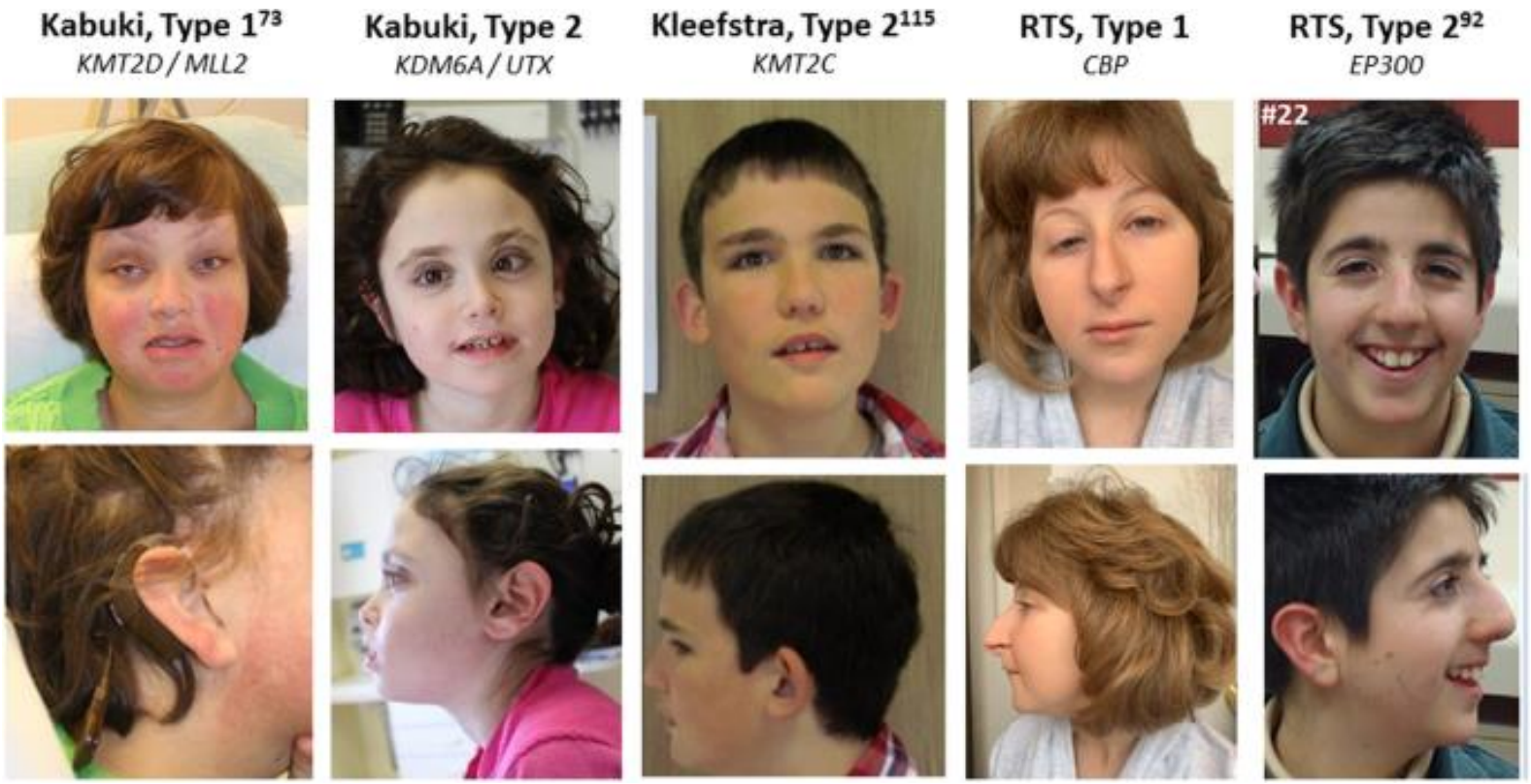
COMPASS complex (histone-lysine methyltransferases)

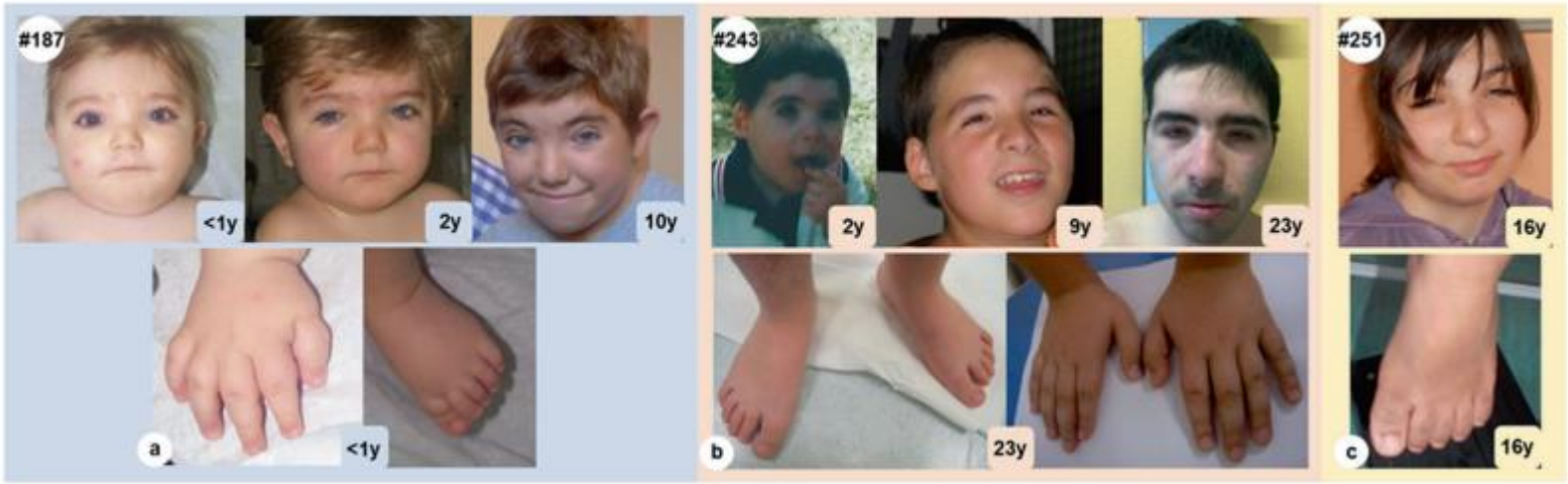


Lavery et al, Clinical epigenetics 2020



Lavery et al, Clinical epigenetics 2020

Wiedemann-Steiner, KMT2A/MLL1



Di Fede et al, Eur J Hum Genet, 2021

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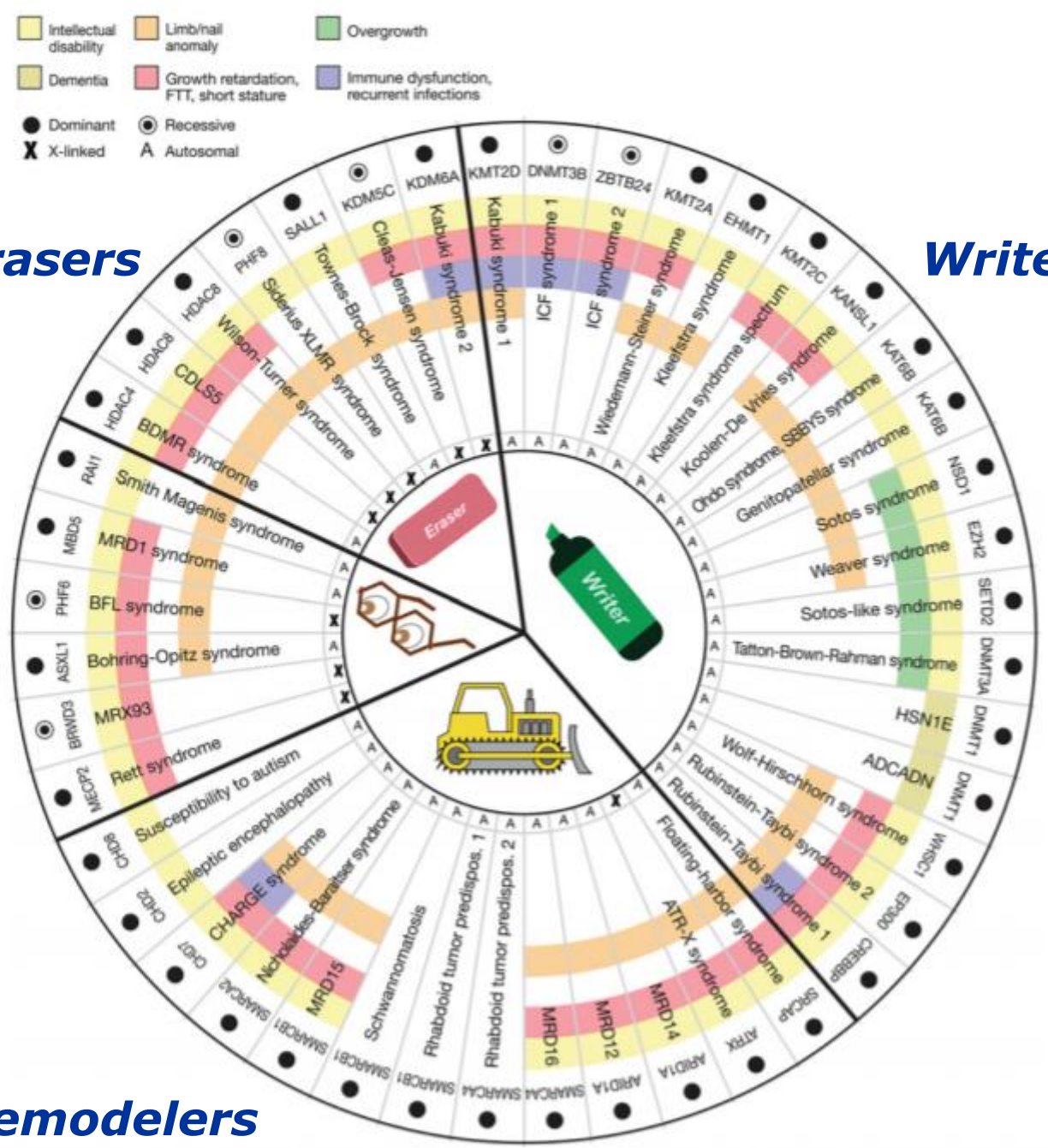

Bjornsson et al, Genome Research, 2015

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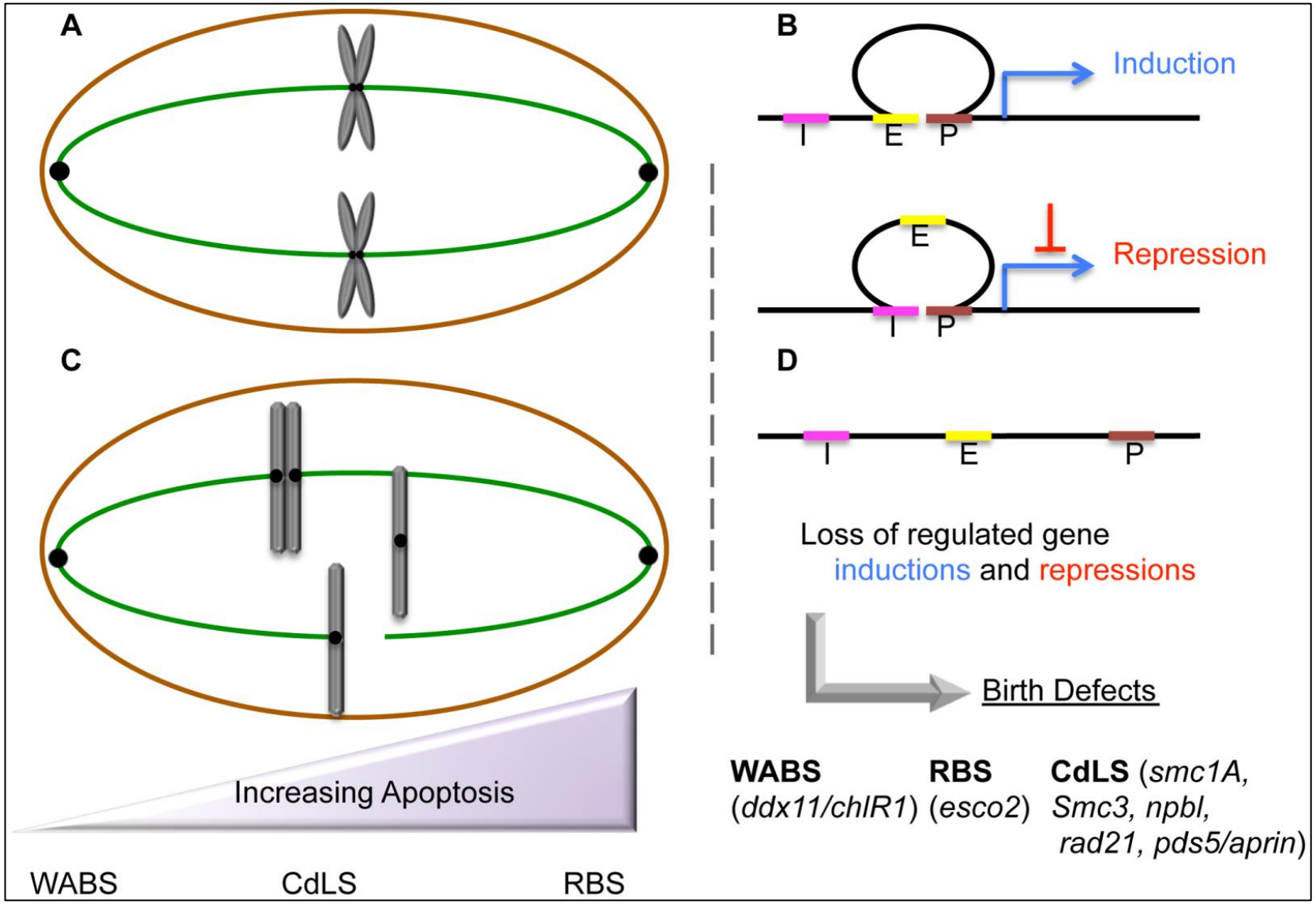
Cohesinopathies



Skibbens et al, Plos Genetics, 2013

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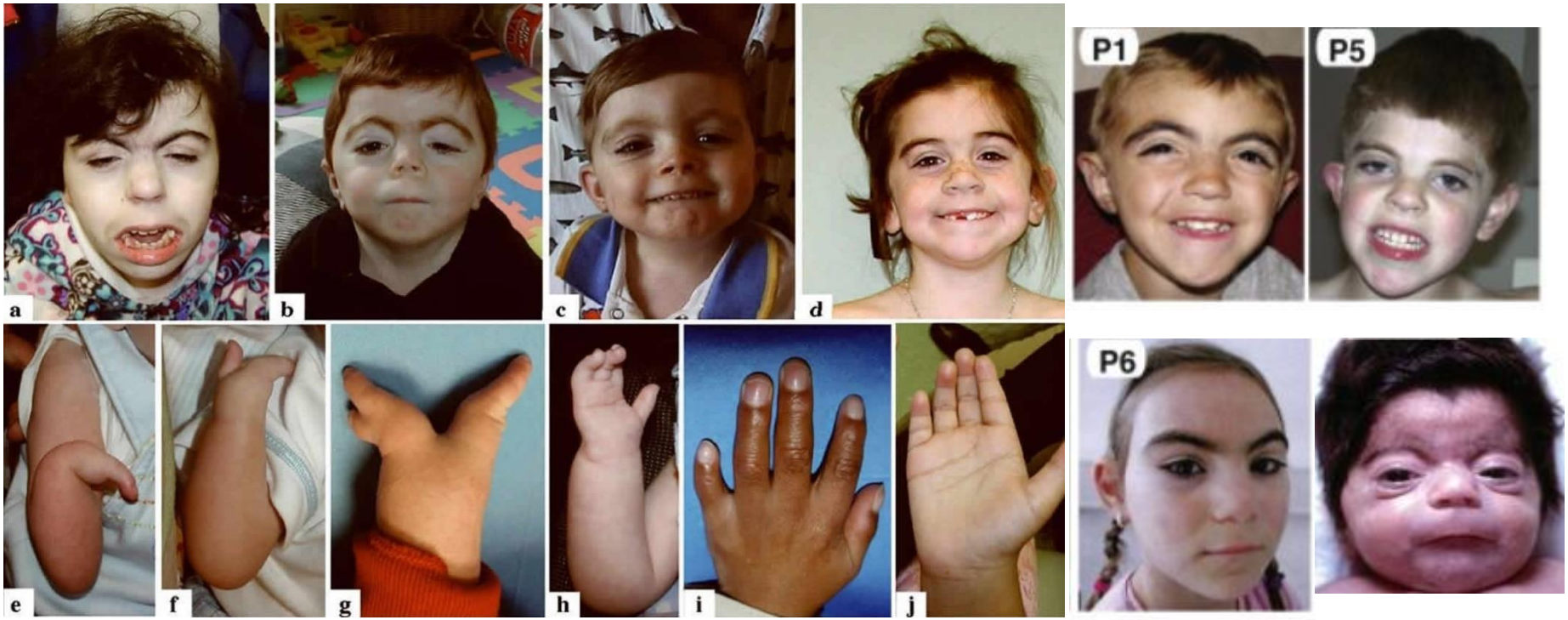
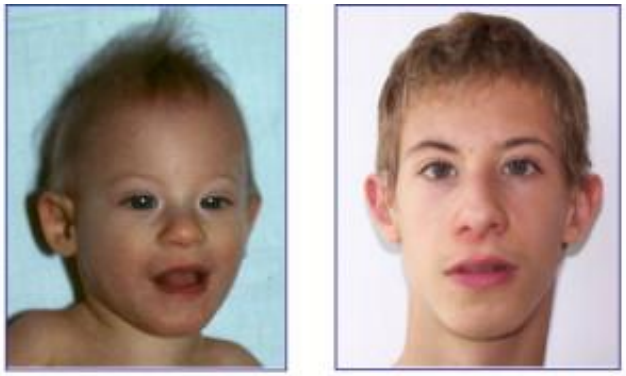
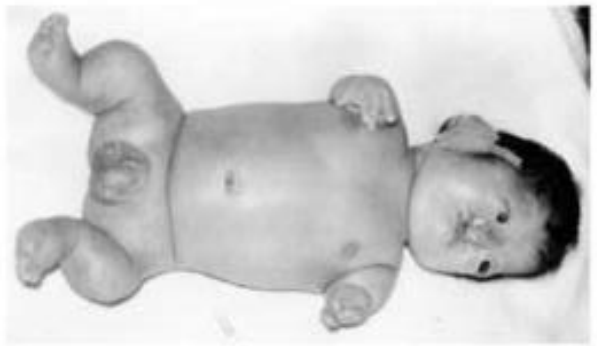
Cohesinopathies



Cornelia de Lange *(NIPBL, SMC1A, RAD21, HDAC8)*



Warsaw breakage syndrome *(DDX11)*



Roberts syndrome *(ESCO2)*

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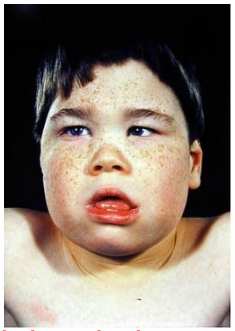
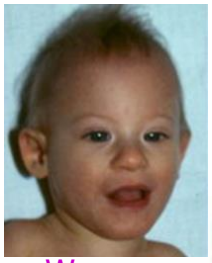
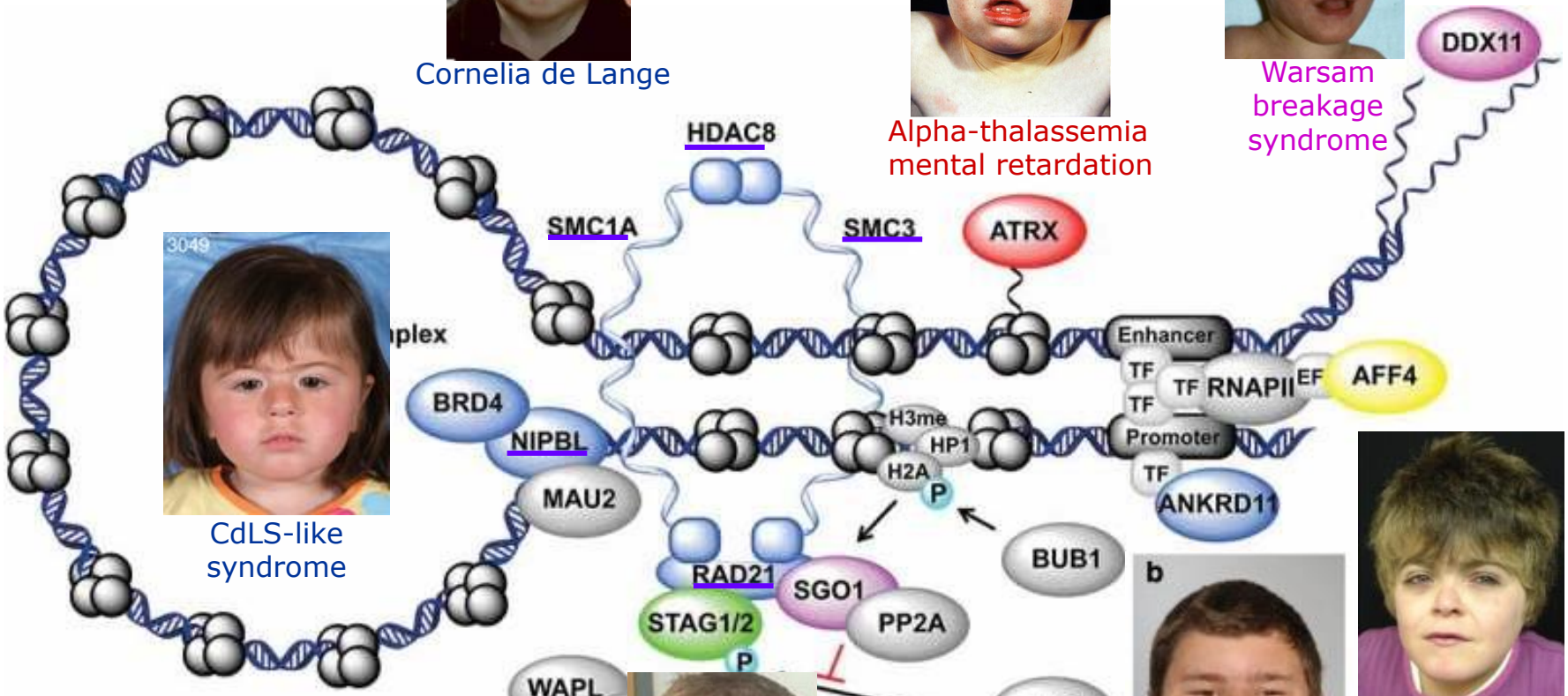
Cornelia de Lange



Alpha-thalassemia mental retardation



Warsam breakage syndrome

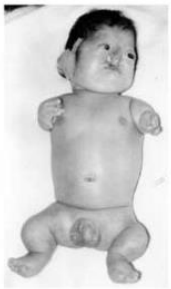


CdLS-like syndrome

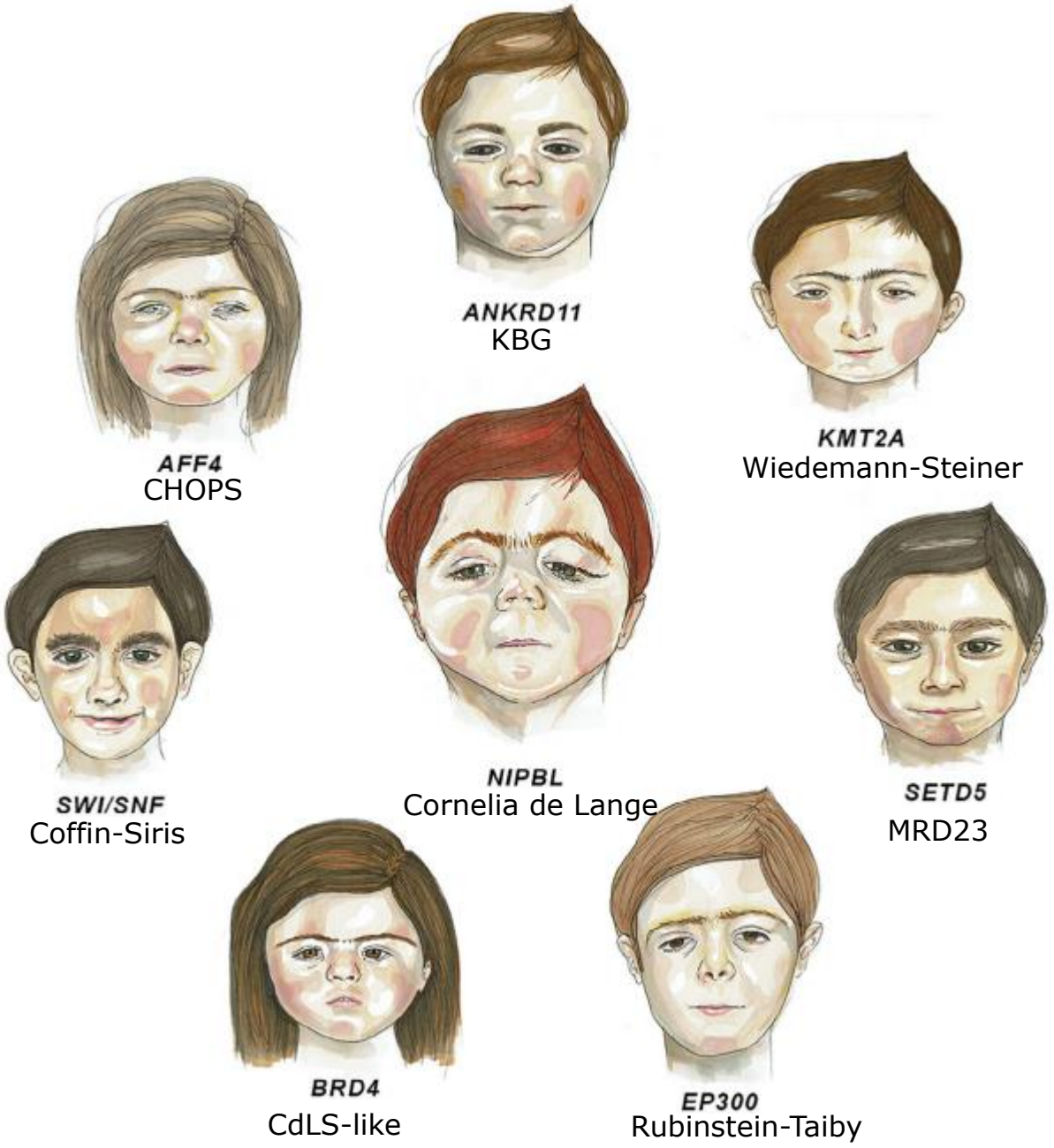
CHOPS syndrome

KBG syndrome

MRD47



Roberts syndrome



Avagliano et al, Clinical Genetics, 2019

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TABLE 3 Patients clinical features accordingly to the first international *consensus* statement on CdLS

	Clinical features	*AFF4*	*ANKRD11*	*BRD4*	*EP300*	*KMT2A*	*SETD5*	*SWI/SNF* complex gene
Cardinal features	Synophrys and/or thick eyebrows	+	+	+	+	+	+	+
	Short nose concave nasal ridge and/or upturned nasal tip	+	–	+	–	+	+/–	+
	Long and/or smooth philtrum	+	+	+		+	+	+
	Thin upper lip vermilion and/or downturned corners of mouth		+	+	–	+	+/–	+
	Hand oligodactyly and/or adactyly	–	–	–	–	–	–	–
	Congenital diaphragmatic hernia							
Suggestive features	Global developmental delay and/or intellectual disability	+	+	+	+	+	+	+
	Prenatal growth retardation		+		+	+		+
	Postnatal growth retardation	+	+	+	+	+	+	+
	Microcephaly	+	+	+	+	+	–	+
	Small hands			+		+		+
	Short fifth finger	–	–	+	–	–	–	–
	Hirsutism		+	–	+	+	+	

Note: Empty cells indicate unreported clinical sign.

Abbreviation: +, present; –, absent; +/–, seldom; CdLS, Cornelia de Lange syndrome; SWI/SNF, SWItch/sucrose non-fermentable.

Avagliano et al, Clinical Genetics, 2019

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OXFORD

Human Molecular Genetics, 2020, Vol. 29, No. R1 R43–R51

doi: 10.1093/hmg/ddaa175
Advance Access Publication Date: 7 August 2020
Invited Review Article

INVITED REVIEW ARTICLE

The phenomenal epigenome in neurodevelopmental disorders

Ummi Ciptasari[1] and Hans van Bokhoven[1,2,*]

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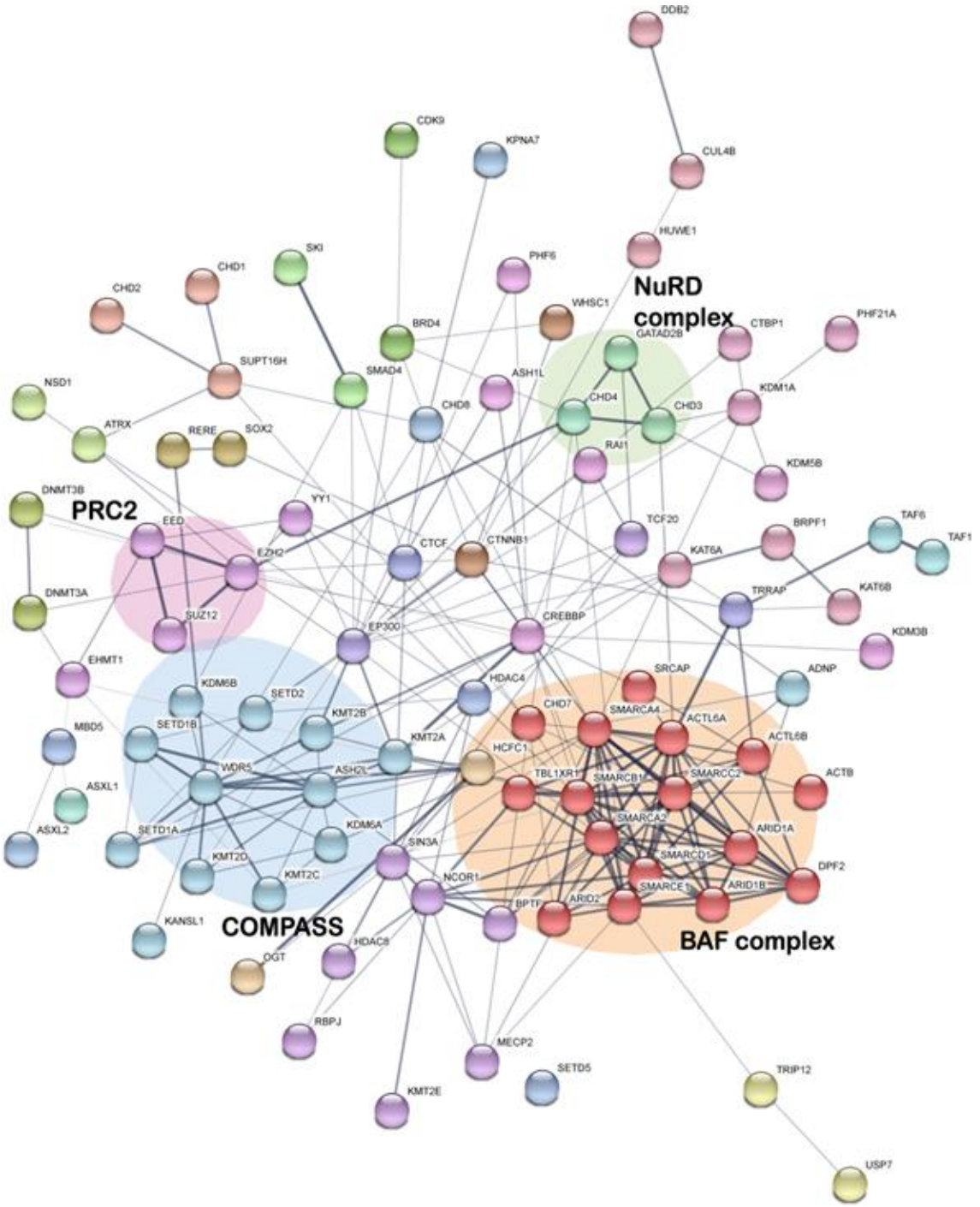
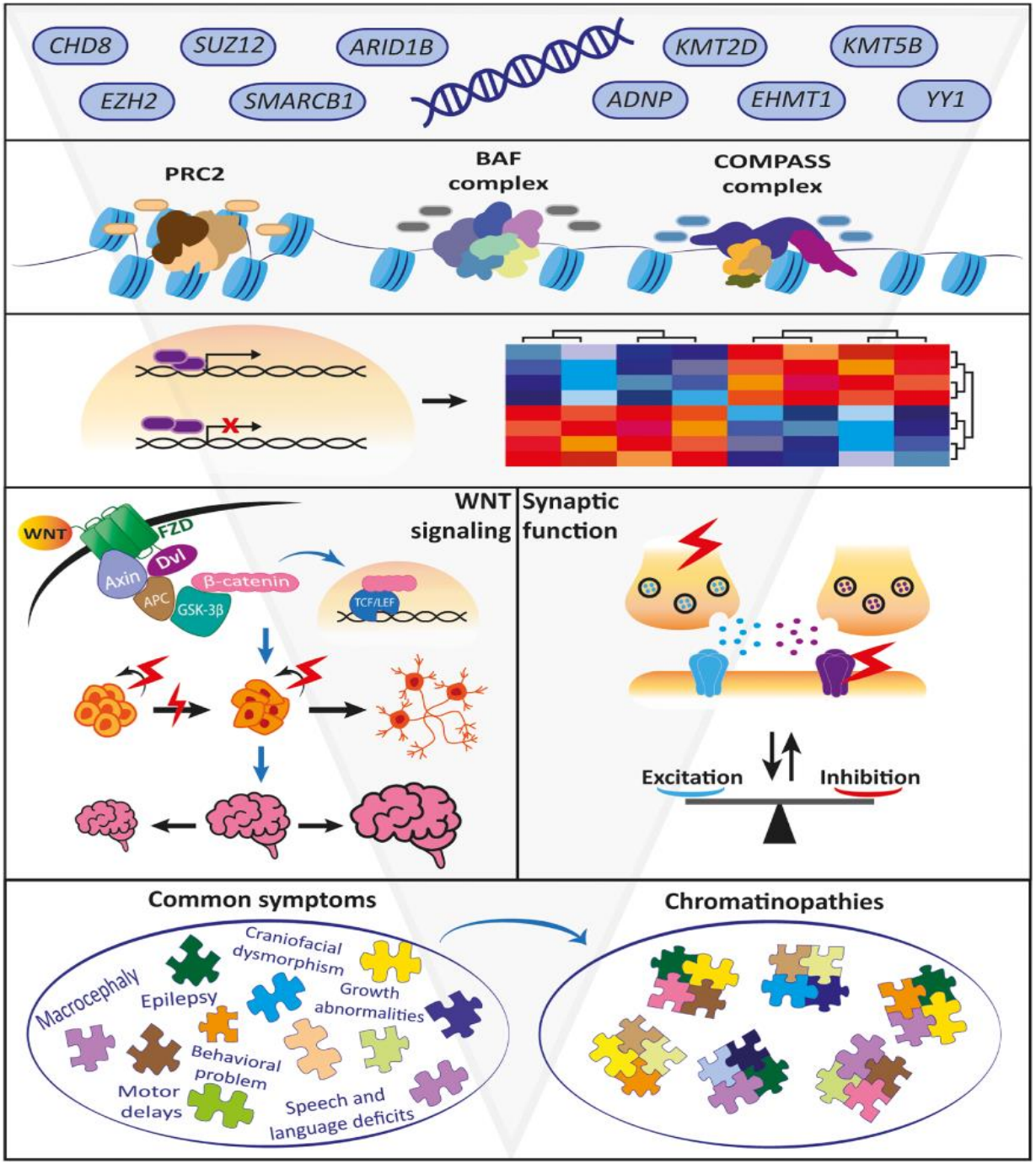
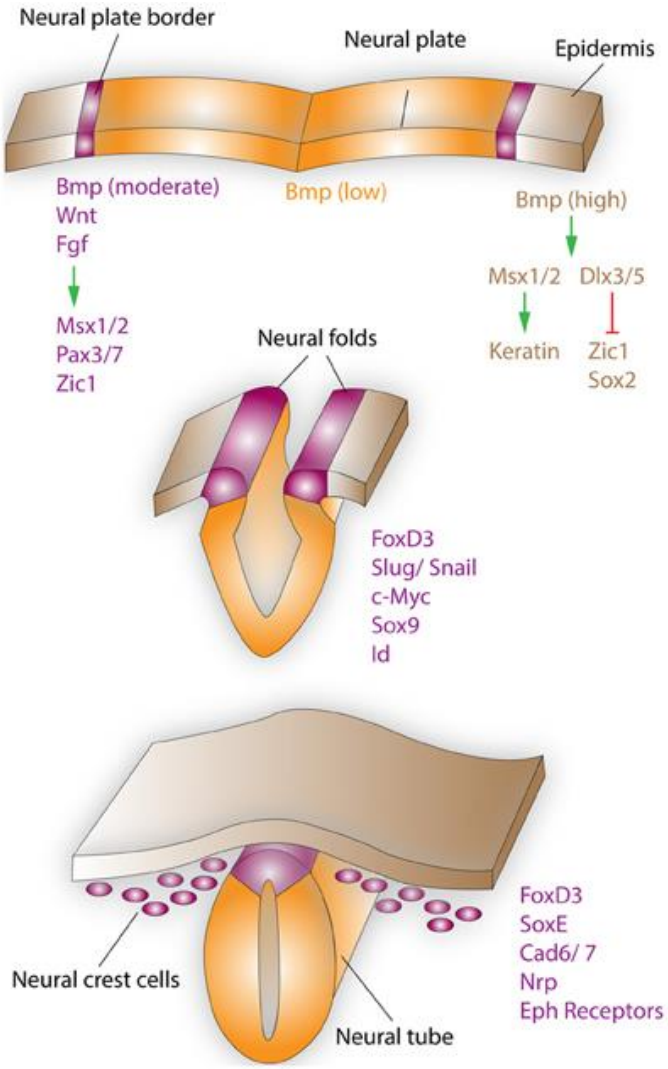
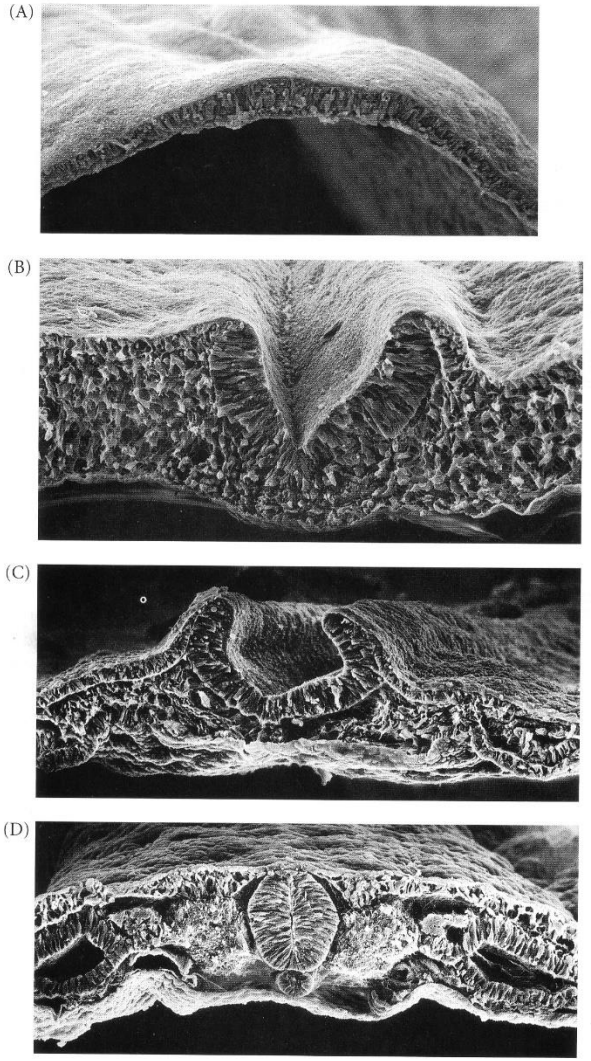

DDB2
CUL4B
HUWE1
CDK9
KPNA7
SKI
CHD1
CHD2
PHF6
WHSC1
NuRD
complex
BRD4
SMAD4
SUPT16H
NSD1
ATRX
RERE
SOX2
ASH1L
CHD8
GATAD2B
CHD4
CHD3
CTBP1
PHF21A
KDM1A
RAI1
KDM5B
DNMT3B
PRC2
EED
EZH2
SUZ12
DNMT3A
YY1
CTCF
CTNNB1
TCF20
KAT6A
BRPF1
TAF6
TAF1
KAT6B
TRRAP
KDM3B
EP300
CREBBP
EHMT1
KDM6B
SETD2
SETD1B
MBD5
ASXL1
ASXL2
KMT2B
KMT2A
HDAC4
SRCAP
ADNP
CHD7
SMARCA4
ACTL6A
ACTL6B
ACTB
HCFC1
WDR5
ASH2L
TBL1XR1
SMARCB1
SMARCC2
SMARCA2
ARID1A
SMARCD1
DPF2
SMARCE1
ARID1B
ARID2
BPTF
SETD1A
KDM6A
SIN3A
KMT2D
KMT2C
NCOR1
KANSL1
COMPASS
BAF complex
HDAC8
OGT
RBPJ
MECP2
SETD5
KMT2E
TRIP12
USP7



NEUROCRISTOPATHIES

4th week of development: neurulation





Ross et al, Frontiers in Physiology. 2014

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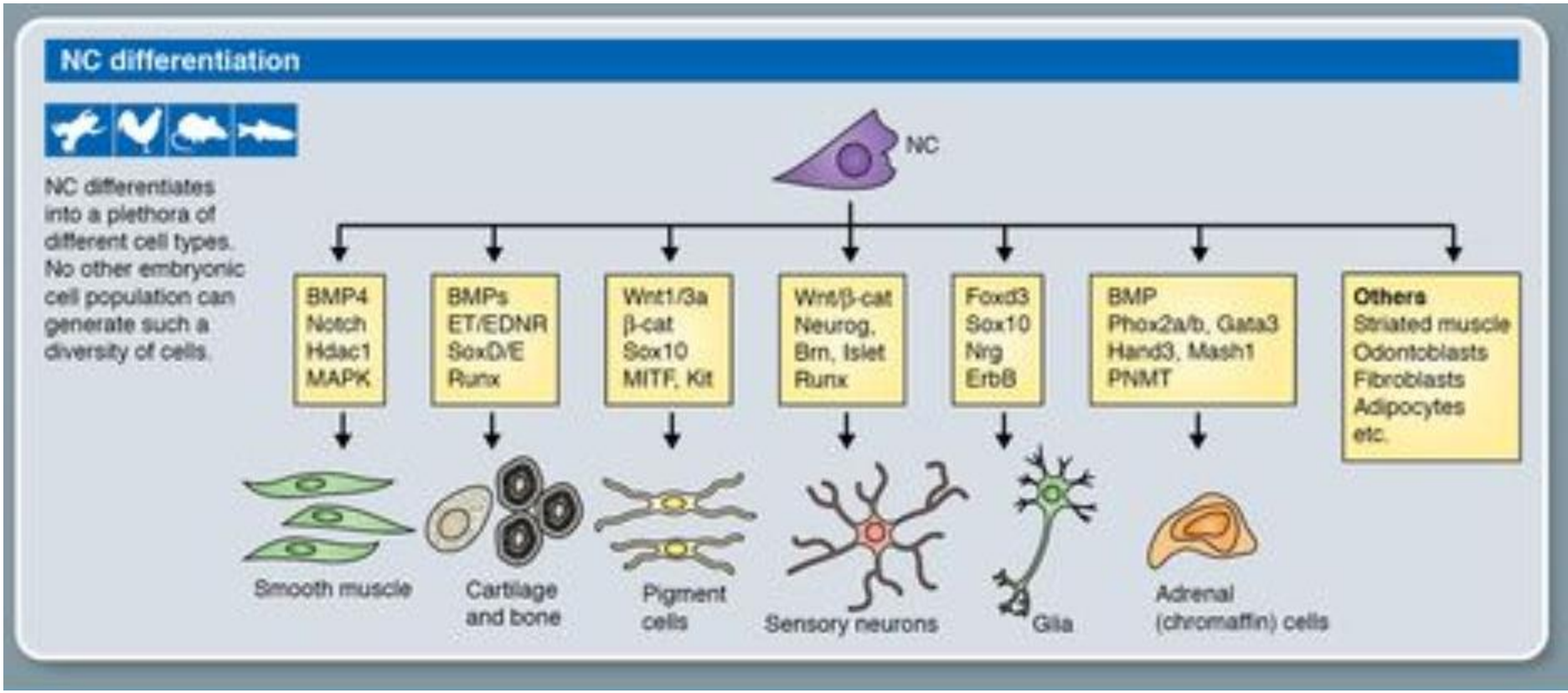
Neural crests: multipotent stem cells



Mayor et al, Development, 2013

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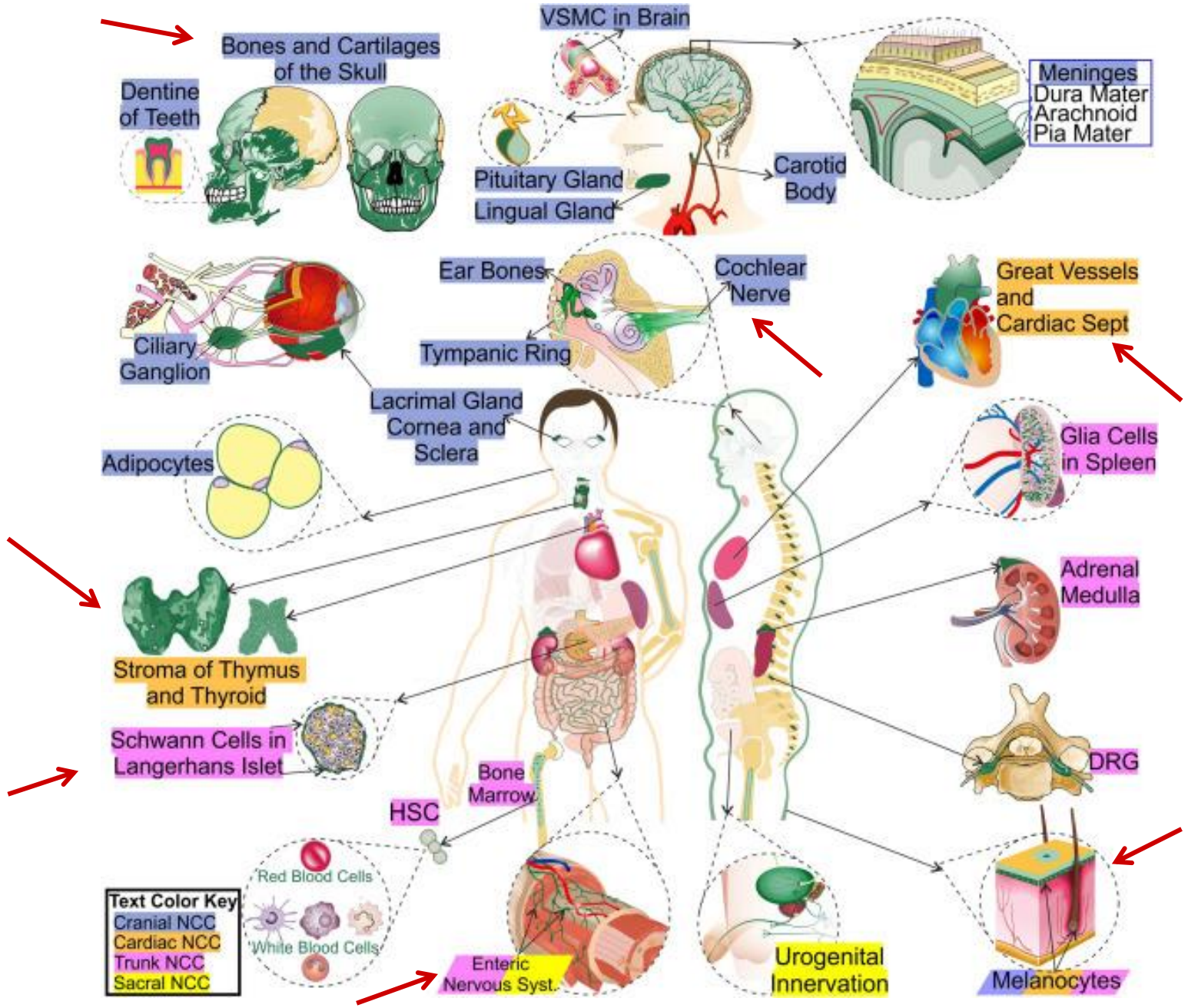

Vega Lopez et al, Developmental Biology, 2018

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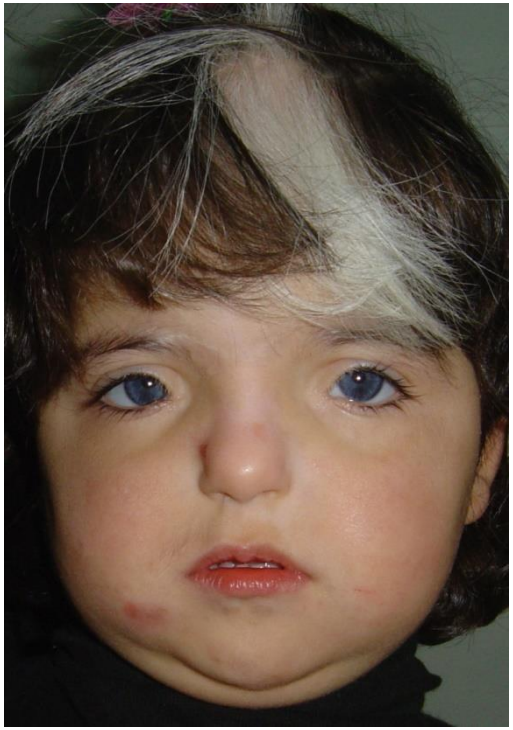
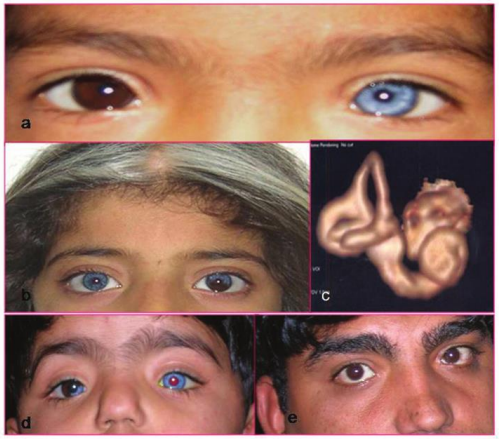
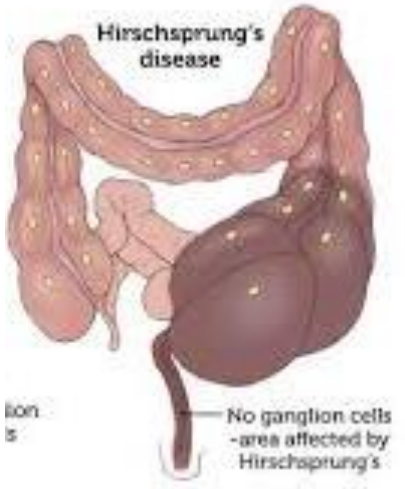




Waardenburg syndrome(PAX3)

22q11 deletion



Hirschsprung


Take home
message

Clinical syndromes

↓

Molecular syndromes

↓

Common signaling pathways

↓

Therapeutic perspectives

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AATDGTCGCGTTAACGTACTGACTTGACCATTT
AAATTGGTTCHGTAGACGAAGTCTATGGCTGG
CCGTCTGCATTGAAATGATGAAACGCGCGTGC
CGATACGATAGGAGGTCACTGCCGNCTGNCAT
TGAAACACCCATTGCAAGTCTATGGTTGGCCK
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CCGATAGCGCGTGCCGATACGATAGGAGGTCA
CTAATTGGTTCCGYAGACGCGTAGACTGTAATC
GTGGTTGAAATGAATTGGTOCCGTAGACTGATA
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